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**Basic Science**

**OC-BA-001**

Characterization of trigeminal ganglion cell spontaneous calcium signalling and responses to ATP, PACAP and CGRP

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**Objectives:** The trigeminal ganglion (TG) consists of bipolar neurons of different cell sizes and two types of glial cells; satellite glial cells and Schwann cells. The satellite glial cells surround neuronal cell bodies. The CGRP receptor is localized on the large-sized neurons and satellite glial cells in rat and human TG. The TG neurons also express PAC1 receptors. It is not known if and how PACAP and CGRP effect the calcium signaling in TG. We aimed to characterize the different cell types of TG based on their spontaneous calcium signaling activity and responses to ATP. We also examined the responses of satellite glia and neighbouring TG neurons to acute and chronic application of CGRP or PACAP.

**Methods:** Primary cultures of TG were prepared from mice p5-p7. Cultured cells were then loaded with the Ca\(^{2+}\)-specific fluorescent indicator fluo-4AM, and Ca\(^{2+}\) responses were quantified using a custom confocal imaging system. Responses of different cell types in the TG culture to ATP, CGRP or PACAP were analyzed. Parameters quantified included baseline intracellular calcium, spontaneous calcium transients, and the amplitude and duration of response to applied ligands. To confirm our results, we used two different cell lines with spontaneous calcium oscillations; GT1-7 (mouse hypothalamic tumor neurons) and GH3 (rat pituitary tumor cells) expressing CGRP and PAC1 receptor.

**Results:** We have established a cell culture system in which TG neurons develop characteristic cell morphology with extensive processes. Satellite glial cells grow in close contact with the neuronal cell bodies, with morphology similar to that observed in vivo. Spontaneous neuronal calcium transients were observed in neurons and satellite glial cells, with differences in their temporal and spatial characteristics. Addition of ATP activated an increase in [Ca\(^{2+}\)]\(_i\) in both neurons and glia, with neurons showing a rapid and transient response and glia showing a slower and more sustained response. CGRP induced Ca\(^{2+}\) increase in some TG neurons, while PACAP induced Ca\(^{2+}\) increase in some cells, mostly in glia cells. However, this was observed in very few cells. CGRP and PACAP did not change intracellular calcium in either the GT1-7 cell line or the GH3 cell line.

**Conclusion:** This result suggests that the different cell types of TG may be defined based on their spontaneous activity and their intercellular Ca\(^{2+}\) response to ATP. Our results also indicate that CGRP and PACAP do not consistently change intracellular Ca\(^{2+}\) in TG cells.

**Disclosure of Interest**

None Declared

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**Basic Science**

**OC-BA-002**

LOCUS COERULEUS NORADRENERGIC PROJECTIONS MODULATE CORTICAL SPREADING DEPRESSION THRESHOLDS IN RATS

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**Objectives:** The noradrenergic locus coeruleus (LC) is a key modulator of the sleep-wake cycle, acting as a promoter of arousal. Additionally, noradrenergic projections are involved in the regulation of cerebral blood flow and LC stimulation reduces cerebral blood flow. To explore further a potential role for the LC in migraine pathophysiology, we aimed to test whether LC disruption would modulate cortical spreading depression (CSD) thresholds.

**Methods:** Sprague-Dawley rats (\(n = 28\)) were randomly treated with vehicle (saline) or N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP4), a selective neurotoxin that initially induces degeneration of LC noradrenergic axon terminals followed by their cell bodies. Two weeks after treatment, rats were anesthetized with isoflurane and maintained with propofol infusion (33–50 mg/kg/h). Two cranial windows were drilled in each parietal bone for electrical or chemical induction of CSDs and for DC cortical recordings. Following 30 minutes of baseline recordings in the left hemisphere, the left cortex was electrically...
stimulated with increasing electric charge until a CSD was induced. Afterwards, baseline recordings were performed for 30 minutes in the right hemisphere, then a cotton ball soaked in 1M KCl was placed on the right cortex and CSDs were counted for 1 hour, with KCl refreshed every 15 minutes (5 μl).

**Results:** DSP4 treatment resulted in selective loss of 49% (±6.5) of the noradrenergic cells in the LC ($t_{26} = 5.083, p \leq 0.01$) and rats demonstrated a lethargic phenotype. This loss of LC noradrenergic cell bodies was associated with an increased propagation of KCl-induced CSDs ($t_{23} = -3.164, p \leq 0.001$), more pronouncedly during the last 30 minutes of recordings ($t_{23} = -3.215, p \leq 0.01$). In agreement with the increased propagation of KCl induced CSD’s the electrical threshold for CSD induction was significantly lower in LC ablated rats ($U = 43, p = 0.028$).

**Conclusion:** The LC sends dense noradrenergic projections to the entire cortex to induce wakefulness, loss of LC neurons resulted in the induction of a lethargic phenotype in rats and a significantly reduced threshold for CSD. As such, perturbation of the brainstem LC may play a critical role in migraine attack susceptibility and explain in part the increased prevalence of attacks during the early arousal phase.

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**Disclosure of Interest**


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**Basic Science**

**OC-BA-003**

**Dissecting Migraine with Optogenetics:**

**An aversive circuit from the periaqueductal gray to the ventral tegmental area**

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**Objectives:** Imaging studies of patients have shown that migraine attacks correlate with evidence of increased activity in the periaqueductal gray (PAG). However, it is unclear how these changes contribute to headache. Using optogenetic circuit manipulation, we present data demonstrating a connection between the PAG to the ventral tegmental area (VTA) and evaluate its contribution to pain processing in a rodent model of headache.

**Methods:** In Sprague Dawley rats, adeno-associated virus containing a light-activated cation channel (AAV2-hSynapsin-ChR2-mcherry) is stereotaxically delivered to bilateral ventrolateral PAG. Four weeks later, acute horizontal VTA slices are prepared for intracellular recordings. Mcherry-positive fibers originating in the PAG can be visualized in horizontal VTA slices and light-evoked post-synaptic potentials (PSPs) can be elicited from them using whole cell patch clamp techniques to record from VTA neurons. In behavioral experiments, animals receive PAG injections with ChR2 or sham virus. After 3–5 weeks of viral expression, optical fibers are implanted into the bilateral VTA. In a real-time place preference (PP) assay, animals are placed in a chamber separated into 2 areas with distinct contextual cues. When the animal enters the side designated for light stimulation, the laser is turned on (473 nm, 5 ms pulses at 20 Hz, 15 mW) and remains on until the animal exits the light-paired side. After three 20-minute sessions on one side, light is activated on the opposite side for an additional 3 sessions.

To determine whether this circuit alters behavior in an animal model of headache, the inhibitory chloride pump (AAV2-hSynapsin-eNpHR3.0-mcherry) is delivered into bilateral PAG. Three to five weeks later, rats undergo placement of optical VTA fibers and a dural cannula for inflammatory soup (IS) infusion, an established headache model in rodents. Real-time conditioned PP sessions with activation of halorhodopsin (525 nm, continuous, 10 mW) are performed in the presence and absence of inflammatory soup.

**Results:** Light stimulation (473 nm, 5 ms, 3 mW) of PAG axon terminal fibers in the VTA produces PSPs at a short fixed latency in a subset of VTA neurons, indicating these neurons receive direct synaptic input from the PAG. A majority of these connections are excitatory, as
light-evoked responses are inhibited by the AMPA receptor antagonist, DNQX.
Activation of these PAG inputs to the VTA is also adequate to induce avoidance behavior. After two 20 minute sessions, rats with active ChR2 virus in the PAG demonstrate aversion to the light-paired chamber. Animals with sham virus exhibit a difference score (ds) of 180.8 ± 134.1 s, while animals with ChR2 have an average ds of −456.9 ± 91.2 s (p = 0.003, n = 6 per condition). Furthermore, this avoidance behavior reverses sides within one session when light stimulation is alternated between the 2 sides of the chamber.

In preliminary experiments, inactivation of PAG to VTA projections with halorhodopsin elicits a conditioned place preference in animals receiving dural IS, but not in animals receiving dural phosphate buffered saline (PBS) infusion. After 2 conditioning sessions, animals with dural IS spend more time on the side where they received light-activated inhibition (ds 360.5 ± 175.7 s, n = 5), while animals without headache (receiving dural PBS) do not demonstrate a preference (ds −108.5 ± 201.5 s, n = 2).

**Conclusion:** These studies demonstrate an excitatory glutamatergic connection from the PAG to the VTA. Activation of this circuit is aversive, and this connection appears to be active during headache, but not at baseline. This circuit may be sensitive to therapeutic targets for migraine and become upregulated or refractory to treatment in chronic headache.

**Disclosure of Interest**
None Declared

**Basic Science**

**OC-BA-004**

Nociceptive trigeminal neurotransmission is inhibited by a PAC-1 receptor antibody in an in vivo model relevant to migraine

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**Objectives:** Pituitary adenylate cyclase-activating polypeptide 38 (PACAP-38) is released into the cranial circulation during an acute migraine attack and returns to its normal concentration after successful abortive treatment with sumatriptan. When infused systemically PACAP-38 induces migraine-like attacks in migraineurs. In line with these observations preclinical data from in vivo studies show that PACAP-38 increases spontaneous as well as stimulus-induced neuronal activity within the trigeminal complex (TCC) and suggest that this effect may be mediated by PAC-1 receptors.

The aim of the study was to investigate the efficacy of a PAC-1 receptor antibody on nociceptive neuronal transmission in the trigeminocervical complex in an in vivo model of migraine.

**Methods:** Male Sprague-Dawley rats were anesthetized using a single dose of pentobarbital (60 mg kg⁻¹) for induction and propofol (20–25 mg kg⁻¹ h⁻¹) for maintenance throughout the experiment. For electrical stimulation a cranial window was opened in the parietal bone and a bipolar stimulating electrode was placed on the intact dura mater above the middle meningeal artery. For extracellular recordings of nociceptive neuronal activity a C1 laminectomy was performed and a tungsten electrode was placed within the TCC. During the experiment primary trigeminal afferents were stimulated supramaximally with square wave pulses.

A PAC-1 receptor antibody (10 mg kg⁻¹) or its vehicle were administered intravenously followed by a resting period of 2.5 hours. Sumatriptan (10 mg kg⁻¹) or its vehicle were then administered intravenously followed by a resting period of 30 minutes. Post-stimulus histograms and background activity were then recorded in the TCC over 45 minutes.

**Results:** The systemic administration of the PAC-1 receptor antibody induced an inhibition of stimulus-evoked nociceptive activity in the TCC (−40 ± 11%, F₁,₅₄, 6.17 = 9.30, p = 0.016) when compared to its baseline. Likewise, sumatriptan, which served as a positive control, significantly inhibited stimulus-evoked neuronal activity (−30 ± 11%, F₁,₁₀, 14.67 = 5.11, p = 0.020), whereas vehicle control did not show a significant effect (−18 ± 9%, F₁,₉₈, 13.83 = 2.31, p = 0.136). In none of the groups a significant effect on spontaneous background activity was observed.

The PAC-1 receptor antibody had no effect on arterial blood pressure whereas sumatriptan induced a minor decrease (−12.9 ± 3%, F₂,₄₁, 16.89 = 5.75, p = 0.009).

**Conclusion:** The PAC-1 receptor antibody effectively inhibits stimulus-evoked neuronal activity in the TCC. Taken together with experimental medicine studies the new results support targeting the PAC-1 receptor with an antibody as a novel and promising mechanism for the preventive treatment of migraine.

**Disclosure of Interest**
J. Hoffmann Conflict with: Dr. Hoffmann received honoraria for consulting from Allergan, Autonomic Technologies Inc. (ATI) and Novartis, Conflict with: Dr. Hoffmann received
Results: Available CaMEO respondents with migraine (16,763) were sent the Comorbidities/Endophenotype module and 12,810 (76.4%) provided valid responses: 11,669 with EM; 1,111 with CM. Compared with the EM group, the CM group had a similar mean age (EM, 41.3 years; CM, 41.9 years), was more likely to be female (EM, 74.2%; CM, 81.5%; \( P < 0.001 \)) and white (EM, 84.0%; CM, 88.7%; \( P < 0.001 \)), and had a mean higher body mass index (EM, 27.7 kg/m\(^2\); CM, 28.7 kg/m\(^2\); \( P < 0.001 \)). The relative frequencies were significantly higher for 29 (93.5%) of the 31 SR symptoms and SR-PD conditions assessed. Conditions or groups of conditions with relative frequencies \( >10\% \) higher in CM than EM included allergies/hay fever/allergic rhinitis (EM, 37.4%; CM, 51.0%), sinusitis/sinus infection (EM, 47.3%; CM, 58.8%), insomnia (EM, 35.6%; CM, 50.2%), vertigo/dizziness/balance problems (EM, 17.8%; CM, 29.7%), and gastroesophageal reflux disease (EM, 14.3%; CM, 24.4%; Table).
Conclusion: Overall, significantly more respondents with CM vs. EM reported medical symptoms or conditions. Multiple mechanisms might explain this association including manifestations of migraine, direct causality (e.g., CM directly causes the comorbidity), reverse causality (e.g., the condition increases the risk of CM), and shared genetic or environmental risk factors. Confounding or detection bias (i.e., “Berkson’s Bias”) could contribute to the findings. Future analyses will address naturally occurring subgroups (taxa) defined by migraine phenotypes and comorbidities and assess the relationships of these groups to external validators such as treatment response and clinical course.

Disclosure of Interest
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Epidemiology

OC-EP-002
Use and overuse of triptans in Austria – a survey based on nationwide sickness claims data
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Objectives: The aim of our study was to evaluate the prescription of triptans in Austria. With only minor exceptions, every inhabitant has to be insured by one of the social security institutions. A nationwide research database (GAP-DRG) of the Hauptverband der Österreichischen Sozialversicherungsträger provides anonymous data on dispensed drugs, sex, age and other details for particular years.

Methods: For 2007 data on 7 426 412 insured persons were available. We included persons aged 18–99 years with known sex and with billable insurance benefits in 2007, this excludes benefits to persons released of pre-terminal illness and others who should not be insured. We included persons aged 18–99 years who were living in predominantly urban areas compared to all insured persons. For 2007 data on 7 426 412 insured persons were available. We included persons aged 18–99 years with known sex and with billable insurance benefits in 2007, this excludes benefits to persons released of pre-terminal illness and others who should not be insured. We included persons aged 18–99 years who were living in predominantly urban areas compared to all insured persons.

Results: Among all included persons 54 % were female, 46 % male, median age was 47 years, 33062 persons (0.56 %) received a at least one triptan prescription in 2007, 1970 persons were triptan overusers (5.9 % of triptan users, 0.033% of the research population), thereof 45 % overused triptans in one quarter, 21% in two quarters, 16% in three quarters and 18 % in four quarters of 2007. Triptan users were significantly younger than non-users (44 vs. 47 years, p < 0.001), and comprised significantly more women (82 % vs. 54 %, p < 0.001). The median number of dispensed triptans per year was 12 in non-overusers and 102 in overusers. (p < 0.001). Compared to non-users triptan users had significantly more median days of sick-leave in general (12 vs. 10, p < 0.001) and sick-leave due to migraine (3 vs. 2 days, p < 0.001). Significantly more triptan users and overusers were living in predominantly urban areas compared to all insured persons.
Conclusion: In the general population of Austria a triptan prescription rate of 0.56 % contrasts with a migraine prevalence of 10 %. Thus, the estimated proportion of persons with migraine using a triptan is less than 6 %. Triptan overuse is uncommon in the general population, but affects 1 of 17 triptan users. The finding that both use and overuse of triptans is more common in urban areas may be explained by socioeconomic conditions or by the availability of physicians. Our study suggests that migraine attacks are severely undertreated in Austria and that triptan overuse is not uncommon among triptan users. Management of migraine requires further improvement by promoting the use of triptans in patients who do not achieve freedom from migraine within 2 hours with two or more adequately dosed analgesics or NSAIDs taken early during the attack and by educating about the consequences of triptan overuse.

Disclosure of Interest
None Declared

Epidemiology

OC-EP-003

Association of 30 year Cardiovascular Disease Risk with Migraine Diagnosis and Childhood Abuse in Young Adults - Findings from the Add Health study

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Objectives: Both migraine and childhood abuse have been found to be associated with cardiovascular disease (CVD) risk. Further, migraine has been linked with childhood abuse, especially emotional abuse. The 30 year Framingham CVD risk scoring is an evidence based method for calculating cardiovascular risk for young adults, 20–30 year old. Previous studies looking at the association of migraine and Framingham risk score focused on an older population using the 10 year CVD risk. The current study investigates the independent effects of migraine and childhood abuse on 30 year Framingham (CVD) risk score in young adults. We also assess the interaction effect of migraine and childhood abuse on the 30 year Framingham (CVD) risk.

Methods: We analyzed retrospective, cross-sectional data from 12,606 adults aged 24–32 years in Wave 4 of the Add Health study (2008). Participants were queried regarding maltreatment (emotional, physical and sexual) during childhood, diagnosis of migraine and other health conditions by a health care provider, health behaviors, and socio-demographics. Height, weight, blood pressure, glycated hemoglobin (HbA1c), and list of medications were also documented during in-home visits. 30 year risk score for cardiovascular diseases was calculated for each participants using Framingham based prediction model using their age, sex, body mass index, smoking status, systolic blood pressure, diabetes and use of antihypertensive medications. Linear regressions were used to assess the main independent effect and the interaction effect on the log transformed 30 year Framingham (CVD) risk Score.

Results: About 14% of the total sample reported a migraine diagnosis. The 30 year Framingham (CVD) risk score was positively and independently associated with migraine diagnosis ($b = 0.084, \text{SE} = \pm 0.02, p < 0.05$) and self-reported frequency of childhood emotional abuse ($b = 0.010, \text{SE} = \pm 0.001, p < 0.05$), after controlling for age, sex, race, ethnicity and income. Subsequent subgroup analysis showed that the associations differed by the sex. In females, both migraine diagnosis ($b = 0.095, \text{SE} = \pm 0.03, p < 0.05$) and self-reported frequency of childhood emotional abuse ($b = 0.018, \text{SE} = \pm 0.01, p < 0.05$) had a significant effect on Framingham (CVD) risk score which was independent of each other. However, in males, only migraine diagnosis ($b = 0.080, \text{SE} = \pm 0.04, p < 0.05$) showed a significant main effect on the Framingham (CVD) risk score. There was no significant interaction between migraine diagnosis and the self-reported frequency of any type of childhood abuse ($p > 0.05$) in the entire sample nor in the subgroup analysis.

Conclusion: Both childhood abuse and migraine significantly increase the risk of cardiovascular disease, independently of each other. However, there is no interaction of these two variables on CVD risk, meaning the effects of
both are additive but not synergistic. These findings need to be corroborated by future studies.

Disclosure of Interest
M. Karmakar: None Declared, A. Amialchuk: None Declared, G. Tietjen Conflict with: owns common stock in Johnson & Johnson, and Stryker, Conflict with: serves on advisory boards of Eli Lilly, and Dr. Reddy’s

Epidemiology

OC-EP-004
Validation of a Questionnaire to Assess Photophobia

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Objectives: A number of neurologic and ophthalmic conditions are associated with abnormal light sensitivity (photophobia), but the most prevalent condition is migraine. We previously developed a questionnaire to quantify patients’ light sensitivity symptoms and the effects of their light sensitivity on activities of daily living. The objective of the current investigation was to validate this photophobia questionnaire by 1) comparing the psychometric properties of the photophobia questionnaire against a recently validated Korean questionnaire, and 2) to determine the relationship between patients’ photophobia questionnaire scores and their level of light sensitivity.

Methods: We randomly recruited subjects from the neurology and ophthalmology clinics. After informed consent, subjects completed our 16-item photophobia questionnaire and the Korean 8-item questionnaire. Subjects were then seated in front of a calibrated light source. Following a period of dark adaptation, the examiner gradually increased the luminance of the source until the participant said, “stop”, at which point their experience of the light became painful (designated as their light sensitivity threshold). This process was repeated three times and the average log lux of the stop points was recorded. We used descriptive statistics to examine patient demographic characteristics and applied Pearson correlations to assess the associations between measures. An alpha of 0.05 (two-sided) was considered significant. Rasch analyses were conducted on the Korean and Photophobia questionnaires using the Rasch rating scale and the partial credit models respectively, from cross-sectional data.

Results: We included subjects both with and without light sensitive conditions. The study sample consisted of 95 patients: 72 females (75.8%), 83 Caucasians (87.4%), mean age of 47 years (range 18 to 79). There was a significant correlation between our 16-item photophobia questionnaire and the Korean questionnaire $r = 0.787$ ($p < 0.05$). Our photophobia questionnaire was found to have relatively good instrument targeting that was much better than the Korean questionnaire. Light sensitivity thresholds were significantly correlated between both the Korean 8-item questionnaire $-0.535$ ($p < 0.05$) and our 16-item photophobia questionnaire $-0.411$ ($p < 0.05$).

Conclusion: By including subjects with a wide range of photophobia (from no photophobia to severe photophobia) we were able to rigorously evaluate our photophobia questionnaire. Scores on our 16-item photophobia questionnaire correlated well with light sensitivity thresholds and with the previously validated Korean questionnaire. This study indicated that our photophobia questionnaire may have some advantages over the Korean questionnaire. Our questionnaire may be a reasonable surrogate measure in future studies designed to better understand the causes of and treatments for photophobia.

Disclosure of Interest

Imaging and Human Studies

OC-IH-001
Reproducibility of migraine-like attacks induced by phosphodiesterase-3-inhibitor cilostazol

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Objectives: The phosphodiesterase-3-inhibitor cilostazol induces migraine-like attacks in patients with migraine without aura and may be used as a pharmacological trigger in human experimental models of migraine. However, the reproducibility of cilostazol-induced migraine-like attacks has never been investigated.

Methods: We performed a post-hoc analysis of clinical data from two brain-imaging studies including subjects who had received cilostazol 200 mg orally. Only subjects who developed migraine-like attacks on study day 1 were included on study day 2. After cilostazol ingestion, subjects and the investigator recorded headache intensity and characteristics once every hour on a purpose-developed
questionnaire. Primary end-points included incidence and time to onset of migraine-like attacks between two separate study days.

**Results:** Thirty-four subjects completed both experimental days and were included in this study. Thirty-four out of 34 subjects (100%) developed migraine-like attacks after cilostazol ingestion on both study days 1 and 2. Time to onset of migraine was 5 hours (range 1–8 hours) on study day 1 and 4 hours (range 1–8 hours) on study day 2, \( p = 0.16 \). We found no difference in median peak headache score, median time to peak headache score, or median time to intake of rescue medication between study days 1 and 2.

**Conclusion:** A second-time administration of cilostazol reproduces migraine-like attacks in all subjects who report an attack after their first cilostazol induction. There was no difference in time to migraine onset between separate inductions. Experimental migraine-provocation using cilostazol is a highly efficient and useful approach for studying the ictal phase of migraine without aura.

**Disclosure of Interest**

S. Khan Conflict with: S. Khan has acted as invited speaker for Novartis during the conduct of this study., M. Deen: None Declared, A. Hougaard: None Declared, F. Mohammad Amin: None Declared, M. Ashina Conflict with: M. Ashina reports grants from Lundbeck Foundation (R155-2014-171) and Novo Nordisk Foundation (NNF11OC101433) during the conduct of the study., Conflict with: M. Ashina is a consultant or scientific advisor for Allergan, Amgen, Alder, ATI, Eli Lilly, Novartis and Teva, primary investigator for Amgen 20120178 (Phase 2), 20120295 (Phase 2), 20130255 (OLE), 20120297 (Phase 3) and GM-11 gamma-Core-R trials

**Imaging and Human Studies**

**OC-IH-002**

**ALTERATIONS IN CEREBRAL BLOOD FLOW DURING THE POSTDROME PHASE OF A MIGRAINE ATTACK CAPTURED WITH ARTERIAL SPIN LABELLED (ASL) MRI**

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**Objectives:** Migraine has four main phases: premonitory, aura, headache and postdrome. Symptoms patients experience in the premonitory and postdromal phase of migraine are broadly similar. The postdrome of a migraine attack, however, is poorly characterised. Functional imaging methods have not been used to evaluate the postdrome phase in depth. Given that there are some similar symptoms experienced by subjects in the premonitory phase and postdrome phase, we wanted to study the premonitory and postdrome phase using a nitroglycerin induced human migraine model combined with arterial spin labelled (ASL) MRI to see if the activations involve similar brain regions. Pulsed continuous arterial spin labelled (pCASL) MRI is a non-invasive MRI technique to measure tissue perfusion that does not use ionizing radiation.

**Methods:** Sixteen subjects completed three study visits. ASL MRI scans over the course of triggered migraine attacks were analysed (SPM 12, www.fil.ion.ac.uk/spm). Voxel based analysis of premonitory scans of all subjects compared to postdrome scans of all subjects was carried out. Region of interest analysis (ROI) of key brain areas selected from previous functional imaging studies, such as the hypothalamus, pons, midbrain, thalamus, and anterior cingulate cortex was also carried out.

**Results:** With voxel based analysis, significant reductions were detected in rCBF (regional cerebral blood flow) over the superior frontal gyrus, medial frontal gyrus, middle frontal gyrus, putamen, superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, thalamus, hypothalamus, midbrain, posterior cingulate, anterior cingulate, claustrum (\( P < 0.001 \)) in the postdrome phase compared to premonitory phase at a whole brain analysis level. Small volume correction showed additional areas of reduction in rCBF over the frontal medial orbital gyrus, insula, caudate, with peak reduction in rCBF over the left medial globus pallidus (\( P = 0.027 \), sphere set at 12mm radius of Voxel of interest) along with areas with reductions seen in rCBF at a whole brain level analysis.

With region of interest (ROI) analysis, we found statistically significant reductions in rCBF over the anterior cingulate cortex (ACC) in the postdrome phase compared to the premonitory phase (\( P = 0.002 \)). The mean rCBF in the ACC during the premonitory phase was 58 ml/min/100ml tissue (mean \( \pm \) SE; \( \pm 9 \)) and mean rCBF in the ACC during the postdrome phase was 53 ml/min/100ml tissue (\( \pm 7 \)). Statistically significant reduction in rCBF were also seen in the insula in in the postdrome phase compared to the premonitory phase (\( P = 0.002 \)). The mean rCBF in the Insula during the premonitory phase was 59 ml/min/100ml tissue (\( \pm 10 \)) and mean rCBF in the Insula during the postdrome phase was 54 ml/min/100ml tissue (\( \pm 7 \)).

**Conclusion:** The brain processes involved in the premonitory phase and postdrome phase are different. The symptoms experienced by subjects in the postdrome are associated with a near global reduction in cerebral blood flow. A computer based analogy of the postdrome would...
be the phase of migraine where the brain ‘re-boots’ itself before returning to normal function.

Disclosure of Interest
None Declared

Imaging and Human Studies

OC-IH-003
The similarities between spontaneous and nitroglycerin-triggered premonitory symptoms in migraineurs

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Objectives: Human models of migraine are required to understand the neurobiology of this disabling condition. Nitroglycerin (NTG) effectively triggers migraine headache in 60–80% of migraineurs, and has also been shown to trigger premonitory symptomatology. We aimed to study the triggering of premonitory symptomatology with NTG, comparing the phenotype of triggered attacks to spontaneous attacks.

Methods: Migraineurs who reported spontaneous premonitory symptoms were recruited following informed consent (n = 49). A detailed migraine history was taken from each subject at screening, eligibility was rechecked, an electrocardiogram and physical examination were conducted and observations were documented. NTG (0.5mcg/kg/min over 20 minutes) was administered intravenously to each subject. The phenotype of premonitory symptoms where present (n = 47) following triggering was recorded for each subject. A standardised physician-administered symptom questionnaire was used for both spontaneous and triggered attacks. Statistical analyses were performed to assess the correlation between common spontaneous and triggered symptoms using the Chi-squared test. P < 0.05 was considered significant. Analyses were performed for fatigue, concentration difficulty, irritability, neck stiffness and yawning, as these were the most commonly displayed symptoms.

<table>
<thead>
<tr>
<th></th>
<th>Fatigue</th>
<th>Yawning</th>
<th>Irritability</th>
<th>Concentration change</th>
<th>Neck stiffness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>39</td>
<td>24</td>
<td>26</td>
<td>42</td>
<td>28</td>
</tr>
<tr>
<td>Triggered</td>
<td>39</td>
<td>19</td>
<td>11</td>
<td>31</td>
<td>28</td>
</tr>
<tr>
<td>P value</td>
<td>0.002*</td>
<td>0.030*</td>
<td>0.004*</td>
<td>0.053</td>
<td>0.004*</td>
</tr>
</tbody>
</table>

Cross tabulation of numbers of subjects with self-reported spontaneous and triggered common premonitory symptoms. P < 0.05 was considered significant (*).

Results: Triggered premonitory symptomatology was similar to spontaneous symptomatology, with a statistically significantly increased likelihood of reporting most of the common symptoms following triggering if reported in spontaneous attacks. Significant associations between spontaneous and triggered symptoms were found for fatigue (p = 0.002), neck stiffness (p = 0.004), irritability (p = 0.004) and yawning (p = 0.030). There was a trend towards significance for concentration difficulty (p = 0.053).

Conclusion: The similarities between spontaneous and triggered attacks suggest that NTG triggering is an effective model to study premonitory symptoms in migraine.

Disclosure of Interest
N. Karsan Conflict with: Dr Karsan is an Association of British Neurologists/Guarantors of Brain Clinical Research Training Fellow. P. Bose: None Declared. C. Thompson: None Declared. P. Goadsby Conflict with: Dr. Goadsby reports grants and personal fees from Allergan, Amgen, and Eli-Lilly and Company; and personal fees from Akita Biomedical, Alder Biopharmaceuticals, Autonomic Technologies Inc, Avanir Pharma, Cipla Ltd, Colucid Pharmaceuticals, Ltd, Dr Reddy’s Laboratories, eNeura, Electrocore LLC, Novartis, Pfizer Inc, Promius Pharma, Quest Diagnostics, Scion, Teva Pharmaceuticals, Trigemina Inc., Scion. Conflict with: personal fees from MedicoLegal work, Journal Watch, Up-to-Date, Oxford University Press; and in addition, Dr. Goadsby has a patent Magnetic stimulation for headache pending assigned to eNeura
Imaging and Human Studies

OC-IH-004

Hemiplegic migraine: the elusive fourth gene and clinical differences between monogenic and complex polygenic forms

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Objectives: Hemiplegic migraine is a rare clinically and genetically heterogeneous subtype of migraine with aura which in a proportion of patients is caused by autosomal dominant mutations in CACNA1A, ATP1A2 or SCN1A. It is unknown whether the clinical characteristics of patients with and without such mutations differ, and whether the disease may also be caused by mutations in other genes.

Methods: We compared the clinical characteristics of 208 patients with familial (n = 199) or sporadic (n = 9) hemiplegic migraine due to a pathogenic mutation in CACNA1A, ATP1A2 or SCN1A with the clinical characteristics of 73 patients with familial (n = 49) or sporadic (n = 24) hemiplegic migraine without mutations in these genes. In addition, 47 patients (familial: n = 33; sporadic: n = 14) without mutations in CACNA1A, ATP1A2 or SCN1A were screened for mutations in novel genes using whole exome sequencing.

Results: Patients with mutations in CACNA1A, ATP1A2 or SCN1A had lower age at disease-onset, larger numbers of affected family members, and more often attacks which were: (i) triggered by mild head trauma; (ii) characterised by extensive severe motor weakness; and (iii) associated with brainstem features, confusion and brain oedema. Mental retardation and progressive ataxia were exclusively found in patients with a mutation. Whole exome sequencing failed to identify pathogenic mutations in new genes.

Conclusion: Most patients with hemiplegic migraine without a mutation in CACNA1A, ATP1A2 or SCN1A display a remarkably mild phenotype which seems more akin to that of common (non-hemiplegic) migraine and which most likely is caused by complex polygenic rather than by simple monogenic mechanisms. A fourth autosomal dominant gene for hemiplegic migraine remains elusive. These observations might guide physicians in selecting patients for mutation screening and in providing adequate genetic counselling.

Disclosure of Interest
None Declared

Imaging

OC-IM-001

Increased intrinsic brain connectivity between pons and somatosensory cortex during attacks of migraine with aura

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Objectives: The neurological disturbances of migraine aura are caused by transient cortical dysfunction due to waves of spreading depolarization that disrupt neuronal signaling. The effects of these cortical events on intrinsic brain connectivity during attacks of migraine aura have not previously been investigated. Studies of spontaneous migraine attacks are notoriously challenging due to their unpredictable nature and patient discomfort.

Methods: We investigated sixteen migraine patients with visual aura during attacks and in the attack-free state using resting state fMRI. We applied a hypothesis-driven seed-based approach focusing on cortical visual areas and areas involved in migraine pain, and a data-driven independent component analysis approach to detect changes in intrinsic brain signaling during attacks. In addition, we performed the analyses after mirroring the MRI data according to the side of perceived aura symptoms.

Results: We found a marked increase in connectivity during attacks between the left pons and the left primary somatosensory cortex including the head and face somatotopic areas (peak voxel: P = 0.0096, (x,y,z) = (−54, −32, −10).
32), corresponding well with the majority of patients reporting right-sided pain. For aura-side normalized data, we found increased connectivity during attacks between visual area V5 and the lower middle frontal gyrus in the symptomatic hemisphere (peak voxel: P = 0.0194, (x,y,z) = (40,40,12).

**Figure legend:** Intrinsic connectivity for seed placed in the left pons, data in the original orientation (not flipped according to visual aura lateralization). A. The red sphere marks the seed location. Green: Areas functionally connected to the seed during the interictal phase. Blue: Areas functionally connected to the seed during spontaneous attack of migraine with aura. R marks the right hemisphere side; x, y, and z gives MNI coordinates for the slices. B. Areas of significantly increased connectivity during attacks compared to the attack-free state. Connectivity did not decrease in any areas during attacks.

**Conclusion:** The present study provides evidence of altered intrinsic brain connectivity during attacks of migraine with aura, which may reflect consequences of cortical spreading depression, suggesting a link between aura and headache mechanisms.

**Disclosure of Interest**
A. Hougaard: None Declared, F. Amin: None Declared, H. Larsson: None Declared, E. Rostrup: None Declared, M. Ashina Conflict with: Allergan, Amgen, Alder, ATI and Eli Lilly

**Imaging**

**OC-IM-002**

**Resting-state functional connectivity in the visual network: a possible predictor for treatment response in chronic migraine**

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**Objectives:** Up to 25% of migraineurs progress to chronic migraine (headache on ≥15 days per month, of which ≥8 migraine days). Although predisposing factors, such as depression and acute headache medication overuse, have been established, the exact mechanisms leading to migraine chronification and reversion are still uncertain. We investigated whether Resting-State functional connectivity (RS-fc) findings in chronic migraine patients predict good outcome after treatment.

**Methods:** Resting-state functional MR imaging was conducted in 112 participants with chronic migraine and medication overuse before and after treatment. Responders to treatment (≥50% reduction in headache days) were compared with non-responders (<50% reduction in headache days), using RS-fc within ten well-known functionally correlated networks. Data were preprocessed using a standard FSL pipeline (FSL v5.0.8) with addition of the AROMA motion correction tool, followed by analysis using a General Linear Model and permutation testing with 5000 permutations. Results were corrected for multiple comparisons within subject and between groups.

**Results:** Data of 99 participants was complete and usable for analysis (artifacts n = 7, incidental findings n = 2, lost to follow-up n = 4). Mean number of headache days at baseline was 21.2 per month. RS-fc analysis of the lateral visual network showed a large cluster of voxels in the right lateral occipital cortex stretching to the left lateral occipital cortex. This area showed a higher connectivity in responders versus non-responders at baseline (p = .015), and this higher functional connectivity decreased within responders from baseline to follow-up (p < .001).

**Conclusion:** Chronic migraineurs who responded to treatment, and reversed to episodic, showed a significantly higher RS-fc within the lateral visual network as compared to non-responders at baseline, as well as a significant decrease of RS-fc in this area after treatment.

**Disclosure of Interest**
None Declared

**OC-IM-003**

**Reduced grey matter density in chronic migraine patients: correlations with clinical features**

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3Headache Center, IRCCS-Neuromed, Pazzilli, Italy

**Objectives:** Few MRI studies have been performed so far in patients affected by chronic migraine (CM) and especially in those without medication overuse. Here, we performed voxel-based morphometry (VBM) analysis to investigate the grey matter (GM) density of the whole brain in patients affected by CM. Our aim was to investigate whether there are fluctuations in the GM densities in relation to CM clinical features.

**Methods:** Twenty untreated CM patients without a past medical history of medication overuse underwent 3T MRI
scans and were compared to a group of 20 healthy volunteers (HV). SPM12 and CAT12 toolbox were used to process MRI data and to perform VBM analysis of structural T1-weighted MRI scans. The patients’ versus HV relative GM density was assessed with an uncorrected threshold of \( p < 0.01 \). To check for possible correlations, patients’ clinical features and GM maps were regressed.

**Results:** Compared to HV, CM patients showed 4 clusters of significantly lower GM densities: I) the cerebellar hemispheres/vermis, II) the left occipital areas (BA17/BA18), III) the left middle temporal gyrus, and IV) the left temporal pole /amygdala /pallidum /orbitofrontal cortex. The GM density of cerebellar hemispheres correlated negatively with the years of headache disease, and positively with the number of tablets intake per month.

**Conclusion:** CM is thus associated with lower GM density in several brain areas known to be involved in nociception/antinociception, multisensory integration, and analgesic dependence. The GM density within the cerebellum was significantly related to longer duration of headache disease, and positively with the number of tablets intake per month.

**Disclosure of Interest**
None Declared

**Imaging**

**OC-IM-004**

**Effect of hypoxia on BOLD fMRI response and total cerebral blood flow in migraine with aura patients**

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\(^2\)Functional Imaging Unit, Department of Clinical Physiology, Nuclear Medicine and PET  
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**Objectives:** Experimentally induced hypoxia triggers migraine and aura attacks in patients suffering from migraine with aura. We investigated the blood-oxygenation level dependent (BOLD) signal response to visual stimulation during hypoxia in migraine aura patients and healthy volunteers.

**Methods:** In a randomized double-blind crossover study design, 15 migraine with aura patients were allocated to 180 min of hypoxia (capillary oxygen saturation 70 – 75%) or sham (normoxia) on two separate days and 14 healthy volunteers were exposed to hypoxia. The BOLD functional MRI (fMRI) signal response to visual stimulation was measured in the visual cortex ROIs V1-V5. Total cerebral blood flow was measured by phase-contrast mapping (PCM) MRI.

**Results:** Hypoxia induced a greater decrease in BOLD response to visual stimulation in V1-V4 in migraine with aura patients compared to controls. There was no group difference in hypoxia-induced total CBF increase.

**Conclusion:** In conclusion, the study demonstrated a greater hypoxia-induced decrease in BOLD response to visual stimulation in migraine with aura patients. We suggest this may represent a hypoxia-induced changed neuronal excitability or abnormal vascular response to visual stimulation, which may explain the increased sensitivity to hypoxia in these patients leading to migraine attacks.

**Disclosure of Interest**
None Declared

**Migraine & Cluster Headache**

**OC-MC-001**

**Comparative Effects of 3 Doses of Zolmitriptan Patch (M207) and Placebo on Pain and Most Bothersome Symptom for the Acute Treatment of Migraine: The Zotrip Study**

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\(^4\)Geisel School of Medicine, Dartmouth University, Hanover, United States

**Objectives:** The Zotrip study was designed to compare the efficacy and safety of 1 mg, 1.9 mg and 3.8 mg of M207 (ZP-Zolmitriptan Patch) to placebo in the acute treatment of adults with migraine.

**Methods:** This was a double-blind, placebo-controlled, randomized trial of three doses of M207 compared to placebo. Subjects with a history of 2–8 migraines per month were enrolled into a run-in period of at least 28 days during which the frequency of migraines was established. Subjects declared their most bothersome symptom (MBS) of photophobia, phonophobia or nausea at study
entry. Qualifying subjects were randomly assigned to 1 mg, 1.9 mg, or 3.8 mg of M207 or placebo and instructed to treat the next qualifying migraine with study drug. Subjects recorded migraine symptoms and rescue medication use at 15, 30, 45, 60 minutes, and 2, 3, 4, 12, 24, and 48 hours. Subjects also recorded patch application observations at 30 min, 4, 12, 24 and 48 hours. Sequential statistical testing was performed beginning with the highest dose and the co-primary endpoints, stepping down to the other doses and endpoints. When significance was not observed for a comparison, subsequent results could no longer be evaluated for statistical significance, and results are expressed as nominal p-values.

**Results:** 589 subjects were enrolled in the trial. Of these 365 met randomization criteria and were dispensed study drug. Of the 365 randomized, 321 treated a migraine with study drug and had at least one post-treatment diary assessment (mITT). The study population was similar across treatment groups: 87% of subjects were female and the mean age was 41.7 years. At the time of treatment, 51% of subjects had severe migraine pain, 49% moderate, 70% had nausea, 37% had aura, and 51% woke up with their migraine. For the co-primary endpoints of pain freedom and MBS freedom, both at 2 hours post treatment, M207 3.8 mg was superior to placebo (pain freedom 41.5% for M207 vs 14.3% for placebo - p = 0.001 and MBS 68.3% for M207 3.8 mg vs 42.9% for placebo, p = 0.0009). M207 1.9 mg was superior to placebo for pain freedom at 2 hours (27.7% for M207 vs 14.3% for placebo, p = 0.0351), but not for MBS. M207 3.8 mg was superior to placebo (nominal p < 0.05) for multiple subgroup analyses including subjects who woke up with their migraine, subjects with nausea at the time of treatment and subjects with aura. The most common adverse events were application site reactions (redness and bruising) and >90% of these were considered mild. The most common neurologic adverse event was dizziness, reported in 4.4% on M207 3.8 mg subjects.

**Conclusion:** M207 (ZP-Zolmitriptan) 3.8 mg was effective and well-tolerated for the acute treatment of migraine. Efficacy was robust across several subgroups of traditionally difficult to treat subjects.

**Disclosure of Interest**

**Migraine & Cluster Headache**

**OC-MC-002**

**Efficacy of Erenumab in Subjects with Episodic Migraine with Prior Preventive Treatment Failure(s)**
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⁶Amgen Inc., Thousand Oaks, CA, United States

**Objectives:** There is a high unmet need for new preventive migraine treatments, especially for patients who have failed existing migraine therapies. Erenumab is a fully human monoclonal antibody that blocks the calcitonin gene-related peptide receptor. In a large, multicenter, double-blind, placebo controlled, phase 3 study (STRIVE), erenumab 70 mg and 140 mg demonstrated efficacy in subjects with episodic migraine and showed a safety profile similar to placebo. Here we report efficacy results in a subgroup of trial subjects with prior preventive treatment failure(s).

**Methods:** Subgroup analyses were conducted in subjects from the STRIVE trial who had failed ≥ 1 (n = 369) or ≥ 2 (n = 161) prior preventive treatments due to lack of efficacy and/or tolerability. Analyses included change from baseline in mean monthly migraine days (MMDs) and achievement of ≥ 50% reduction from baseline in MMDs, assessed over weeks 13–24 (months 4, 5, and 6). In the full trial, subjects (N = 955) were randomized 1:1:1 to subcutaneous monthly placebo or erenumab 70 mg or 140 mg for 24 weeks (6 months). P values for subgroup analyses are descriptive and not adjusted for multiple comparisons.

**Results:** Greater reductions from baseline in MMDs were observed for the erenumab 70 mg and 140 mg groups compared with placebo in both treatment failure subgroups (Table 1). More subjects who received erenumab achieved ≥ 50% reduction in MMD in both subgroups compared with placebo. For the 70 mg group, the odds (95% confidence interval) of achieving ≥ 50% reduction in MMD were 2.9 times higher than that of placebo for both treatment failure subgroups. For the 140 mg group, the odds were 3.1 and 4.5 times higher than placebo, respectively.

**Conclusion:** Robust treatment effects were observed for both 70 mg and 140 mg erenumab in subjects who
had previously failed preventive migraine treatments. For 140 mg, effects were numerically greater in this sub-
population than in the overall trial population, and as in the 
overall population, erenumab 140 mg showed numerically 
greater efficacy than erenumab 70 mg. These results 
suggest that erenumab may have particular utility in this 
subgroup of patients.

Disclosure of Interest

P. Goadsby Conflict with: Allergan, Amgen, Eli-Lilly and 
Company, and eNeura, Conflict with: Allergan, Amgen, Eli-
Lilly and Company, and eNeura, Ajinomoto Pharmaceuticals 
Co. Akita Biomedical, Alder Biopharmaceuticals, Autonomic 
Technologies Inc, Avanir Pharma, Cipla Ltd, Colucid 
Pharmaceuticals, Ltd, Dr Reddy’s Laboratories, Electrocore 
Therapeutics, Novartis, Nupathe Inc, Pfizer Inc, Promius 
Pharma, Scion, Teva Pharmaceuticals, Trigema Inc., 
Conflict with: personal fees from MedicoLegal work, 
Journal Watch, Up-to-Date, Oxford University Press, K. 
Paemeleire Conflict with: Amgen, Conflict with: Amgen, 
Conflict with: Amgen (study investigator), G. Broesner: 
None Declared, J. Brandes Conflict with: Allergan, Amgen, 
Clinvest, Teva, Colucid, Zozano, Conflict with: Amgen, 
Supernus, Conflict with: Depomed, Pernix, TEVA, Avanir, 
Conflict with: Advisory Board for Avanir, Supernus, 
TEVA, Supernus, J. Klatt Conflict with: Novartis, Conflict 
with: Novartis, Conflict with: Novartis, F. Zhang Conflict 
with: Amgen, Conflict with: Amgen, H. Picard Conflict 
with: Amgen, Conflict with: Amgen, D. Mikol Conflict 
with: Amgen, Conflict with: Amgen, R. Lenz Conflict with: 
Amgen, Conflict with: Amgen

**Migraine & Cluster Headache**

**OC-MC-003**

Non-invasive Vagus Nerve Stimulation for the 
Acute Treatment of Episodic and Chronic
Cluster Headache: Findings From the
Randomized, Double-blind, Sham-Controlled
ACT2 Study

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**Objectives:** Recent study results support the use of non-
invasive vagus nerve stimulation (nVNS) for the acute 
and prophylactic treatment of cluster headache (CH). In the 
ACT2 study, (ClinicalTrials.gov: NCT01958125), nVNS 
(gammaCore®) and a sham device were compared with 
regard to efficacy, safety, and tolerability for the acute

| Table 1. Change from Baseline in MMD and ≥ 50% Responder Rate |
|-----------------|-----------------|-----------------|
|                  | PLACEBO         | ERENUMAB 70MG   | ERENUMAB 140MG   |
| MMD, LS mean (%)
| Overall* n=316  | -1.8 (0.2)      | -3.2 (0.2)      | -3.2 (0.2)       |
| Failed ≥1 n=128 | -0.6 (0.4)      | -2.4 (0.6)      | -2.4 (0.6)       |
| Failed ≥2 n=54  | -0.2 (0.8)      | -1.6 (0.7)      | -1.6 (0.7)       |
| Differences from placebo (% CI)
| Overall* n=312  | -1.4 (-19.0, 0.9) | -2.0 (-28.1, -1.2) | -1.6 (-26.0, 0.0) |
| Failed ≥1 n=127 | -1.6 (-1.9, 0.3) | -2.0 (-28.1, -1.2) | -1.6 (-1.3, 0.1) |
| Failed ≥2 n=49  | -1.2 (-6.1, 3.7) | -2.0 (-28.1, -1.2) | -1.6 (-1.3, 0.1) |
| p value         | p<0.001*        | p>0.001         | p>0.001          |
| ≥ 50% responder rate *%
| Overall* n=316  | 26.8 (15.3, 30.9) | 43.3 (15.3, 30.9) | 50.0 (15.3, 30.9) |
| Failed ≥1 n=128 | 17.5 (10.8, 24.3) | 38.6 (10.8, 24.3) | 39.7 (10.8, 24.3) |
| Failed ≥2 n=54  | 11.1 (4.5, 17.6) | 26.5 (4.5, 17.6) | 26.5 (4.5, 17.6) |
| Odds ratio (% CI)
| Overall* n=312  | 2.1 (1.5, 2.9) | 2.9 (1.5, 2.9) | 2.9 (1.5, 2.9) |
| Failed ≥1 n=127 | 1.6 (1.0, 2.3) | 2.1 (1.0, 2.3) | 2.1 (1.0, 2.3) |
| Failed ≥2 n=49  | 1.0 (0.5, 1.5) | 1.6 (1.0, 2.3) | 1.6 (1.0, 2.3) |
| p value         | p>0.001         | p>0.001         | p>0.001          |

Abstract number: **OC-MC-002**
treatment of CH attacks in patients with episodic CH (eCH) or chronic CH (cCH).

**Methods:** Adults with CH were randomly assigned (1:1) to receive nVNS or sham treatment during the 2-week double-blind phase of the study. Subjects self-administered three consecutive 120-second stimulations to the cervical branch of the vagus nerve at CH attack onset. For attacks not aborted (pain free) within 9 minutes of treatment initiation, a second set of three stimulations was permitted. Subjects were asked to refrain from using rescue treatments for 15 minutes from treatment initiation. The primary end point was the proportion of treated attacks achieving pain-free status (pain score = 0); key secondary end points included change in pain intensity score (scale, 0–4 points) and percentage of subjects with responder status (pain score = 0 or 1) for ≥50% of treated attacks. The measurement time point for all parameters was 15 minutes after treatment initiation. The incidence and seriousness of adverse device effects (ADEs) were monitored to assess safety and tolerability.

**Results:** Subjects (n = 102; 30 eCH, 72 cCH) from nine EU sites were randomly assigned to receive nVNS (n = 50) or sham (n = 52) treatment. The intent-to-treat population included 48 nVNS-treated subjects (14 eCH, 34 cCH) and 44 sham-treated subjects (13 eCH, 31 cCH). In the total cohort, the proportions of treated attacks that achieved pain-free status at 15 minutes did not differ significantly between treatments (nVNS, 14%; sham, 12%). In the eCH subgroup, nVNS (48%) was significantly superior to sham (6%; P < 0.01), and there was no treatment difference in the cCH subgroup (nVNS, 5%; sham, 13%). The mean decrease in pain intensity score from attack onset to 15 minutes after treatment initiation did not differ significantly between treatments in the total cohort (nVNS, −1.3; sham, −0.9) and was significantly greater with nVNS (−1.7) than sham (−0.6) for the eCH subgroup (P = 0.01); the cCH subgroup showed no significant treatment difference (nVNS, −1.2; sham, −1.0). The proportion of subjects who achieved responder status for ≥50% of treated attacks at 15 minutes was significantly higher with nVNS in the total cohort (nVNS, 40%; sham, 14%; P < 0.01) and the eCH subgroup (nVNS, 64%; sham, 15%; P < 0.01) but not in the cCH subgroup (nVNS, 29%; sham, 13%). The proportion of subjects with ≥1 ADE was similar between the nVNS (18%) and sham (19%) groups, and no ADEs were considered serious.

**Conclusion:** Acute use of nVNS was superior to sham in patients with eCH but not in those with cCH or in the total cohort, 71% of whom had cCH. These results confirm that nVNS is a safe and effective acute treatment for patients with eCH.

**Disclosure of Interest**

P. Goadsby Conflict with: Grants from Allergan, Amgen, Eli Lilly and Company, Conflict with: Personal fees from Akita Biomedical; Alder Biopharmaceuticals; Allergan; Amgen; Autonomic Technologies; Avanir Pharmaceuticals; Cipla Ltd; CoLucid Pharmaceuticals, Inc.; Dr. Reddy’s Laboratories; electroCore, LLC; eNeura; Eli Lilly and Company; Novartis; Pfizer Inc; Promius Pharma; Quest Diagnostics; Scion; Teva Pharmaceuticals; Trigemina, Inc.; Medico-Legal Journal; Journal Watch; UpToDate; and Oxford University Press. In addition, Dr. Goadsby has a patent for magnetic stimulation for headache pending assigned to eNeura., I. de Coo Conflict with: Travel grants from electroCore, LLC, N. Silver Conflict with: Honoraria from Allergan and electroCore, LLC; investigator fees paid to the Walton Centre, A. Tyagi Conflict with: Honoraria from Allergan and electroCore, LLC, F. Ahmed Conflict with: Honoraria paid to the Migraine Trust and British Association for the Study of Headache for advisory board participation: Allergan; eNeura; electroCore, LLC; and Novartis, C. Gaul Conflict with: Honoraria from Allergan; electroCore, LLC; St. Jude Medical; Grünenthal; Desitin; Bayer; Boehringer Ingelheim; Autonomic Technologies; Reckitt Benckiser; Ratiopharm GmbH; Novartis; Lilly Deutschland; and Hormosan, R. Jensen Conflict with: Given lectures and conducted clinical trials for Autonomic Technologies; Neurocore; and Eli Lilly and Company., H.-C. Diener Conflict with: Research funding from Allergan; Almirall; AstraZeneca; Bayer; electroCore, LLC; GlaxoSmithKline; Janssen-Cilag; MSD; and Pfizer. Additional research support from the German Research Council; the German Ministry of Education and Research; and the European Union., Conflict with: Honoraria for participation in clinical trials and for contributions to advisory boards and oral presentations sponsored by Addex Pharma; Adler; Allergan; Almirall; Amgen; Autonomic Technologies; AstraZeneca; Bayer; Vital; Berlin-Chemie; Boehringer Ingelheim; Bristol-Myers Squibb; Chordate Medical; Coherex Medical; CoLucid Pharmaceuticals; electroCore, LLC; GlaxoSmithKline; Grünenthal; Janssen-Cilag; Labrys Biologics; Eli Lilly and Company; La Roche; 3M Medica; Medtronic; Menarini; Minster Pharmaceuticals; MSD; NeuroScore; Novartis; Johnson & Johnson; Pierre Fabre; Pfizer; Schaper and Brümmer; Sanofi; St. Jude Medical; and Weber & Weber, E. Liebler Conflict with: electroCore, LLC, Conflict with: electroCore, LLC, M. Ferrari Conflict with: Netherlands Organisation for Scientific Research (NWO); the European Community; ZonMw; and the Dutch Heart Foundation, Conflict with: Medtronic, Conflict with: Member of the Editorial Board for Cephalalgia

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Migraine & Cluster Headache

OC-MC-004

A Single Intravenous Administration of ALD403 (Eptinezumab) Reduces Use of Triptans Among Patients with Chronic Migraine

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5Alder BioPharmaceuticals
6Pacific Northwest Stats, Bothell, United States

Objectives: Patients with chronic migraine (CM) who are high users of triptans (defined as ≥10 days per month) can be difficult to treat. ALD403 (eptinezumab) is a genetically engineered humanized anti-CGRP antibody, for migraine prevention. A single intravenous (IV) administration of ALD403 (eptinezumab) has demonstrated a reduction in migraine frequency with efficacy maintained through 12 weeks. This exploratory analysis was conducted to examine the change in triptan use among patients with CM 12 weeks following administration of ALD403 (eptinezumab).

Methods: Patients with CM aged 18 to 55 years were randomized to receive a single IV infusion of 300mg ALD403 (n = 113) or placebo (n = 116) in this Phase 2 parallel group, double-blind study. The primary endpoint was ≥75% responder rate (RR) for reduction in migraine days in Weeks 1–12. Acute use of triptans was recorded daily during the pre-treatment baseline and throughout the study. Patients completed the Headache Impact Test (HIT-6) questionnaire at baseline, Weeks 4 and 12. Percent of days of triptan use and changes in HIT-6 score for patients classified as high triptan users (patients who use triptans on more than 33% of days (i.e. 10 or more days in every 4 weeks) were assessed by post hoc analysis.

Results: Days of triptan use in ALD403-treated patients exhibited a rapid decline from baseline. The rate of high triptan use decreased from 18.6% to 3.5% during Weeks 1–4 for ALD403-treated patients compared to 14.7% to 12.1% for placebo. The decline in triptan use continued through Week 12. At Week 4, the reduction in HIT-6 score was greater for ALD403 (−9.4) than placebo (−5.5); a trend that continued through Week 12. The reduction in HIT-6 score for ALD403-treated patients was unaffected by baseline triptan use, with high triptan users having a larger change (−10.7) than the ALD403 group as a whole. A similar pattern was seen for the 75% responder rate endpoint, where the ALD403-treated high triptan users had a larger responder rate (38.1%) than the ALD403 group as a whole (36.8%).

Conclusion: High triptan users who received a single IV administration of ALD403 (eptinezumab) demonstrated a rapid and sustained reduction in triptan use through the 12 weeks following the infusion and improved HIT-6 scores. More high triptan users treated with ALD403 also achieved a ≥75% RR at Week 12. These findings suggest ALD403 (eptinezumab) may provide a treatment strategy that enables difficult to treat patients with CM and triptan overuse headache to reduce their use of acute headache medications and minimize headache-related disability.

Disclosure of Interest


Migraine & Cluster Headache

OC-MC-005

Genomic variants related to Verapamil response in the treatment of Migraine

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Objectives: At present, there is no biologically based rationale for drug selection among at least five pharmacologically distinct classes of prophylactic treatment in migraine, a disorder that afflicts over 40 million people in the United States. Verapamil is an L-type calcium channel blocker that exerts a prophylactic effect in a subgroup of migraine patients.

Methods: We documented the number of headache days in the four weeks prior to treatment with Verapamil monotherapy and then in the four weeks prior to a return visit after treatment with Verapamil for at least 3 months in 349 patients and obtained a DNA sample from 225 of those patients. Whole Exome sequencing (WES) was performed in 22 patients who were highly responsive to Verapamil (range 58–100% mean 77% decrease in headaches) and in 15 patients who were poorly responsive (range −17 to 20% mean 3% decrease in headache days). After filtering out SNPs that did not show evidence of differing between these two groups and removing synonymous variants, we identified 588 SNP's...
with \( p < 0.01 \). We then genotyped 188 different patients in a validation cohort from whom we had Verapamil monotherapy treatment response data using the 524 most significant SNP's identified by WES and tested for a correlation with reduction in headache days (both absolute arithmetic and percent reduction). We then used all SNP's that correlated with Verapamil treatment response \(( p < 0.05)\) in a pathway analysis to identify potential functional molecular cascades carrying a disproportionate number of Verapamil-migraine implicated SNP's. We assessed the change in the number of headache days using the percentage change \((\text{Pre-treatment} - \text{Post treatment}) / \text{Pre-treatment values}\). A negative value indicates an increase in headache days after treatment. 

Table:

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Pre-Post Treatment change (Percentage reduction) 
**Results:** We carried out a pathway analysis using the SNP’s which were most highly correlated with change in headache days after Verapamil monotherapy treatment \(( p < 0.05)\). Two pathways were implicated. When SNP’s with \( p < 0.05 \) correlation is used, the myo-inositol pathway is implicated. When the SNP’s are further restricted to those with a \( p < 0.01 \) then the phospholipase C signaling cascade is implicated. 

**Conclusion:** We propose that response to prophylactic treatment is an element of phenotype that is informative of the molecular pathophysiology of migraine susceptibility in individuals whose migraine is suppressed by a specific drug. We have demonstrated that using WES in highly responsive vs non-responsive subjects we can identify variants that implicate functional molecular cascades that are relevant to the anti-migraine action of the drug investigated. The presence of some of these variants may also ultimately be useful in the prediction of response or non-response to treatment with verapamil. To our knowledge, this is the first work of its kind in migraine.

**Disclosure of Interest**
None Declared

**Secondary Headache**

**OC-SH-001**

GLP-1 Reduces Cerebrospinal Fluid Secretion And Intracranial Pressure: A Novel Treatment For Idiopathic Intracranial Hypertension?

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**Objectives:** Current therapies for reducing raised intracranial pressure (ICP) in conditions such as idiopathic intracranial hypertension have limited efficacy and tolerability. As such, there is a pressing need to identify novel drugs. Glucagon-like peptide-1 receptor (GLP-1R) agonists are used to treat diabetes and promote weight loss but have also been shown to affect fluid homeostasis in the kidney. Here, we investigate whether exendin-4, a GLP-1R agonist, is able to modulate cerebrospinal fluid (CSF) secretion at the choroid plexus and subsequently reduce ICP.

**Methods:** GLP-1R mRNA and protein was assessed by quantitative PCR, immunohistochemistry and fluorescently tagged exendin-4 in human and rat choroid plexus. The effect of exendin-4 on ICP was assessed in adult female rats with normal and raised ICP.

**Results:** GLP-1R activation and CSF secretion was evaluated in cultured rat choroid plexus epithelial cells using cAMP assays and a Na⁺ K⁺ ATPase activity assay. The effect of Exendin-4 on ICP was assessed in adult female rats with normal and raised ICP.

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Exendin-4 also significantly reduced Na\(^+\) K\(^+\) ATPase activity, a marker of CSF secretion (39.3 ± 9.4% of control; P < 0.05). Finally, in vivo ICP recording in adult rats demonstrated that subcutaneous administration of 20 \(\mu\)g/kg exendin-4 significantly reduced ICP in normal (65.2 ± 6.6% of baseline; P < 0.01) and raised ICP rats (56.6 ± 5.7% of baseline; P < 0.0001).

**Conclusion:** We demonstrate that exendin-4 reduces CSF secretion by the choroid plexus and ICP in normal rats and rats with raised ICP. Repurposing existing GLP-1 drugs may represent a novel therapeutic strategy for conditions of raised ICP such as idiopathic intracranial hypertension. Additionally, GLP-1R agonist therapy promotes weight loss which would be advantageous in idiopathic intracranial hypertension.

**Disclosure of Interest**
None Declared

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**Secondary Headache**

**OC-SH-002**

**DISSECTING THE ANDROGEN EXCESS PHENOTYPE OF WOMEN WITH IDIOPATHIC INTRACRANIAL HYPERTENSION**

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**Objectives:** Idiopathic intracranial hypertension (IIH) is a devastating neurological condition characterised by elevated intracranial pressure of unknown aetiology. IIH is largely a disease of obese females of reproductive age. The clinical phenotype of IIH overlaps with polycystic ovary syndrome (PCOS), an endocrine condition of young women associated with prevalent obesity, hyperandrogeinism and anovulation.

In this study, we aimed to delineate the androgen excess phenotype of IIH women compared to those with PCOS and simple obesity.

**Methods:** Women with IIH (n = 70), alongside age- and BMI-matched cohorts with PCOS (n = 60) and simple obesity (n = 40), were recruited to an in vivo study. All patients underwent comprehensive metabolic phenotyping and steroid profiling. Serum classic and 11-oxygenated androgens were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) and urinary steroid excretion by gas chromatography-mass spectrometry (GCMS). Cerebrospinal fluid (CSF) androgens were quantified by LC-MS/MS in IIH women (n = 49) and a female cohort with non-IIH neurological disease (n = 30). A subset of IIH patients (n = 25) was studied before and after a weight loss intervention.

**Results:** Serum testosterone was higher in IIH compared to both PCOS and control women (p < 0.001 for both); conversely, serum androstenedione was higher in PCOS women than in IIH (p < 0.001) and controls (p < 0.01). Serum levels of the 11-oxygenated androgen precursors 11b-hydroxyandrostenedione and 11-ketoandrostenedione were increased in PCOS (p < 0.0001), while levels in IIH patients did not differ from controls. Systemic 5a-reductase activity, as measured by the ratio of 5a-tetrahydrocortisol/tetrahydrocortisol, was higher in IIH women compared to both PCOS and controls (p < 0.05 for both). IIH women had increased CSF androstenedione and testosterone compared to controls (all p < 0.0001). PCOS patients had increased insulin resistance, as measured by HOMA-IR (p < 0.05), while HOMA-IR in IIH and controls did not differ.

Following weight loss, serum testosterone and markers of systemic 5a-reductase activity were significantly reduced (p < 0.01), with improvement in clinical markers of IIH such as headache severity, lumbar puncture (LP) pressure and markers of papilloedema, which correlated significantly with systemic 5a-reductase activity.

**Conclusion:** We show that women with IIH have a distinct androgen excess phenotype compared to PCOS and simple obesity, characterized by higher active serum androgens (increased testosterone), 5a-reductase activity and increased CSF androgens. Weight loss in IIH correlates with a reduction in serum androgens and systemic 5a-reductase activity. Further studies are needed to understand the role of androgen excess in the pathogenesis of IIH.

**Disclosure of Interest**
None Declared

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Secondary Headache

OC-SH-003

Correlations between spinal and brain MRI findings in spontaneous intracranial hypotension

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1Department of Neurology, Taipei City Hospital 2Department of Neurology, Taipei Veterans General Hospital 3Faculty of Medicine, National Yang-Ming University School of Medicine 4Department of Radiology 5Department of Anaesthesiology, Taipei Veterans General Hospital, Taipei City, Taiwan, Republic of China

Objectives: The aims of present study were: 1) to determine the association between the spinal and brain MRI signs in spontaneous intracranial hypotension and 2) to examine the application of the Monro-Kellie doctrine in SIH based on the severity of spinal leakage and brain neuroimaging abnormalities.

Methods: A total of 150 SIH patients were recruited in the study. We reviewed the heavily-T2 weighted magnetic resonance myelography (MRM) and brain MRI with or without contrast. The severity of spinal CSF leakage was described as number of segments of anterior, posterior, either anterior or posterior epidural CSF collections, periradicular leaks or C1-C2 extra-spinal leaks. The brain MRI signs included diffuse pachymeningeal enhancement, presence/absence and severity (depicted as angle) of venous distention sign, brain sagging, midbrain-pons angle, angle between vein of Galen and straight sinus, and presence/absence and thickness of subdural hematoma (SDH). Since the brain MRI signs may be interfered by SDH, we also performed the subgroup analyses based on presence or absence of SDH.

Results: In patients with SIH (n = 150), the length of anterior epidural CSF collections was negatively correlated with midbrain-pons angle (r = −0.39, p < 0.001). Patients with venous distention sign had longer segments of posterior epidural CSF collections (13.2 ± 5.1 vs. 10.3 ± 4.3, p = 0.008) and epidural CSF collection (either anterior or posterior) (15.5 ± 5.3 vs. 13.1 ± 4.5, p = 0.03). Other brain MRI signs had no association with severity of spinal CSF leakage. In patients without SDH (n = 111), the length of anterior epidural CSF collection correlated with midbrain pons angle (r = −0.40, p < 0.001). Longer segments of epidural CSF collection associated with more severe venous distention (r = 0.23, p = 0.016) and presence of venous distention sign (15.8 ± 4.9 vs. 12.9 ± 4.5, p = 0.01). In patients with SDH (n = 39), no brain MRI signs associated with spinal MRI findings.

Conclusion: Our study showed severity of venous distension was associated with severity of spinal CSF leak in SIH patients without SDH, which coincides with the Monro-Kellie doctrine. Closure of midbrain-pons angle reflects the severity of spinal CSF leak in all SIH patients. Therefore, diencephalic-mesencephalic deformity may be an alternative compensatory mechanism in spinal CSF leak.

Disclosure of Interest
None Declared

Secondary Headache

OC-SH-004

Headaches in the Idiopathic Intracranial Hypertension Treatment Trial: Six Month Outcomes

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Objectives: Headache is the most common symptom of IIH. The IIHTT prospectively enrolled 165 participants with mild visual field loss to assess whether acetazolamide (ACZ) plus dietary management was superior to placebo (PBO) tablets plus dietary management in improving visual function. We report the headache outcomes of participants in the IIHTT.

Methods: Participants completed the Headache Impact Test -6 (HIT) and headache symptom questionnaires at each study visit. The Short Form-36 (SF-36) and National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) and neuro-ophthalmic supplement (NOS) assessed quality of life at baseline and at 6 months. Group comparisons pertaining to HIT-6 total score were performed using two-sample t-tests. Bivariate associations between variables were assessed using Spearman rank correlation coefficients. Logistic regression analyses determined the associations between baseline variables and the development of headache after baseline.

Results: 139 (84%) enrollees had headaches at baseline and another 21 (13%) reported headaches in follow-up. 69% in the ACZ group and 68% in the PBO group had persistent headaches at 6 months. There was no
**Disclosure of Interest**
None Declared

**REFERENCES**


**Table:** Cross-validated classification accuracies (avg +/- std error) of the MMI-DDS applied to MRI alone, fMRI alone, and MRI+fMRI combined

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<th>fMRI</th>
<th>MRI+fMRI</th>
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<tr>
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**Results:** Data were available from 57 individuals with migraine and 49 healthy controls. Migraine and healthy control cohorts were of similar ages (migraine: 36.6 ± 11.5 years vs. healthy: 36.1 ± 11.1 years; p = 0.8214) and gender distribution (migraine: 44 F, 13 M vs. healthy: 35 F, 14 M; p = 0.7515). The migraine cohort averaged 7.6 ± 5.3 headache days per month and had migraine for an average of 16.7 ± 10.4 years. MMI-DDS showed significantly improved diagnostic accuracy compared to single imaging modalities alone. (see Table) Using a two-sample t-test, the cross validation error of MRI and fMRI data combined was significantly lower than MRI alone with p values of 0.0062, 2.2 × 10⁻⁵ and 2.8 × 10⁻⁴ for linear discriminant analysis (LDA), quadratic discriminant analysis (QDA), and linear support vector machine (LSVM) classifiers, respectively. Among the three classifiers, LSVM achieved the highest
classification accuracy of 83%, using MRI and fMRI data combined. 

**Conclusion:** A high accuracy for migraine classification was achieved by integrating structural and functional imaging modalities together. The accuracy of the multimodality imaging based classifier was significantly higher than the accuracy achieved when using single imaging modalities alone. Future research (1) will investigate if even better classification accuracy can be achieved by the inclusion of additional imaging modalities, (2) will extend the system’s capability to classify subtypes of migraine, and (3) will aim to develop models that predict clinical variables related to migraine.

**Disclosure of Interest**
None Declared

**Trainees Tournament**

**OC-TR-002**

Topiramate inhibits thalamic activity during trigeminal pain in humans

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²Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

**Objectives:** Topiramate (TPM) is a first-choice medication in migraine preventive treatment¹. Although very effective, little is known about its underlying central mechanism of action in migraine treatment. The aim of this study was to investigate the effect of TPM on trigeminal pain processing in healthy human subjects.

**Methods:** The effect of TPM on experimental trigeminal nociceptive processing, compared to placebo (PBO), was examined using fMRI. In a within subject and placebo-controlled design, 23 healthy subjects received either TPM or PBO and a standardized nociceptive trigeminal stimulation²,³. TPM and PBO were administered orally in a randomized, crossover, double blind procedure. Subjects with a history of neurological, psychiatric or pain disorders were excluded. Blood samples were obtained to determine the plasma concentration of TPM.

**Results:** The mean plasma concentration of TPM was 1.38 mg/L (SD = 0.8). Treatment-emergent adverse events were reported by 16 subjects. These included mild to moderate dizziness, difficulty with concentration, paresthesia and fatigue. No significant differences in the behavioral responses of the intensity and (un-)pleasantness of the painful stimuli were observed between TPM and the PBO. Under PBO a significantly increased blood oxygen level-dependent (BOLD) signal in the thalamus (SVC: p < 0.001 uncorrected) was observed, compared to TPM. In a second analysis we found that TPM treatment was associated with an enhanced functional coupling between the thalamus and several cortical and subcortical regions such as the bilateral Precuneus, posterior cingulate cortex, secondary somatosensory cortex and cerebellum.

**Conclusion:** The main finding of this study is that the thalamus is significantly more active during PBO compared to TPM during trigeminal pain. At the same time the functional coupling of the thalamus to other pain transmitting areas changes as well. This suggests that TPM exhibits modulating effects on the thalamo-cortical networks processing trigeminal pain. Hence, the preventive migraine effect of TPM may be mediated by an inhibiting effect on these thalamo-cortical networks⁴.

**Disclosure of Interest**
None Declared

**References**


**Trainees Tournament**

**OC-TR-003**

The clock gene CRY1 is associated with cluster headache in Sweden

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**Objectives:** Cluster headache (CH) is a devastating neurovascular disorder characterized by a striking circadian and circannual attack pattern. Genetic studies suggest an association between CH and the CLOCK gene, which has a critical role in the generation of circadian rhythms. Other key regulators of the circadian clock are for example cryptochrome (CRY) 1 and 2. The genes encoding CRY1 and
CRY2 have been reported to be associated with several neurological disorders, such as depression, bipolar disorder, and schizophrenia. In this study, we investigated a possible association of the CRY genes with CH.

**Methods:** We screened 518 CH patients and 581 controls for four different single nucleotide polymorphisms (SNPs) in the CRY genes (rs2287161 and rs8192440 in CRY1, rs10838524 and rs1554338 in CRY2) using pre-designed TaqMan® assays and compared genotype, allele, and haplotype frequencies between the two groups. In addition, we analyzed CRY1 gene expression in fibroblasts, obtained from 12 CH patients and 8 controls, using qRT-PCR.

**Results:** We found an association between the exonic CRY1 variant rs8192440 and CH on the allelic level ($P = 0.0048$). The minor allele A is more common in controls than in CH patients. The association becomes even stronger when stratifying the patient group for diurnal rhythmicity of attack occurrence ($P = 0.0036$). When comparing CRY1 gene expression levels between CH patients and controls, the relative CRY1 gene expression was significantly higher in CH patients ($P = 0.0001$).

**Conclusion:** A genetic variant in CRY1 which leads to a synonymous amino acid change in the CRY1 protein is associated with CH in our Swedish case-control material. The minor allele of this SNP seems to be a protective factor. Furthermore, CRY1 gene expression levels are significantly higher in CH patients compared to controls. By which mechanisms rs8192440 may affect the CRY1 gene remains to be determined. Increased CRY1 expression may trigger the periodically reoccurring CH attacks in a yet unknown manner. Although a lot more research needs to be done, this study points to a role of the clock gene CRY1 in the pathophysiology of CH.

**Disclosure of Interest**
None Declared

**Trainees Tournament**
OC-TR-004

**Functional characteristics of non-invasively optogenetically induced csd in fhm1 mutant mice**

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**Objectives:** Cortical spreading depression (CSD) is the likely correlate of the migraine aura. In experimental models CSD is typically studied using highly invasive CSD-induction methods. Earlier it was shown that susceptibility to KCl or electrically induced CSD is enhanced in familial hemiplegic migraine type 1 (FHM1) transgenic mice expressing human pathogenic R192Q or S218L nonsense mutations in voltage-gated CaV2.1 calcium channels. With optogenetics technology, neurons expressing light-sensitive channelrhodopsin-2 ion channels (ChR2) can be depolarized by blue light. This can be used *in vivo* to activate deep layer cortical neurons by using mice expressing ChR2 under control of the neuronal Thy1 promoter (Thy1-ChR2 mice). Previously, we used this approach for non-invasive induction of CSD in freely behaving Thy1-ChR2 mice by cortical illumination through the intact skull. We here will compare characteristics of non-invasively induced CSD by optogenetics of Thy1-ChR2 ‘wild-type’ mice and Thy1-ChR2 mice cross-bred with FHM1 R192Q or S218L mice.

**Methods:** Under anesthesia, a 400-μm optic fiber for CSD induction was placed on the skull overlaying the visual cortex for light-activation while intracortical platinum electrodes were implanted in the motor and parietal cortex for CSD and multi-unit activity recordings and additional skull laser Doppler probes for non-invasive CSD detection. In awake freely behaving mice, CSD was induced using blue light pulses (470 nm) delivered at different intensities and durations. Simultaneous video-recordings allowed for behavioral analysis and wire grip tests were performed to assess motor function related to CSD. Experiments were approved by the LUMC Animal Experiment Ethics Committee with care and handling according to the Dutch Law on animal experimentation.

**Results:** In wild-type mice and R192Q mutants, optogenetic stimulation resulted in a single CSD wave, whereas multiple CSD waves were observed in the majority of S218L mutants. CSD propagation rate was elevated in FHM1 mice compared to wild-type, most pronounced in S218L mutants. CSD caused a short increase in active behavior followed by prolonged reduction. Motor function was transiently and unilaterally suppressed following CSD.

**Conclusion:** Optogenetic CSD induction has significant advantages over current CSD models in that CSD events can be elicited repeatedly in freely behaving mice in a non-invasive manner and is able to reveal changes in FHM1 mutant mice.

**Disclosure of Interest**
None Declared
Trainees Tournament

OC-TR-005

Pleasure and pain: exploring neurobiological mechanisms of food craving before migraine pain

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Objectives: Migraine premonitory symptoms can include food craving and imaging studies show increased activation of the ventral tegmental area (VTA) during the premonitory phase. Since VTA dopaminergic neurons are involved in hedonic feeding, we aimed to determine the effect of pharmacological manipulation of the VTA on the trigeminocephalonic complex (TCC) neuronal activity in response to nociceptive activation, mechanical facial stimulation, as well as the effect on glucose metabolism.

Methods: Male Sprague Dawley rats (n = 41) were anesthetized, the parietal bone was removed over the middle meningeal artery for dura mater electrical stimulation, and over the midbrain for local microinjections. Using in vivo electrophysiology, TCC neurons were recorded before and after administration into the VTA of glutamate, a dopamine D2/D3 receptor agonist (quinpirole), naratriptan, pituitary adenylate cyclase activating peptide (PACAP38) or saline as vehicle control. Moreover, mechanical facial stimulation was performed using innocuous and noxious stimuli throughout the study. Additionally, glycemic levels were measured before and after microinjection of drugs.

Results: Dural-evoked neuronal firing in the TCC was significantly reduced by glutamate (p < 0.05, max inhibition 37%), quinpirole (p = 0.005, max inhibition 19%), naratriptan (p < 0.005, max inhibition 38%) and PACAP38 (p < 0.05, max inhibition 30%). Noxious mechanical stimulation was significantly inhibited by glutamate (p < 0.05, max inhibition 30%), quinpirole (p < 0.005, max inhibition 35%), naratriptan (p < 0.005, max inhibition 56%) and PACAP38 (p < 0.05, max inhibition 40%). Innocuous mechanical stimulation was significantly inhibited by naratriptan (p < 0.005, max inhibition 48%) and PACAP38 (p < 0.05, max inhibition 41%); but not glutamate or quinpirole (p > 0.05). Regarding blood glucose levels, local VTA microinjection of glutamate and naratriptan significantly decreased (p < 0.05); quinpirole significantly increased (p < 0.05); and PACAP38 had no significant effect (p > 0.05) on blood glucose levels after 60min post-injection. Vehicle control injections had no significant effect on TCC nociceptive neuronal firing, mechanical facial responses or blood glucose levels (p > 0.05).

Conclusion: These results show that VTA is able to modulate trigeminocephalonic nociceptive activity, as well as central glucose metabolism in a migraine animal model. Moreover, we confirm that naratriptan can act within the VTA to modulate TCC neuronal firing and glucose metabolism. Importantly, we show that PACAP38 plays an antinociceptive role when microinjected into the VTA. The VTA is also capable of modulating facial mechanical responses in a migraine animal model, suggesting a physiological role in the control of mechanisms underlying symptoms of allosthenia and hyperalgesia. Overall, these results could be explained by indirect projections to the TCC, via neuronal connections with other pain modulating structures. Furthermore, dysfunctional VTA dopaminergic activity in migraineurs could potentially disrupt feeding mechanisms and affect downstream pain pathways.

Acknowledgments

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Disclosure of Interest

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Objectives: The orexins are two neuropeptides that are exclusively synthesised in the hypothalamus and play a key role in the modulation of feeding, sleep-wake regulation and stress responses suggesting a potential role in migraine. In support of an orexinergic involvement in migraine, we have previously identified a differential trigeminovascular response to orexinergic modulation in descending pain networks. Our unpublished data shows that microinjection of orexin A into the ventrolateral periaqueductal gray (vlPAG) in the rat is anti-nociceptive by inhibiting medullary trigeminovascular neural responses to meningeal electrical stimulation, while conversely, orexin B facilitates these responses. Orexin peptides exhibit a preferential affinity for two orexin receptors (OX1R and OX2R), and therefore, to account for these differential responses, we hypothesized this was likely due to differential orexin receptor expression in the vlPAG. Here, we sought to characterise the cellular localisation of the two orexin receptors in the vlPAG of the rat.

Methods: We used fluorescent immunohistochemistry with avidin-biotin amplification in order to visualise the cellular expression of the two orexin receptors (OX1R and OX2R) in the vlPAG, while also co-localising receptor expression with the expression of orexin peptides A and B.

Results: We demonstrate that the OX1R is preferentially expressed in neural cell bodies within the vlPAG while the OX2R is preferentially expressed on cell fibres. Both OX1R expressing cell bodies and OX2R expressing fibres have close appositions to orexin expressing fibres projecting from the hypothalamus.

Conclusion: Hypothalamic orexinergic expressing neurons send projections to the vlPAG where they contact OX1R and OX2R expressing cell bodies and fibres, respectively. This differential receptor localisation likely underlies the previously identified differential modulation of medullary trigeminovascular neural responses to meningeal electrical stimulation following orexin A and B administration into the vlPAG.

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Disclosure of Interest
None Declared
IHC Electronic Posters – Thursday and Friday

Headache Pathophysiology - Imaging and Neurophysiology

EP-01-001

Ambient light color variably influences migraine pain intensity and discomfort in the ictal and interictal phase.

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Objectives: Light stimuli exacerbate migraine headache. Previous studies also speculated that the sensitivity to light during attacks of migraine may be color-dependent. In patients with photophobia, light in the blue, red, amber and white increased migraine headache, while green light decreased the intensity of migraine headache. Since previous studies used direct application of light to the patient, we studied the effect of different colors of ambient light on aversiveness and migraine pain intensity during the ictal and interictal phase, respectively.

Methods: The study involved 936 patients with chronic headaches both during the headache and interictal phase. Subjects aged 12-77 years old were eligible for this study if they met ICHD-3beta. Episodic migraine (EM) was 392 patients and chronic migraine (CM) was 152 patients. For comparison 203 patients with tension type headache (TTH) and 74 with chronic TTH, 73 with trigeminal autonomic cephalalgias (TACs), 42 with new daily persistent headache (NDPH) were also evaluated. The intensity of light was 100 cd m⁻² (equivalent to a normally lit office space) and the different colors were provided by using Macintosh hue system (Philips Hue, version 1.12.2, 2015). Patients were exposed to a fixed sequence of colors (yellow, white, gray, blue green, and red sequentially) for a period of 30 seconds. Yellow was chosen as the reference color because this color light is present in the waiting room. To evaluate the degree of discomfort, patients were asked to choose from six grades 0 (none), 1 (slight), 2 (mild), 3 (moderate), 4 (severe), to 5 (unbearable) for each color. The colors transitioned from one to another immediately in order to minimize additive effects. When the headache intensity was worsened by any color stimulus, the color of light was turned to the initial yellow once again at the end of each color stimulus, so that the patients could be given sufficient time to return to the baseline level of headache intensity.

Results: White, blue and red lights aggravated discomfort to color during both ictal and interictal phases and increased pain during migraine. Green light reduced discomfort during the interictal phase and pain intensity during the ictal phase only in patients with migraine (Figure) regardless of the presence or absence of photophobia. Significant change was seen both in EM and CM patients. CTTH patients demonstrated mild but significant discomfort only from white light in ictal phase (Figure). TACs and NDPH patients demonstrated no intensification of discomfort by any color light stimuli either in the interictal or headache phase.

Conclusion: Ambient light color, specifically blue and white, exacerbated discomfort and headache in patients specifically with migraine. These results support the observation that migraine photophobia may originate in cone-driven retinal pathways and be dependent on its luminous sensitivity. We hypothesize that ambient light color may be an important exacerbating factor in patients with migraine. In addition, surrounding green light may be a nonpharmacological treatment of migraine. The absence of discomfort or light induced exacerbation of pain in patients with other primary headache disorders is a novel finding and warrants further exploration.

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**Disclosure of Interest**
None Declared.

**Headache Pathophysiology - Imaging and Neurophysiology**

**EP-01-002**

**Chronic migraine is mediated by the Hypothalamus**

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**Objectives:** Chronic migraine is a debilitating disease. Identifying the pathophysiological characteristics of chronic migraine is thus of vast importance. Using a recently developed protocol for high resolution brainstem imaging of standardized trigeminal nociceptive stimulation1 we aim at elucidating mechanisms of migraine chronification.

**Methods:** 17 chronic migraineurs (CM), 18 episodic migraineurs (EM) and 19 healthy controls (HC) underwent a standardized paradigm of painful stimulation of the left nostril using gaseous ammonia. Functional images were acquired within a 3 T MRI scanner using an optimized protocol for high resolution echoplanar brainstem imaging2.

**Results:** The anterior right hypothalamus (HT) was significantly stronger activated in CM as compared to Con. We then compared all migraineurs with headaches (EM and CM) with all migraineurs without headaches (EM and CM) and Con, to exclude that the headache on the day of the scanning was a prime mediator of the observed hypothalamic activation, and found a more posterior region of the HT to be stronger activated during headaches.

**Conclusion:** Our data corroborate a crucial role of the HT for migraine chronification as well as for the sustainment of acute migraine pain3. While the more posterior part of the HT seems to be a mediator of the acute pain stage, the more anterior part seems to be important for the pathophysiology of chronic migraine.

**Disclosure of Interest**
None Declared.

**References**

**Headache Pathophysiology - Imaging and Neurophysiology**

**EP-01-003**

**TMS evoked potentials demonstrate altered cortical excitability in migraine with aura**

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**Objectives:** Migraine is associated with altered processing of sensory input that may be due to cortical hyper-excitability. Cyclical changes in cortical excitability have been suggested around the migraine attack. The visual cortex is believed to be of particular interest, especially in migraine patients with visual aura. Transcranial magnetic stimulation with concomitant electroencephalography recordings (TMS-EEG) is a new method to measure cortical excitability from the direct response to non-invasive stimulation over the skull. Recent studies have shown that phase clustering in EEG responses is linked to cortical excitability. We quantified differences in TMS evoked EEG potentials (TEP) between healthy controls and patients with migraine with aura, to study TEP’s possibility as biomarker of cortical excitability in migraine.

**Methods:** We included nine patients with migraine with aura and nine age- and sex-matched healthy controls. All underwent single-pulse TMS on the vertex with simultaneous 64-channel EEG recording. Migraine patients were recorded interictally (at least three days before and after an attack). On average 300 pulses were delivered between -8% and +8% of the resting motor threshold. We compared averaged TEP waveforms and phase clustering over trials between the groups of participants.

**Results:** TEP waveforms differed between migraine patients with aura and healthy controls around the N100 and P180 peaks, mostly located at frontal and centro-parietal regions respectively. Hundred ms after the stimulus, phase clustering in the occipital lobe remains stronger in healthy controls than in patients, indicating reduced phase consistency after the N100 peak in migraine patients.

**Conclusion:** Patients with migraine with aura show different cortical responses to non-invasive magnetic stimulation compared to healthy controls. This suggests that cortical excitability is altered in migraine with aura, also between migraine attacks. Our findings are in line with studies that used indirect cortical stimulation with e.g. visual or somatosensory inputs and magnetic stimulation with peripheral readouts. We conclude that TMS-EEG...
could be useful to directly study changes in cortical excitability during the migraine cycle.

Disclosure of Interest
None Declared

Headache Pathophysiology - Imaging and Neurophysiology

EP-01-004
Normalization of the Resting-State Network of Ventral Posteromedial Nucleus in Patients with Chronic Migraine Is Associated with Good Clinical Outcome to Prevention
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Objectives: Chronic migraine (CM) affects about 2% of the general population. Previous task functional magnetic resonance image (fMRI) and electrophysiological studies suggested hyperactivation of the ventral posteromedial nucleus (VPM) of thalamus to pain stimuli play an important pathophysiology role in CM. However, the resting-state network (RSN) of VPM in patients with CM (PT) has not been studied yet. Thus, we aimed to evaluate (1) the difference of the VPM-RSN between control subjects (CS) and PT prior to prevention, and (2) the change of the VPM-RSN in PT before and after prevention within the regions derived from the first aim.

Methods: Experimental design: PT were recruited from the Headache Clinic of Taipei Veterans General Hospital. Upon first visit, all potential participants completed a structured headache questionnaire. Once the diagnosis of CM was considered, the subjects were asked to keep headache diaries for the following 2 weeks (T0) in order to confirm the headache profile. Subjects who had ≥7 days of headache, and migrainous headache on ≥4 of these days proceeded to undergo the 1st MRI scan. Afterwards, PT received preventive treatment, either Topiramate 50 mg/d or Flunarizine 10 mg/d, in divided doses. A 2nd MRI scan was arranged 2 weeks after prevention. After a treatment course of 8 weeks (T1 - T4, 2-week each), the effectiveness was determined, i.e. those with ≥50% reduction of migraine days (T4 vs. T0) were categorized as responders while those without were non-responders.

MRI acquisition and analysis: Anatomical and resting-state fMRI (rs-fMRI) data were acquired on a 3 Tesla MRI scanner. RS-fMRI data were preprocessed and analyzed by statistical parametrical mapping (SPM8) and the DPARSF toolbox. A seed-based correlation analysis was performed, with bilateral VPM (averaged signal) as seeds. Initially, the VPM-RSN was generated in the CS group. We then evaluate (1) the difference of the VPM-RSN between CS and PT prior to prevention, and (2) within these regions, the changes after prevention in responder and non-responder groups.

Results: Fifty-six PT and 32 age- and gender-matched CS were recruited. The anatomical images of all subjects showed no gross abnormality except for some white matter lesions. The VPM-RSN derived from CS group included nearly whole brain structure, which is consistent with previous studies.

Before prevention, there existed enhanced functional connectivity (FC) between VPM and bilateral occipital as well as auditory cortices in PT as compared to CS. No correlation between the FC and disease severity (including baseline migraine disability assessment score [MIDAS], T0 migraine or headache days) or CM duration was found.

Three PT failed to undergo the 2nd MRI scan due to claustrophobia (n = 1), or severe migraine attack on the scheduled day (n = 2). Three other PT responded to prevention with marked fluctuation during T3 and T4, and were also excluded from the analysis of treatment effects. In the remaining 50 PT, 33 were responders. The average FC between VPM and occipital region (results from aim 1) showed significant reduction after prevention in responder group. While in non-responder group (n = 17), the FC remained unchanged.

Conclusion: In this study, enhanced resting FC between VPM and visual as well as auditory cortices were found in patients with CM. Moreover, the observation that a reduction of such hyper-connectivity early after prevention is associated with good clinical outcome may provide clinicians an early neuroimaging biomarker for treatment efficacy.

Disclosure of Interest
None Declared
Headache Pathophysiology - Imaging and Neurophysiology

EP-01-005

Alterations in regional cerebral blood (rCBF) during the premonitory stage of nitroglycerin (NTG) triggered migraine attacks assessed using arterial spin-labelled (ASL) functional magnetic resonance imaging (fMRI)

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Objectives: The premonitory stage of migraine is an increasing area of interest within headache research, because of the insights it can offer into the early pathophysiology of the migraine attack, which could then lead onto identification of novel therapeutic targets. We aimed to study the phenotype and imaging characteristics of this stage of the migraine attack using NTG triggered attacks, which have been shown to be phenotypically similar in premonitory symptomatology and headache phenotype. We used the methodology of pulsed continuous Arterial Spin Labelling (pCASL), performed on a 3T General Electric MR750 MRI scanner.

Methods: Subjects (n = 18) were recruited following screening and informed consent. Each subject was exposed to either a 0.5 mcg/kg/min NTG infusion over 20 minutes or placebo, depending on randomisation. Each subject received both infusions on two different visits and was blinded to which treatment was administered. Following the infusion, the timeline and phenotype to development of premonitory and headache symptoms was documented. A standardised physician administered symptom checklist was used for data collection. The premonitory stage of migraine was defined as the presence of at least 3 premonitory symptoms without the presence of migraine headache which the subject would usually associate with a spontaneous attack. Migraine headache was defined as moderate-severe headache which developed after the infusion and was associated with other migraine symptomatology that the subject would usually associate with spontaneous attacks. Imaging (structural T1, T2 and FLAIR, resting state blood oxygen level dependant (rsBOLD) imaging and two six minute ASL scans) was conducted over 30-40 minutes at baseline, with ASL and rsBOLD scans acquired during the premonitory stage and during migraine headache. For the placebo visit the imaging was conducted at the same times following infusion in the absence of symptoms. Images were analysed using SPM 12 (www.fil.ion.ac.uk/SPM). Voxel-wise analysis of all subjects’ premonitory scans compared to baseline was carried out.

Results: Significant increases in rCBF were detected in a large cluster that included the medial and superior frontal gyri and anterior cingulate cortices (p = 0.001 corrected for multiple comparisons at the cluster level). Small volume correction revealed significant increases in blood flow in the hypothalamus (p = 0.028), consistent with a previous investigation using Positron Emission Tomography (PET) imaging. Significant reductions in rCBF were detected in the middle occipital gyrus (p = 0.019).

Conclusion: The premonitory stage of migraine is associated with significant areas of increased rCBF compared to baseline, in frontal cortex, anterior cingulate cortex and hypothalamus, before the onset of migraine pain. These areas are functionally consistent with some of the main symptoms displayed during this phase, including mood and cognitive change, neck stiffness and yawning. ASL is promising non-invasive imaging modality, using rCBF as a correlate of neuronal activity, and could be increasingly used in migraine research.

Disclosure of Interest

N. Karsan Conflict with: Dr Karsan is an Association of British Neurologists/Guarantors of Brain Clinical Research Training Fellow, P. Bose: None Declared, F. Zelaya: None Declared, P. Goadsby Conflict with: Dr. Goadsby reports grants and personal fees from Allergan, Amgen, and Eli-Lilly and Company; and personal fees from Akita Biomedical, Alder Biopharmaceuticals, Autonomic Technologies Inc, Avanir Pharma, Cipla Ltd, Colucid Pharmaceuticals, Ltd, Dr Reddy’s Laboratories, eNeura, Electrocore LLC, Novartis, Pfizer Inc, Promius Pharma, Quest Diagnostics, Scion, Teva Pharmaceuticals, Trigemina Inc., Scion, Conflict with: personal fees from MedicoLegal work, Journal Watch, Up-to-Date, Oxford University Press; and in addition, Dr. Goadsby has a patent Magnetic stimulation for headache pending assigned to eNeura
**Headache Pathophysiology - Imaging and Neurophysiology**

**EP-01-006**

Carbon monoxide inhalation induces headache in a human headache model

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**Objectives:** Carbon monoxide (CO) is an endogenously produced signalling molecule which has a role in nociceptive processing and cerebral vasodilatation. We hypothesized that inhalation of CO would induce headache and vasodilation of cephalic and extracephalic arteries.

**Methods:** In a randomized, double-blind, placebo-controlled crossover design, 12 healthy volunteers were allocated to inhalation of CO (carboxyhemoglobin 22%) or placebo on two separate days. Headache was scored on a verbal rating scale from 0–10. We recorded mean blood velocity in the middle cerebral artery (VMCA) by transcranial Doppler, diameter of the superficial temporal artery (STA) and radial artery (RA) by high-resolution ultrasonography and facial skin blood flow by laser speckle contrast imaging.

**Results:** Ten volunteers developed headache after CO compared to six after placebo. The area under the curve for headache (0–12 hours) was increased after CO compared with placebo (P = 0.021). CO increased VMCA (P = 0.002) and facial skin blood flow (P = 0.012), but did not change diameter of STA (P = 0.060) and RA (P = 0.433).

**Conclusion:** In conclusion, the study demonstrated that CO caused mild prolonged headache but no arterial dilation in healthy volunteers. We suggest this may be caused by a combination of hypoxic and direct cellular effects of CO.

**Disclosure of Interest**
None Declared

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**Headache Pathophysiology - Imaging and Neurophysiology**

**EP-01-007**

Unique Infra-Slow Oscillatory Activity in the Prodrome Phase of Migraine

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**Objectives:** Migraine is a highly prevalent and debilitating neurological disorder, but the underlying mechanism responsible for its pathogenesis remains unclear. It is widely assumed that migraineurs exhibit altered brain function in spinal and trigeminal nociceptive pathways between attacks. However, no study has investigated brain changes in the critical period directly prior to a migraine attack. We have recently shown that another orofacial neuropathic pain condition, trigeminal neuropathy, is associated with altered resting activity (increased infra-slow frequency oscillations) within trigeminal nociceptive pathways and within parts of the thalamocortical circuitry which we hypothesise is related to glial activation. It is possible that a similar situation also occurs in individuals with migraine and that this predisposes an individual to a migraine event. In this study, we aimed to investigate whether individuals in their prodrome phase showed alterations in brain function. Given this, we hypothesise that migraineurs will present with altered resting activity, characterized by increased infra-slow oscillatory power during the 24 hours before a migraine attack.

**Methods:** In twenty six subjects with migraine (21 females; mean age 31.2 ± 2.1 years [±SEM]) and 103 pain-free controls (69 females; mean age 30.7 ± 1.1 years) we measured resting blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) over the entire brain (180 volumes, TR = 2 seconds). All migraineurs were scanned during an interictal period, that is, at least 72 hours after and 24 hours prior to a migraine event. Eight of these migraineurs were scanned during the prodrome phase (within 24 hours prior to a migraine) and 11 during the postdrome phase (during the 72 hours following a migraine attack). Using SPM12, fMRI images were realigned, intensity normalized and spatially normalized to the Montreal Neurological Institute template. On-going signal intensity fluctuations of the whole brain were analysed by performing fast fourier transforms on each voxel using REST software. Significant differences in power in the frequency band 0.03-0.06 Hz in migraineurs compared with controls were determined using a random effects procedure (FDR p < 0.05).

**Results:** Significant increases in infra-slow oscillatory power occurred in migraineurs during the prodrome...
phase compared with controls in the brainstem, hypothalamus and thalamus. During prodrome, increased oscillatory power occurred in the region of the right (ipsilateral to side of most frequent migraine) spinal trigeminal nucleus (SpV) extending into the rostral ventromedial medulla (RVM), dorsomedial pons, midbrain in the region of the midbrain periaqueductal gray matter (PAG), posterior hypothalamus and in the thalamus in the region of the somatosensory nucleus. Importantly, no change in infra-slow oscillatory power occurred during either the interictal or postdrome phases. Furthermore, in no brain region and during no migraine phase was infra-slow oscillatory power reduced in migraineurs compared with controls.

**Conclusion:** These findings provide evidence revealing altered brainstem and hypothalamic function in the period directly prior to a migraine attack. It is possible that increased infra-slow oscillatory power represent changes in underlying astrocytic modulation of synaptic function since activated astrocytes display similar infra-slow oscillatory activities. These on-going activity changes alone, or in combination with an external trigger, may underlie the initiation of a migraine attack and the presence of head pain.

**Disclosure of Interest**
None Declared

**Headache Pathophysiology - Imaging and Neurophysiology**

**EP-01-008**

**WHITE MATTER LESIONS IN CRONIC MIGRAINE ARE NOT ASSOCIATED WITH CEREBRAL VASOREACTIVITY.**

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**Objectives:** White matter lesions (WML) are more prevalent in migraine, it seems that mainly with a high attack frequency. A vascular etiology has been proposed, but the pathogenesis and clinical significance remains unknown. Cerebral Vasoreactivity (CVR) reflects the vasodilation of microvasculature mediated via endothelial pathway, and its impairment is a marker of endothelial dysfunction. The aim of this study is to assess whether differences in CVR can explain the mechanisms behind the WML described in MRI studies in chronic migraine (CM) patients.

**Methods:** This series includes 91 women meeting current IHS diagnostic criteria for CM. CVR was assessed by Breath Holding Index (BHI) on transcranial Doppler in middle cerebral arteries (MCA), posterior cerebral arteries (PCA) and in the basilar artery (BA). MRIs were acquired on a 1.5T unit following the CAMERA protocol.

**Results:** 58 patients (aged 46.76 ± 10.11 years) had WML whereas 33 patients (35.64 ± 11.98 years) did not. Except for age (p < 0.001), the rest of clinical features and comorbidities -including history of aura, vascular risk factors and acute/preventive treatments- were similar between both groups. BHI was within range in all arteries examined. In patients with WML, mean BHI was: MCA 1.512 ± 0.371, PCA 1.402 ± 0.382, BA 1.450 ± 0.322. In patient without WML, mean BHI was: MCA 1.597 ± 0.450, PCA 1.440 ± 0.391, BA 1.541 ± 0.240. There were no differences in mean BHI in any of the different arteries explored (MCA p = 0.423, PCA p = 0.697, BA p = 0.447) for patients with and without WML.

**Conclusion:** In our series of CM there were not differences in BHI values in the different arteries explored, according to the presence of WML. This finding does not support endotelial dysfunction alone as the underlying pathophysiology of WML.

**Disclosure of Interest**
D. Larrosa: None Declared, A. Meilán: None Declared, C. Ramón Carbajo: None Declared, E. Cernuda Morollón: None Declared, P. Martínez-Camblor: None Declared, J. Pascual Gómez Conflict with: Supported by the PI14/00020 FISSSS grant (Fondos Feder, ISCIII, Ministry of Economy, Spain)

**Headache Pathophysiology - Imaging and Neurophysiology**

**EP-01-009**

**The resting state connectivity between default-mode network and insula encodes intensity of migraine headache**

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Objectives: Previous functional magnetic resonance imaging (fMRI) studies have revealed that greater ongoing clinical pain in different chronic pain disorders, such as fibromyalgia and chronic low-back pain, is associated with proportional greater resting default mode network (DMN) to insula connectivity. Here, we investigated seed-based resting state DMN-insula connectivity during the acute head pain that characterizes spontaneous recurrent migraine attacks.

Methods: Thirteen patients with untreated migraine without aura (MI) underwent 3T MRI scans during the initial 6 hours of a spontaneous full-blown migraine attack and were compared to a group of 19 healthy volunteers (HV). We collected seed-based resting state data in the four core regions consistently identified in the DMN: medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), and left and right inferior parietal lobules (IPLs). Moreover, we collected seed-based resting state data from the insula bilaterally.

Results: Compared to HV, MI patients showed stronger bilateral insula connectivity to the medial prefrontal cortex (MPFC) region of interest. In MI, the strength of insula-MPFC connectivity, as measured by calculating the correlation coefficient, was negatively correlated with pain intensity (visual analogue scale) during migraine.

Conclusion: We documented for the first time that greater subjective intensity of pain during migraine is associated with proportional weaker DMN-insula connectivity. Notably, this is at variance with other chronic extra-cephalic pain disorders where the opposite was found, and may thus be a hallmark of acute migraine head pain.

Disclosure of Interest: None Declared
Recently, she had a worsening of her psychiatric condition. In the day she restarted aripiprazole, as expected, she experienced AIWS characterized by her usual symptoms and also apraxia of the left arm. During the AIWS episode, we performed a video-EEG, resulted normal, and a 99mTc-HMPAO brain SPECT. The perfusion SPECT images showed a reduced activity of the whole right hemisphere, associated with a focal area of hyperactivity in right cuneus/precuneus regions and an area of severe hypoaactivity in the right primary parietal regions. A control SPECT study was repeated 2 weeks later and showed a normal brain perfusion pattern.

**Conclusion:** To date, this is the first case of AIWS caused by aripripazol, a drug that lowers the threshold of neuronal excitability (4). By using SPECT, we observed significant decrease in brain activity in the right hemisphere during the occurrence of a AIWS episode. This overall reduction may let us speculate that it is linked to a thalamic dysfunction. In addition, SPECT showed an area of hyperactivity of the cuneus/precuneus regions, which are involved in own body perception and awareness (3), as well as a severe hypoactivity in the primary sensory regions. These results may suggest the occurrence during AIWS of an imbalance between the lower and higher associative cortices.

**Disclosure of Interest**
None Declared

**References**
1 Mastria et al. Biomed Res Int; 2016;8243145
2 Argo et al. Pharmacotherapy 2004;24(2):212
3 Cavanna et al. Brain 2006, 129, 564

**Migraine Acute Therapy**

**EP-01-011**

**Sumatriptan Response and Predictors in Migraine Patients: A Large Clinic-Based Cohort Study**

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**Objectives:** Triptans are widely used in acute migraine treatment; however, individual effectiveness varies. Sumatriptan is the first in the genre, and remains the most widely used triptan worldwide. We aimed to investigate sumatriptan efficacy and factors associated with its effectiveness in a large cohort.

**Methods:** We conducted an observational cohort study in a headache clinic in a tertiary medical center. This study is a collaborative study of the original genome-wide association study of migraine. Patients with migraine, who had been prescribed with sumatriptan were enrolled. Patients were asked to record their response after taking sumatriptan. Effectiveness of sumatriptan, i.e. responder, was defined as freedom from pain, or reduction to mild intensity in headache severity within 2 hours in at least 3 of 2 of 3 migraine attacks after the use of sumatriptan tablet (50mg). When sumatriptan was used in combination with other abortive medications, those who reported effectiveness were excluded, but those who reported no response were retained as non-responders.

**Results:** A total of 1,499 migraine patients were enrolled in the study, of whom 1,195 (79.7%) were women, with a mean age of 38.7±11.3 years. Most patients (90.5%) were diagnosed with migraine without aura; while 33.4% fulfilled the diagnosis of chronic migraine, 21.5% medication overuse headache. Effectiveness of sumatriptan was reported in 1,033 (68.9%) of 1,499 patients. Compared to non-responders, sumatriptan responders were older (39.7±11.3 vs. 36.5±11.1 years old, \(p<0.001\)), had a lower baseline headache frequency (9.8±7.9 vs. 11.6±9.1 days per month, \(p<0.001\)), less likely to have chronic migraine (30.4% vs. 39.8%, \(p<0.001\)), with lower psychiatric measures (Beck Depression Inventory 10.5±7.8 vs. 11.8±8.7, \(p=0.007\)), and were less likely to have fibromyalgia (6.1% vs. 10.5%, \(p=0.014\)). Regular coffee consumption was positively associated with effectiveness (\(\geq 1\) cup per day vs. non-drinker, odds ratio = 1.603, \(p=0.003\)). Gender or status of aura were not associated with sumatriptan response.

**Conclusion:** In our large cohort, two thirds of migraine patients responded to sumatriptan. Certain demographic data, severity measures and comorbidities measures were associated with triptan responses. A link to coffee consumption is interesting and worth further investigation.

**Disclosure of Interest**
None Declared
Migraine Acute Therapy

EP-01-012

Intranasal ketamine for abortive migraine therapy in pediatric patients: a case series

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Objectives: Migraine is a common presentation in adolescents and children in emergency departments (EDs) and inpatient visits. It is often treated with nonsteroidal anti-inflammatory drugs, dopamine receptor antagonists, triptans, or dihydroergotamine. Some cases, however, are refractory to traditional medications and options become narrowed [1,2]. Restricting therapy further, dihydroergotamine is currently on indefinite shortage [3]. Ketamine, a lipophilic, rapid-acting, N-methyl-D-aspartate (NMDA) antagonist, has emerged as a promising therapeutic option [4,5]. Excitatory glutamate signaling may be inhibited by ketamine via NMDA antagonism. This action could suppress cortical spreading depression (CSD) and alleviate migraines with and without aura [5].

Reports in mixed migraine patient populations described statistically significant pain score reductions (7.1 to 3.8; p < 0.0001) with intermittent intravenous ketamine[6] and diminished severity with ketamine infusions (0.12-0.42 mg/kg/hour)[7] without serious adverse effects (AEs) [6,7]. Intranasal (IN) ketamine 25 mg in migraine patients with prolonged aura demonstrated statistically significant reduced aura severity (p = 0.032) [4]. Reports of efficacy and safety with IN ketamine (0.3-0.5 mg/kg/dose) in pediatric patients with various pain diagnoses have been published[8-13], but pediatric migraine data with IN ketamine is lacking. Given minimal evidence and therapeutic options, our experience with IN ketamine was recorded to better understand potential efficacy and safety.

Methods: A retrospective case series was performed in 8 pediatric patients (12-17 years old) with refractory migraine who received IN ketamine between December 2016 and February 2017. In total, 11 encounters were recorded. Pain scores were obtained utilizing a 0–10 numeric pain scale [14]. Ketamine 0.1-0.2 mg/kg/dose (mean = 0.15 mg/kg/dose) was administered intranasally every 15 minutes (maximum: 5 doses).

Results: Migraine resolution was seen in 63.6% of encounters (n = 7/11); most responders achieved their lowest pain score with dose four or five (n = 5/7; 71.4%). Mean pain reduction from admission to ketamine completion for responders was -6.8. Non-responders (n = 4) saw only -0.5 reduction.

Conclusions: Intranasal ketamine appears to be safe and effective for pediatric migraine treatment, particularly in patients with prolonged migraine. Our experience supports efficacy with lower IN ketamine doses (0.1-0.2 mg/kg/dose) in abortive migraine therapy with minimal AEs. Larger trials are warranted to substantiate ketamine’s efficacy, optimal dose, and safety for abortive migraine therapy in pediatric patients.

Disclosure of Interest
None Declared

Migraine Preventive Therapy

EP-01-013

Efficacy of erenumab for the treatment of patients with chronic migraine in presence of medication overuse

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Objectives: Efficacy of erenumab, a human anti-CGRP receptor antibody, was evaluated in chronic migraine
(CM) patients with medication overuse (MO) in prespecified subgroup analyses of a phase 2 study (NCT02066415).

**Methods:** CM patients ($\geq 15$ headache [HA] days/month over 3 months with $\geq 8$ migraine days) were randomized to erenumab (70 mg or 140 mg QM) or placebo for 12 weeks, stratified by region and MO. Data from patients with MO at baseline were used to assess changes in monthly migraine days (MMD), acute migraine-specific medication (AMSM) days, monthly HA hours, and proportion of patients achieving $\geq 50\%$ reduction in MMD. P-values for pairwise comparisons were not adjusted for multiple comparisons.

**Results:** Of 667 patients randomized, 41% (n = 274) met MO criteria. Mean (SD) baseline MMD in the MO subgroup were 19.6 (4.4), 18.8 (4.6), and 18.8 (4.5) in the placebo, 70–mg, and 140-mg groups. Compared with placebo, erenumab 70-mg or 140-mg groups had a greater reduction in change in MMD at week 12 (LS mean [SE]: -6.6 [0.7] and -6.6 [0.7] vs -3.5 [0.6]; p < 0.001 for both) and a greater reduction in change in AMSM days (LS mean [SE]: -5.4 [0.6] and -4.9 [0.5] vs -2.1 [0.5]; p < 0.001 for both). In the placebo, 70-mg, and 140-mg groups, $\geq 50\%$ reductions in MMDs were achieved by 18%, 36% (OR: 2.51; p = 0.007), and 35% (OR: 2.51; p = 0.007). Respective changes in monthly HA hours were -56.9 [10.6] and -42.0 [8.7] (p = 0.28 and p = 0.04).

**Conclusion:** Erenumab showed efficacy in CM patients with medication overuse in this study.

**Disclosure of Interest**

**Migraine Acute Therapy**

**EP-01-014**

**Efficacy of erenumab for the treatment of patients with chronic migraine and aura**

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Abstract number: EP-01-014

**Table 1. Change from baseline at week 12**

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<th>Erenumab 140 mg</th>
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<tbody>
<tr>
<td></td>
<td>Aura</td>
<td>Non-aura</td>
<td>Aura</td>
</tr>
<tr>
<td></td>
<td>N = 151</td>
<td>N = 130</td>
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<td>-6.6 (0.7)</td>
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<tr>
<td>p-value</td>
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<td>LS Mean (SE)</td>
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<tr>
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<td>-1.7 (0.4)</td>
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<td>p-value</td>
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Objectives: Efficacy of erenumab, a human anti-CGRP receptor antibody, was evaluated in chronic migraine (CM) patients in a phase 2 study (NCT02066415). Here we report a subgroup analysis of patients with aura and patients without aura.

Methods: CM patients (≥15 headache [HA] days/month over 3 months with ≥8 migraine days) were randomized to erenumab (70 mg or 140 mg QM) or placebo for 12 weeks. Data from patients with at least one aura and patients without any aura during the 4-week baseline period were used to assess changes in monthly migraine days (MMD), acute migraine-specific medication days (MSMD), and proportion of patients achieving ≥50% reduction in MMD. Data from patients with and without history of aura were also analyzed. Nominal p-values are presented without multiplicity adjustment and not used for pre-planned hypothesis testing.

Results: Of 667 patients randomized, 49% (n = 328) had at least one migraine with aura during the baseline period. Mean (SD) baseline MMD in the aura subgroup were 18.6 (4.5), 18.5 (4.1), and 18.1 (4.7) in the placebo, 70-mg, and 140-mg groups. Respective baseline MMD in the non-aura subgroup were 17.8 (4.9), 17.5 (4.5), and 17.5 (4.7). Compared with placebo, treatment with erenumab 70 mg or 140 mg resulted in greater change (reduction) in MMD at week 12 in both subgroups: patients with aura and patients without aura (Table 1). There was also a greater change (reduction) in acute MSMD in both patients with aura and patients without aura (Table 1). The responder rates (≥50% reductions in MMDs) in the placebo, 70-mg, and 140-mg groups were 23%, 41% (odds ratio [95% CI]: 2.5 [1.4, 4.4]; p = 0.003) and 40% (OR: 2.5 [1.4, 4.5]; p = 0.002) for patients with aura and 24%, 39% (OR: 2.0 [1.1, 3.5]; p = 0.020) and 42% (OR: 2.2 [1.3, 4.0]; p = 0.006) for patients without aura. Results from analyses based on history of aura showed a similar pattern.

Conclusion: These data indicate that erenumab has similar efficacy in patients with migraine with and without aura in terms of MMD, MSMD and ≥50% RR.

Disclosure of Interest

Migraine Acute Therapy

EP-01-015

Early Onset of Efficacy in a Phase 2 Clinical Trial of Erenumab in Patients with Chronic Migraine

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Objectives: Erenumab 70 mg and 140 mg reduced monthly migraine days at all time points assessed (weeks 4, 8, and 12) in a phase 2 clinical trial of chronic migraine (NCT02066415). Here we evaluated efficacy prior to week 4.

Methods: Post hoc analyses evaluated achievement of ≥50% reduction in weekly migraine days and change from baseline in weekly migraine days. P-values for these endpoints are based on odds ratios or mean differences from placebo and are not adjusted for multiple comparisons. Also, to evaluate trends, a linear model was fitted to observed daily migraine days from days 1-7 (week 1) and pairwise comparisons of the slopes and moving averages were evaluated and overlaid with observed data.

Results: Both erenumab dose groups had a greater proportion of patients achieving ≥50% reduction in weekly migraine days by week 1 (26% for both doses compared with 16% for placebo [p ≤ 0.011]), increasing to 31%, 41%,
and 21% in the 70 mg, 140 mg, and placebo groups, respectively, at week 2 (p ≤ 0.011). At weeks 1-4, reductions from baseline in weekly migraine days were observed for the 70 mg group (range: -1.5 to -0.9 days [4.5 days at baseline]) and 140 mg group (range: -1.5 to -0.8 days [4.5 days at baseline]) compared with placebo (range: -0.8 to -0.5 days [4.6 days at baseline]); week 1: 70 mg p = 0.047, 140 mg p = 0.18; weeks 2-4 p ≤ 0.002 for both doses vs placebo). Moreover, 7-day moving averages of observed data showed that each treatment arm differed from placebo within the first several days. On pairwise comparisons, slopes for 140 mg differed from placebo by day 4 (p = 0.03). By day 6, both doses differed from placebo (p ≤ 0.03).

Conclusion: Erenumab showed early onset of efficacy with separation from placebo within the first week.

Disclosure of Interest

Migraine Preventive Therapy

EP-01-016

Chronic Migraine Treatment with Erenumab: Responder Rates

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Objectives: Erenumab (AMG 334) is a human anti-CGRP receptor antibody being evaluated as preventive treatment for chronic migraine (CM). When assessing efficacy of CM treatments by responder rates, there is an unmet need for more effective treatments.

Methods: In an analysis of data from a phase 2 study (NCT02066415) in patients with CM (≥15 headache days/month over 3 months with ≥8 migraine days), patients (N = 667) were randomized to erenumab (70 mg or 140 mg QM) or placebo. This analysis included calculation of proportions of patients with ≥50%, ≥75%, or 100% reduction in monthly migraine days (MMD) from baseline to last 4 weeks of a 12-week double-blind phase. P-values are based on odds ratios (OR) from placebo and not adjusted for multiple comparisons.

Results: Mean (SD) baseline MMD were 18.0 (4.6). Significantly higher proportions of patients treated with erenumab 70 mg or 140 mg experienced a ≥50% reduction from baseline in MMD compared with placebo at week 12 (39.9% and 41.2%, vs 23.5%; OR: 2.2 [p < 0.001] and 2.3 [p < 0.001]). The ≥75% responder rates at week 12 were higher for patients treated with erenumab 70 mg or 140 mg compared with placebo (17.0% and 20.9%, vs 7.8%; OR: 2.4 [p = 0.002] and 3.1 [p < 0.001]). Likewise, the 100% responder rates were higher for patients treated with erenumab 70 mg or 140 mg compared with placebo (4.3% and 2.7%, vs 0.4%; OR: 12.6 [p = 0.002] and 8.1 [p = 0.026]).

Conclusion: Erenumab treatment resulted in higher proportions of patients with CM experiencing ≥50%, ≥75%, and 100% reduction in monthly migraine days as compared with placebo.

Disclosure of Interest
Migraine Acute Therapy

EP-01-017

Fremanezumab (formerly TEV-48125) reduces headache pain within the first week of beginning treatment in the phase 2 episodic migraine study

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Objectives: Fremanezumab (formerly TEV-48125) is a fully humanized IgG2α monoclonal antibody that has been shown to selectively block both CGRP isoforms (α- and β) from binding to the CGRP receptor. In addition, fremanezumab inhibited neurogenic vasodilation induced by CGRP release in animal models. Fremanezumab was found to be effective and well-tolerated as a preventive migraine treatment for two 3 month placebo-controlled phase 2 studies. The present study evaluated in post-hoc analyses, the efficacy of two doses of subcutaneous fremanezumab (225 mg and 675 mg) during the first three weeks of therapy in patients with high frequency episodic migraine (HFEM).

Methods: In this multicenter, placebo-controlled, parallel-group study, patients with HFEM were first screened and trained to use an electronic headache diary during a 28 day run-in period. After the run-in period, participants who met inclusion criteria and were 80% compliant with daily diary intake were randomized, and treated once every 28 days for three months with either placebo, fremanezumab 225 mg or 675 mg treatment. Compared to placebo, both doses of fremanezumab significantly reduced the primary endpoint of the HFEM study, change in the number of migraine days in month 3 relative to baseline; herein we performed post-hoc mixed-effects model repeated measures (MMRM) analyses to assess the efficacy of each dose during the first 3 weeks of treatment for several headache parameters.

Results: The sample consisted of 296 subjects. Compared to placebo, decreases in the number of migraine days were seen during 1 week of therapy for both fremanezumab doses (p < 0.0001, Fig. 1, Panel A), a benefit that was maintained through the second and third weeks of therapy (p < 0.0001). Likewise, there were decreases in days with headaches of moderate to severe intensity for both doses at week 1 (p = 0.0062 and p = 0.0005, Fig. 1, Panel B), week 2 (p = 0.0032 and p = 0.0025) and week 3 (p = 0.0094 and p = 0.0042). Both doses decreased the number of days with headache of any severity within week 1 (p < 0.0001), this effect persisted at week 2 (p < 0.0001 and p = 0.0002) and week 3 (p = 0.0002 and p = 0.0011). For headache hours of least moderate or severe intensity and headache hours of any severity, the same pattern of efficacy was seen; there were decreases for both doses at weeks 1, 2, and 3 (all p < 0.01, Fig 2. Panels A and B).

Conclusion: In these post-hoc analyses, fremanezumab treatment resulted in a rapid preventive response in patients with HFEM, with improvements seen in several pain parameters within the first week of therapy initiation.

Disclosure of Interest

**Migraine Acute Therapy**

**EP-01-018**

**Patient Preferences for Preventive Therapy in Headache Medicine**

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¹Neuroscience Institute, University of Washington Medical Center  
²Neurology  
³Psychology and Pain and Anesthesiology, University of Washington, Seattle, United States

**Objectives:** The primary objective of this study was to survey patients referred to a university-based headache clinic regarding treatment preferences. **Methods:** All new patients at a tertiary headache specialty clinic completed a general patient reported outcomes questionnaire prior to their first visit (n = 1826). Treatment preferences are addressed in a section of this questionnaire. Patients chose from the following nine options when asked about preferences: preventive prescription medications, acute prescription medications, supplements/herbs/vitamins, Botox, other non-medication procedures, biofeedback or meditation, hypnosis, stress management or other preferences. **Results:** Only a small percentage of patients preferred prescription medications only (64, 3.5%). A larger group preferred non-medication approaches (301, 16.5%). The majority of patients preferred an integrative approach, combining medications and complementary options (1235, 67.6%). **Conclusion:** The majority of patients with headache are offered only medication treatment options, yet the preference of a majority of patients is an integrative approach that includes a combination of medication and non-medication treatments. Only a small minority of patients prefers medication only. It is important to open a conversation regarding patient preferences when partnering with patients to improve adherence to a treatment plan.

**Disclosure of Interest**

None Declared

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**Migraine Acute Therapy**

**EP-01-019**

**Migraine Preventive Benefits of ALD403 (eptinezumab) begin in the first 24 Hours Following Intravenous Administration**

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**Objectives:** Current options for preventive treatment in chronic migraine (CM) fail to meet the needs of many patients. Calcitonin gene-related peptide (CGRP) is a promising target for treating CM. ALD403 (eptinezumab) is a genetically engineered humanized anti-CGRP antibody, for migraine prevention. Data from a Phase 2b trial demonstrated a persistent reduction in migraine days that was maintained through 12 weeks. During these trials, a reduction in migraine activity was observed 24 hours after intravenous (IV) administration of ALD403 (eptinezumab). Based on this observation, we conducted a further assessment of the time of onset for the migraine preventive action of ALD403 (eptinezumab) in patients with CM. **Methods:** The time to onset of ALD403 migraine preventive efficacy was assessed by post hoc analysis of a parallel group, double-blind, placebo-controlled Phase 2b trial. Patients with CM were randomized to receive a single IV infusion of ALD403 or placebo. Self-reported migraine episodes and migraine hours were recorded daily in an eDiary at baseline and throughout the study. In this analysis, migraine episodes and migraine hours were recorded daily in an eDiary at baseline and throughout the study. **Results:** Of 665 patients randomized, 616 received treatment, and 588 treated patients who provided reliable data were included in this analysis. Analysis of the first full day (24 hours) following a single infusion indicated the percent of patients with a migraine was reduced from baseline in the ALD403 300 mg (59% to 27%) and in the ALD403 100 mg (60% to 29%) and from 59% to 49% in the placebo group. The reduction in daily migraine hours within the 24 hours after administration of study drug compared to the average baseline hours per day was also greater following treatment with ALD403 300 mg (6.1 to 2.9; -3.1 hrs) and 100 mg (6.1 to 2.8; -3.3 hrs) vs. placebo (6.1 to 5.1; -
1.1 hrs). ALD403 was well-tolerated with no serious related adverse events reported. **Conclusion:** In this post hoc analysis, on the first full day (24 hours) after administration of a single IV infusion, reductions in both the proportion of patients experiencing a migraine and the number of migraine hours experienced on that day were greater relative to baseline for patients receiving ALD403 (eptinezumab) compared to those receiving placebo. These observations suggest an early onset of migraine preventive efficacy, which may be related to IV administration, the unique pharmacokinetic and pharmacodynamic attributes of ALD403 (eptinezumab), the specific mechanism of action, or some combination of these attributes.

**Disclosure of Interest**


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**Neuromodulation for Headache**

**EP-01-020**

**Effect of cathodal transcranial direct current stimulation of the primary motor and sensory cortex on migraine**

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3 Neurology
4 Ear, Nase, and throat, Mashhad University of Medical Sciences, Mashhad, Iran, Islamic Republic Of

**Objectives:** Transcranial direct current stimulation is a novel technological method that has been used in the scope of pain related diseases like migraine-as a prevalent and high burden disease extensively. The aim of the present study was to evaluate the effectiveness of cathodal transcranial direct current stimulation (c-tDCS) over the right primary motor (M1) and sensory (S1) areas of the cortex on decreasing the intensity, duration, and frequency of pain in migraineurs.

**Methods:** This study was based on a randomized, double-blind, and sham-controlled design, and it tested 15 seasons (every week three seasons; over 5 consecutive weeks) of c-tDCS (20 min/1000 μA) on forty-five migraineurs (diagnosed according to the IHCD-II) into two experimental (nm = 15; ns = 15) and a control group (nc = 15).

**Results:** The results of a series of one-way ANOVA, c-tDCS showed significant (p < 0.05) reductions in all hypothesized aspects of pain in both experimental groups compared to the control one.

**Conclusion:** Therefore, it seems that c-tDCS can be used as a technological method in the treatment of migraine both therapeutically and prophylactically.

**Disclosure of Interest**

None Declared

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**Neuromodulation for Headache**

**EP-01-021**

**sTMS Blocks Cortical Spreading Depression by Suppressing Spontaneous Cortical Neuronal Firing and by Increasing the Threshold of Activation of the Occipital Cortex**

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**Objectives:** Single-pulse transcranial magnetic stimulation (sTMS) is a non-invasive neurmodulation technique that has been shown to be a successful acute and preventative treatment for migraine patients with and without aura. In vivo, sTMS has been previously shown to block cortical spreading depression (CSD) and thalamic neuronal activity.
sTMS uses a single magnetic pulse of 170 μs duration to induce weak electrical currents via electromagnetic induction, in the underlying cortical tissue.

**Aims:** The aim of this study was to investigate the cortical actions of sTMS.

**Methods:** All procedures were performed under a UK Home Office Licence in accordance to the 1986 Animal (Scientific Procedures) Act in anaesthetised male adult Sprague-Dawley rats. Spontaneous neuronal activity of the visual cortex was recorded using in vivo extracellular electrophysiological techniques. A rat-specific sTMS device was placed above the visual cortex and two pulses were applied at 100 V increments (100-600 V; ~0.2-1.1 T). Spontaneous neuronal activity was recorded for up to 90 minutes post-sTMS and compared to baseline recordings. In a separate set of experiments, the CSD model of migraine with aura was used. CSD induction was monitored through recordings of cortical steady-state potentials and induced via electrical stimulation of the visual cortex. This was repeated following two 600 V (1.1 T) sTMS pulses to the visual cortex. The microcoloums needed to induce a CSD wave were recorded pre- and post-sTMS application. In an independent group, two pulses of sTMS were applied and the microcoloums needed to induce CSD were recorded and compared to a control group.

**Results:** sTMS inhibited spontaneous neuronal activity in a dose-dependent manner. The sTMS treatments with the highest voltage, 500 V (0.9 T) and 600 V (1.1 T) significantly decreased cortical neuronal activity (n = 6; P < 0.001). Additionally, sTMS significantly increased the electrical threshold required to induce CSD (n = 6; P < 0.05). Comparisons within the same group demonstrated that sTMS blocked CSD for up to 2 hours (n = 5; P < 0.001).

**Conclusion:** Twin sTMS pulses demonstrate a dose dependent inhibitory effect on cortical neuronal activity. sTMS also blocked electrically-induced CSD by increasing the threshold of activation required for the induction of a wave. Collectively, these findings suggest a potential mechanism by which sTMS treatment reduces cortical excitability and migraine aura known to occur in migraine patients.

**Disclosure of Interest**


**Other Primary Headache Disorders**

**EP-01-022**

**Outcome of microvascular decompression in trigeminal neuralgia is highly dependent on sex and degree of neurovascular contact – A prospective systematic study using independent assessors**

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**Objectives:** Microvascular decompression (MVD) is first choice neurosurgical treatment in medically refractory trigeminal neuralgia patients with an MRI verified

<table>
<thead>
<tr>
<th>BNI Pain description</th>
<th>12 months assessment n (%)</th>
<th>Severe morphological changes on MRI* n (men)</th>
<th>Neurosurgical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Complete pain relief: No pain and no medication</td>
<td>43 (71.7)</td>
<td>28 (16)</td>
<td>Excellent outcome</td>
</tr>
<tr>
<td>II Partial pain relief: Occasional pain but no medication required</td>
<td>1 (1.7)</td>
<td>0</td>
<td>Good outcome</td>
</tr>
<tr>
<td>IIIA Partial pain relief: No pain but daily medication required</td>
<td>4 (6.7)</td>
<td>0</td>
<td>Good outcome</td>
</tr>
<tr>
<td>IIIB Partial pain relief: Occasional pain but adequately controlled with medication</td>
<td>4 (6.7)</td>
<td>1 (0)</td>
<td>Good outcome</td>
</tr>
<tr>
<td>IV Poor pain relief: Reduced pain but not adequately controlled with medication</td>
<td>1 (1.7)</td>
<td>0</td>
<td>Poor outcome</td>
</tr>
<tr>
<td>VA No pain relief</td>
<td>0</td>
<td>n/a</td>
<td>Failure</td>
</tr>
<tr>
<td>VB Aggravation of pain</td>
<td>7 (11.6)</td>
<td>4 (1)</td>
<td>Failure</td>
</tr>
</tbody>
</table>

Abstract number: EP-01-022
Table 1. Barrow Neurological Institute (BNI) pain intensity score. Outcome 12 month after microvascular decompression. N = 60.
neurovascular contact (NVC). There is a lack of high-quality prospective, systematic studies, using independent assessors of outcome of the procedure. Here we aimed to evaluate whether sex and degree of NVC can predict outcome of MVD.

**Methods:** Clinical characteristics and outcome data were systematically recorded prospectively from consecutive trigeminal neuralgia patients, using standardized semi-structured interviews and schemes. A pre-surgical 3.0 Tesla MRI was performed to evaluate the degree of NVC blinded to symptomatic side. The patients were assessed before and 3, 6 and 12 months after MVD by a neurologist at the Danish Headache Center. The Department of Neurosurgery had no influence on recording or evaluation of data. Data from a self-completed 12 months post-surgical questionnaire including items on pain intensity, complications and satisfaction, were also recorded. The primary outcome was pain relief according to the Barrow Neurological Institute pain score (BNI I-VB), table I. Secondary outcome was patient satisfaction.

**Results:** From May 2012 to February 2016, 27 men and 33 women had completed one year follow-up. Mean age at operation was 59.9 years (range 28-80 years). Mean duration of disease was 6.6 years (range 1-40 years). Thirty-three patients (57%) had NVC with morphological changes.

Forty-three (72%) patients had an excellent outcome defined as ‘no pain, no medication’ (BNI I). Nine (15%) patients had a good outcome, while eight patients (13%) had poor outcome or failure.

At multiple logistic regression the odds ratio of NVC with displacement or atrophy of the trigeminal nerve and excellent outcome was 5.2 (95% CI 1.3 – 20.1, \( P = 0.0183 \)) and the odds ratio between sex (male vs. female) and excellent outcome was 10.6 (95% CI 2.0 – 56.1, \( P = 0.0057 \)). There was no significant interaction between sex and severe NVC (\( p = 0.56 \)).

**Conclusion:** Based on high-quality prospective data collected by independent assessors we demonstrate that patients with morphological changes of the trigeminal nerve and male sex have a considerably better chance of an excellent outcome of MVD. The results should guide decision-making before neurosurgery.

**Disclosure of Interest**
None Declared
that it is important to work jointly with neurosurgeons in order to indicate a right treatment.

Disclosure of Interest
None Declared

Other Primary Headache Disorders

EP-01-024
Pressure-related symptoms of isolated CSF hypertension in headache sufferers

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Objectives: The absence of papilledema makes the diagnosis of isolated CSF hypertension (ICH) difficult and subject to much debate. The objective of this study is to identify the pressure-related symptoms of ICH without papilledema.

Methods: We prospectively performed short-term lumbar CSF pressure monitoring through a spinal needle in order to measure CSF opening pressures and to monitor, for 1 hour, the CSF pressure in 134 consecutive headache sufferers suspected of having high CSF pressure without papilledema. All patients underwent a complete neurological and ophthalmological evaluation, Trendelenburg positioning test, brain MRI, and cerebral MR venography before lumbar puncture.

Results: Of the 134 headache sufferers, 79 of these patients had isolated CSF hypertension without papilledema. The most of these (>90%) had postural headache with nocturnal head pain attacks. Severe headaches and visual disturbances with intracranial noise are common in 2 patients with higher CSF pressure (>300 mmH2O), while chronic headache and vertigo occurred in 20 patients with CSF pressure between 250 and 300 mmH2O. Less severe CSF-pressure elevation (from 200 to 250 mmH2O) with abnormal CSF pressure waves was also detected in 57 patients with moderate chronic headache and tinnitus.

Bilateral transverse sinus stenosis was detected in two third of the patients.

Conclusion: There is a continuous, graded relation between CSF pressure and the symptoms of isolated CSF hypertension without papilledema. Linked to posture/sleep-related changes in CSF pressure are postural and nocturnal headaches. While intracranial noise, tinnitus, and visual disturbances are symptoms fluctuating and variable linked to spontaneous intermittent daily CSF pressure elevation.

Disclosure of Interest
None Declared

Other Primary Headache Disorders

EP-01-025
White Matter Microstructural Changes Associated with Medication Overuse in Patients with Migraine

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Objectives: The objective of this study is to investigate the brain diffusion tensor magnetic resonance imaging (DTMRI) findings in patients with medication-overuse headache (MOH).

Methods: Twenty-three MOH cases and 19 healthy controls were recruited for the DTMRI. Diffusion indices were extracted from the data and clinical headache parameters were recorded for analysis.

Results: A significant difference in the parietal white matter (PWM) was observed between the groups. The fractional anisotropy (FA) value was significantly lower (p = 0.002) and the mean diffusivity (MD) and radial diffusivity (λr) values were higher in MOH patients than in controls (p = 0.01). Several imaging features of PWM and inferior frontal white matter were selected to generate a receiver operating characteristic (ROC) curve. Using an optimal cut-off value, the sensitivity and specificity for predicting the occurrence of MOH were 79% and 84%, respectively. The FA values for PWM correlated inversely with the duration of analgesic usage (r = −0.50, p = 0.01) but not headache parameters such as headache duration, frequency or intensity.

Conclusion: Our study found that microstructural PWM damage is a distinct characteristic of MOH. These white matter changes could be useful for monitoring both tissue damage and therapeutic effects in patients with this disease.

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Disclosure of Interest
None Declared

Other Primary Headache Disorders

EP-01-026

Post-dural puncture headache and CSF collection time for different needle types in migraineurs and healthy controls

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Objectives: Small atraumatic needles are associated with lower risk of post-dural puncture headache but longer cerebrospinal fluid (CSF) collection time. For biochemical CSF studies this might promote ex vivo metabolic breakdown. As part of an extensive biochemical research programme in CSF of migraineurs we prospectively assessed incidence and characteristics of post-dural puncture headache and CSF collection time for different needle types.

Methods: Lumbar punctures (14.6 mL) were performed for research purposes in 216 participants with migraine and 96 age- and sex-matched healthy volunteers. All participants were prospectively and proactively followed for at least three days. CSF collection time and incidence and duration of post-dural puncture headache were noted. The study was approved by the local ethics committee and all participants provided informed consent.

Results: The study population comprised of many subjects with increased risk of post-dural puncture headache (61.9% females with young mean age of 40.3 and normal mean BMI of 23.6). Incidence of post-dural puncture headache was substantially lower (OR 0.391; 95% CI 0.180 - 0.830; p = 0.018) for smaller 22G atraumatic needles (16.7%; 10/60) than for larger 20G traumatic (32.7%; 69/211) and 20G atraumatic needles (33.3%; 13/39). Median duration of headache was 3.5 days for 22G atraumatic needles, 4.0 days for 20G traumatic needles, and 4.0 days for 20G atraumatic needles. Mean collection time of 14.6 mL CSF was higher for 22G (9.06 min) than for 20G (3.47 min; p < 0.001).

Conclusion: In a high risk population 22 G atraumatic needles had substantially lower incidence of post-dural puncture headache and acceptable CSF collection time for biochemical studies.

Disclosure of Interest
None Declared

Other Primary Headache Disorders

EP-01-027

Clinical prediction model for medically urgent secondary causes of headache in children or adolescents presenting to the Emergency Department

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Objectives: Headache is one of the most common pediatric neurological presentations to the Emergency Department (ED). Children who present to the ED with headache and other focal neurological symptoms may be diagnosed with secondary causes like stroke or intracranial infection, but primary headache disorders like migraine with aura are more common. Uncertainty can lead to unnecessary neuroimaging or delayed diagnosis. A predictive model using routinely collected clinical features may help ED physicians more rapidly identify those at highest risk for a secondary cause of headache and help refine timely diagnosis and management. We hypothesize that routinely documented clinical features of children presenting with headache to the ED will predict those at highest risk for secondary headache disorders and may help to reduce unnecessary neuroimaging.

Methods: A retrospective cohort was identified from hospital and ED administration databases using ICD10 codes for all children who were diagnosed with an acute neurological disorder and presented to the ED over one year. The hospital record for each case was manually abstracted for the presenting complaint, clinical features, final diagnosis, and validated for inclusion criteria. The analysis was performed on all cases with a presenting complaint of headache, no history of trauma in the last 7 days, and no previously diagnosed disorder causing headache (e.g. hydrocephalus). A stepwise logistic regression model of clinical predictors associated with secondary causes of headache was derived and validated on a random 33% sample not used in the derivation.

Results: From a total of 1134 presentations, 630 cases with a presenting complaint of headache were identified. The mean age was 11.5 years (SD 3.9; range 0-17). Characteristics of the cohort include: female (57%), history of recurring headache (33%), ambulance transport (8%), and fever (18%). Neuroimaging (CT or MRI) was ordered in 126 (20%) and was abnormal in 38 (29%). A total of 27 (4.4%, 95% CI 2.8 – 6) were diagnosed with a medically urgent secondary cause of headache including intracranial infection (n = 11), intracerebral hemorrhage
or vascular malformation (6), tumour (5), stroke (2), hydrocephalus (2), demyelination (1), and inborn error of metabolism (1). Features positively associated with secondary causes of headache were ambulance transport (OR 8.5, 95% CI 1.7-42.8), decrease consciousness (OR 30.8, 95% CI 2.5-382), ataxia (OR 6.8, 95% CI 1.1-43.9), vomiting (OR 5.4, 95% CI 1.4-20), and progressive headache over days (OR 9.9, 95% CI 2.4-39.8). Age, fever, focal weakness, visual symptoms, and rapid onset headache were included in the model, but not significant. Negative predictors were prior history of headache (OR 0.1, 95% CI 0.01-0.85) and altered speech (OR 0.02, 95% CI 0.01-0.7). The model correctly classified 93% of the validation cohort (n = 200) with receiver operator curve (ROC) of 0.91. The optimal probability cut-off for a secondary cause was 0.15. The specificity was 95%, but sensitivity was low at 55% (false negative rate 45%) with PPV of 33% and NPV of 98%. The prediction model would have decreased the number of scans in the validation cohort by 55%.

Conclusion: The majority of children presenting to the ED with headache do not have medically urgent secondary causes and have normal neuroimaging. A prediction model of routinely collected clinical features was specific and could reduce the number of unnecessary neuroimaging studies by more than half. However, the sensitivity was unacceptably low. Ongoing research will refine the model with a larger cohort, but better predictors (e.g. biomarkers) may be needed to improve prediction in this age group.

Disclosure of Interest
None Declared

Other Primary Headache Disorders

EP-01-028
Developing a cerebrospinal fluid secretion assay using a genetically encoded biosensor to evaluate therapeutic and pathogenic molecules in idiopathic intracranial hypertension

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Objectives: Idiopathic intracranial hypertension (IIH) is characterised by raised intracranial pressure (ICP) and papilledema which primarily affects obese women of reproductive age. Treatment options are limited. Additionally, the aetiology is poorly understood but is driven by the imbalance of cerebrospinal fluid (CSF) secretion (predominantly at the choroid plexus) and CSF drainage.

We aimed to develop an in vitro CSF secretion assay that could be used to evaluate drug therapies, and potential pathogenic molecules of relevance to IIH. CSF secretion is dependent numerous ion channels and pumps where the Na/K ATPase is the rate limiting step. We aimed to develop a novel CSF secretion assay that measures Na/K ATPase activity, a validated surrogate marker of CSF secretion. Additionally, we sought to validate the assay with acetazolamide, a carbonic anhydrase inhibitor which reduces CSF secretion and is used therapeutically in IIH. Finally, our recent ex-vivo studies have highlighted raised serum testosterone in IIH: consequently we evaluated the effect of testosterone on CSF secretion.

Methods: An immortalised rat choroid plexus epithelial cell line (Z310 cells) were infected with an adenoviral vector containing the ATP:ADP ratio sensor Perceval. Na/K ATPase activity was determined following acute administration of the specific Na/K ATPase inhibitor ouabain (1 mM) and measuring the change in ATP:ADP ratio, an indicator of ATP consumption of by the Na/K ATPase. The Z310 cells were treated with 1 mM acetazolamide or 100 nM testosterone (versus vehicle) to determine alterations in Na/K ATPase activity following acute ouabain administration.

Results: Initial experiments were conducted with ouabain and vehicle to determine if ouabain elicits a change in the ATP:ADP ratio. Ouabain increased the ATP:ADP ratio (P < 0.0001) compared to control and allowed resolution of the ATP formation rate. These data indicate that acute administration of ouabain allows detection of Na/K ATPase activity with the Perceval biosensor. Following two days of acetazolamide treatment, ouabain elicited a reduced change in ATP:ADP ratio (P < 0.05) and reduced ATP production (P < 0.05) compared to vehicle treated cells, indicating reduced Na/K ATPase activity. In contrast, following two days of 100 nM testosterone incubation, ouabain administration displayed an increased change in ATP:ADP ratio (P < 0.0001) with larger ATP production (P < 0.01) compared to vehicle treated cells, indicating increased Na/K ATPase activity.

Conclusion: We have developed a novel assay that can specifically measure Na/K ATPase activity through the change in ATP:ADP ratio elicited by ouabain. This assay of Na/K ATPase activity is a potential in vitro surrogate assay for CSF secretion with relevance to ICP, thus has a potential role for evaluating novel therapeutic agents aimed at lowering ICP through reduced CSF secretion. We demonstrate that Na/K ATPase activity can be manipulated with acetazolamide, causing a reduction in Na/K ATPase activity, indicating reduced CSF secretion. Furthermore, we identify testosterone as a molecule
that can increase Na/K ATPase activity, indicating increased CSF secretion. Testosterone elevation in IIH may exert a pathogenic role in modulating ICP though increasing CSF secretion. Future work will examine the relationship of this assay to in vivo ICP measures.

**Disclosure of Interest**
None Declared

**Post-Traumatic Headache**

**EP-01-029**

**Cortical Thickness in Patients with Persistent Post-traumatic Headache**

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**Objectives:** Post-traumatic headache (PTH) is a common and disabling neurological disorder. Recent data from functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) studies indicate network connectivity abnormalities and white matter alterations in patients with PTH. However, whether patients with PTH might have changes specifically to the cortical grey matter is insufficiently understood. In this study, we interrogated cortical thickness, a proxy measure of cortical integrity, in patients who have persistent PTH attributed to mild traumatic brain injury.

**Methods:** Cortical thickness measurements were calculated from T1-weighted images obtained on a Siemens 3 Tesla scanner in 29 patients with PTH attributed to mild traumatic brain injury and 31 age-matched healthy controls. Data were post-processed using a FreeSurfer 5.3 pipeline. Multivariate analyses were performed to compare vertex-by-vertex cortical thickness in patients with PTH compared to healthy controls. Correlations between cortical thickness with headache frequency and time interval since onset of post-traumatic headache were calculated.

**Table:** Figure 1. Areas in which average cortical thickness of patients with PTH differed from healthy controls are demonstrated on the inflated brain surface of the left hemisphere (A) and of the right hemisphere (B). Areas colored blue indicate cortical thinning in patients with PTH compared to healthy controls.

**Image:**

**Results:** Mean age of healthy controls was 33.7 years (SD = 7.2); mean age for PTH patients was 32.1 years, (SD = 10.5); p = 0.48. For patients with persistent PTH, the average headache frequency was 21.8 days per month (SD = 8.7) and average time interval since onset of post-traumatic headache was 80 months (SD = 103.3). Patients with persistent PTH had significantly less cortical thickness compared to healthy controls in left rostral middle frontal and bilateral precentral, superior frontal and caudal middle frontal areas [Figure 1] (p < 0.01, Monte Carlo corrected for multiple comparisons). For patients with PTH, there was a negative correlation between headache frequency and right superior frontal thickness (p = .032).

**Conclusion:** Results suggest bilateral changes in frontal pain processing regions in PTH. Furthermore, patients with more frequent headaches had less cortical thickness in the right superior frontal region suggesting that headache frequency might modulate brain integrity in PTH.

**Disclosure of Interest**
None Declared

**Psychological and Behavioural Factors and Management**

**EP-01-030**

**Pain catastrophizing as predictor of response to topiramate in chronic migraine patients**

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**Objectives:** Pain Catastrophizing (PC) is among psychological factors that might contribute to pain chronicity. It is defined by the presence of persistently negative cognitive and emotional responses to pain. It has been associated with increased pain intensity, mood disturbances, and analgesic overuse. There are three variables considered in PC: rumination, magnification and helplessness. We aimed to evaluate whether PC predicts the response to preventive therapy with topiramate in a population of chronic migraine patients.

**Methods:** We included patients firstly attended in a headache unit of a tertiary hospital. Chronic Migraine was diagnosed accordingly to International Classification of Headache Disorders, III edition, beta version (ICHD-III beta), and preventive therapy with topiramate was indicated. Inclusion period extended from January to June
2016. We collected clinical and demographic variables, including time from onset of migraine and chronic migraine. We excluded patients with a previous diagnosis of a psychiatric illness. We administered in each patient six-item Headache Impact Test (HIT-6) and Hospital Anxiety and Depression Scale (HADS), considering Anxiety or Depression when scored > 10 in any of the subscales. PC was assessed with Pain Catastrophizing Scale (PCS). In PCS, patients are asked to indicate the degree they experienced 13 thoughts or feelings when suffering pain, on 5-point scales with end points 0–not at all and 4–all the time. PCS score over 30 is considered clinically relevant catastrophizing. Topiramate was prescribed at a dose of 100 milligrams per day and the response was evaluated 3 months after initiation of treatment. The patient was considered a responder when a decrease in monthly headache days of at least 50% was achieved.

Results: We included 35 patients in the study. In eight cases topiramate was not tolerated during at least 3 months and they were excluded from the analysis. Among the 27 analyzed patients, 2 were male and 25 female. Age at inclusion was 36.7 ± 9.7 years (range: 18-57), time from migraine onset was 18.5 ± 10.2 years (1-37) and time since chronic migraine onset was 31.3 ± 34.4 months (3-120). Number of headache days per month was 23.8 ± 5.4 days (15-30) and 20 patients (74.1%) met criteria for symptomatic medication overuse. The scores on the administered scales were as follows: HIT-6: 63.5 ± 6.8 (50-74), HADS-anxiety: 9.1 ± 5.1 (1-19), HADS-depression: 4 ± 4.3 (0-15), and PCS: 23.4 ± 12.4 (1-45). 11 patients (40.7%) met criteria for anxiety and 3 (11.1%) for depression according to HADS, and 10 (37%) had a clinically relevant catastrophizing. Response to topiramate was achieved in 17 patients (63%). Scores on the HADS-depression scale (1.7 ± 2.2 vs 7.8 ± 4.5, p: 0.002) and PCS (19.6 ± 11.7 vs 29.8 ± 11.5, p: 0.041) were significantly lower among responders group. None of the other variables analyzed predicted response to treatment

Conclusion: Among our population of chronic migraine patients, a relevant catastrophizing is not uncommon. The presence of lower scores on the Pain Catastrophizing Scale predicted the response to preventive treatment with topiramate.

Disclosure of Interest
None Declared

Psychological and Behavioural Factors and Management

EP-01-031

Life traumatic experiences and stressful events in chronic migraine with medication overuse: Do they impact the outcome of a detoxification therapy?

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Objectives: In this study we evaluated the association between early life traumatic experiences and recent stressful events with the outcome following detoxification therapy in a 2-month follow-up in 171 subjects with medication overuse headache (MOH).

Methods: This study was conducted at the Headache Center of the C. Mondino National Neurological Institute in Pavia, Italy. All consecutive patients with chronic headache and medication overuse undergoing an inpatient detoxification program were enrolled and followed-up in a prospective study. Diagnosis was operationally defined according to ICHD-IIIβ. The protocol consisted in an inpatients detoxification treatment and a 2-month follow-up. Data on early life traumatic experiences – distinguished in term of physical and emotional traumas – and recent stressful events – rated according to the impact patients’ quality of life, from mild to very serious – were collected by means of self-report questionnaires. Data were analyzed with the analysis of variance.

Results: Of the 171 patients who completed the 2-month follow-up, 122 stopped overuse and their headache reverted to an episodic pattern (Group A), 30 stopped overuse without any benefit on headache frequency (Group B), and 19 failed to stop overuse (Group C). A higher number of early life traumatic experiences was detected in the patients who failed to stop overuse when compared to the other groups (Group A: M = 1.2 ± 1.3; Group B: M = 0.9 ± 0.9; Group C: 2.0 ± 1.5; p = .04). The type of stress reported was mainly of the emotional type, rather than physical. No differences were observed when comparing A and B Groups. As regards recent stressful events, a significantly higher number of patients in Group B reported very serious current life events as compared to patients in Group A and B (Group A: 19.7%; Group B: 46.7%; Group C: 15.8%; p = .005) The percentage of patients reporting life
events with lower impact were instead similar in the three groups.

**Conclusion:** Withdrawal from overused drug is the treatment of choice for MOH, reverting the headache from chronic to episodic within two months. Many factors are involved in MOH prognosis and outcome, and their understanding is a topic of interest. MOH patients experience increased psychiatric comorbidity, such as anxiety, depression, or personality disorders (1, 2), even if this cause-effect relationship still needs to be understood. Even less is known about the role of these factors in the response to detoxification treatments. Our data are very interesting and suggest a different impact of life traumas and stressful events on the outcome of a detoxification program. The failure to cease overuse is related to the existence of childhood (mostly emotional) traumas, whereas recent life events, especially when very serious, do not seem to influence the capacity of the patient to stop overuse, but are associated to the persistence of chronic headache. These findings have important practical implications on how to treat these patients.

**Acknowledgements:** This study was supported by a grant of the Italian Ministry of Health to Institute C. Mondino (RC 2014-2016).

**Disclosure of Interest**

None Declared

**References**


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**Psychological and Behavioural Factors and Management**

**EP-01-032**

**Interactions between affective measures and amygdala volume in chronic migraine: associations in the absence of group volumetric differences**

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**Objectives:** Previous studies examining brain structure in patients with chronic migraine (CM) have been mixed, with some reporting volumetric abnormalities compared to controls and others finding no differences. While many of these studies examined the relationship between pain symptoms and brain volumetrics, affective measures have been far less explored. The objective of the current study was to examine the relationship between affective measures and brain volumetry of the amygdala, a structure known for its role in affect, in patients with CM.

**Methods:** We conducted a cross-sectional case-control study comparing participants with CM to healthy controls. Sixty participants (30 patients (24 F, 6 M, mean age ± SD: 40.5 ± 13.9) and 30 age- and sex- matched controls (mean age ± SD: 40.3 ± 14.6)) were recruited for this study. Patients had a diagnosis of CM according to the International Classification of Headache Disorders-3 beta criteria and controls had no history of chronic pain. All participants underwent MRI scans on a 3T GE scanner. A voxel-based morphometry (VBM) approach was implemented in FMRIB’s Software Library v. 5.0.8 and examined left and right amygdala volumes and subregional volumes (superficial, laterobasal, centromedial) as labeled by the Juelich histological atlas. Participants completed the following questionnaires to assess scores of depression, anxiety, and pain catastrophization, respectively: Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7 (GAD-7), and Pain Catastrophization Scale (PCS). Differences in affective measures between patients and controls were evaluated and a multiple linear regression analysis determined the relationship between the affective measures and amygdala volumes.

**Results:** The VBM results indicated that there were no significant differences in left or right amygdala volumes or in subregional amygdala volumes between CM patients and controls. When affective measures were compared between patients and controls, CM patients had significantly higher depression and pain catastrophization scores (p < 0.05). Furthermore, the multiple linear
regression analysis revealed a significant group \times depression interaction for right amygdala volume \((p < 0.05)\), such that there was a positive association between right amygdala volume and depression in CM patients only. This relationship was also evident when right amygdala subregions were examined: centromedial \((p < 0.01)\), laterobasal \((p < 0.05)\), superficial \((p < 0.05)\). A separate multiple linear regression analysis showed a significant group \times PCS interaction for the right amygdala \((p < 0.05)\), such that patients had a positive association between right amygdala volume and pain catastrophization. However, this relationship was only evident when the entire right amygdala volume was examined, but not for any of the subregions \((p > 0.05)\). No significant interactions were found between amygdala volumes and anxiety scores \((p > 0.05)\).

**Conclusion:** We report significant interactions between right amygdala volumes and measures of depression and pain catastrophization in CM patients only. These findings highlight the importance of assessing for abnormal associations between brain volumetry and affective measures even in the absence of group volumetric difference. Additionally, the laterality of the findings and the specific subregional volumes involved may provide insight into the basic mechanisms of CM pathophysiology.

**Disclosure of Interest**

None Declared

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**Psychological and Behavioural Factors and Management**

**EP-01-033**

**Development and Acceptability of a Mindfulness-Based Cognitive Therapy for Migraine (MBCT-M) Individual Treatment Protocol**

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**Objectives:** To adapt existing Mindfulness-Based Cognitive Therapy (MBCT) protocols for migraine, develop a treatment manual for use for individual MBCT-M therapy and report on study enrollment and subject satisfaction to date in the Bronx MBCT-M clinical trial (NCT02443519).

**Methods:** The Bronx MBCT-M manualized study protocol was developed by 1) consulting with expert migraine treatment providers (medical and psychological) 2) converting existing MBCT group protocols for depression relapse (DR) and chronic headache pain (CHP) into session outlines, 3) adapting and creating session and homework materials for migraine, and 4) converting session format from group to individual (Table 1). Major protocol adaptations were made prior to study enrollment. Therapists (advanced doctoral psychology student) engaged in monthly peer-debriefing sessions identified common problems in implementation within the first three months of treatment.

**Abstract number:** EP-01-033

**Table 1: MBCT-M Adaptation**

<table>
<thead>
<tr>
<th>Session Title</th>
<th>Content Changes Made to MBCT-CHP Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Automatic Pilot</td>
<td>Addition of migraine specific psychoeducation and treatment rationale (early warning signs, medication decision making, migraine threshold model, stress and pain management)</td>
</tr>
<tr>
<td>2) Awareness of Appraisals and Stress</td>
<td>Discussion of Stress-Migraine bidirectional relationship</td>
</tr>
<tr>
<td>3) Mindfulness of the Breath</td>
<td>Walking Meditation introduced (moved from session 4)</td>
</tr>
<tr>
<td>4) Recognizing Aversion</td>
<td>Gentle Mindful Movement from MBCT-DR replaced yoga session. Changed title from &quot;Staying Present&quot; to MBCT-DR &quot;Recognizing Aversion&quot; to highlight aversion to pain, worry and disability related to unpredictable nature of migraine onset</td>
</tr>
<tr>
<td>5) Allowing/Letting Be</td>
<td></td>
</tr>
<tr>
<td>6) Thoughts Are Not Facts</td>
<td>Exhaustion Funnel handout from MBCT-DR introduced</td>
</tr>
<tr>
<td>7) How Can I Best Take Care Of Myself?</td>
<td></td>
</tr>
<tr>
<td>8) Using Mindfulness to Cope with Migraines</td>
<td>Focus on early migraine warning signs, trigger and pain management</td>
</tr>
</tbody>
</table>

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the trial (n = 4), which resulted in iterative clarification and increased specificity of the written treatment protocol. Therapists (eight advanced doctoral psychology students) receive weekly individual and monthly group supervision from licensed psychologists. Participants are randomized to active treatment or a wait list control followed by treatment. Thirty eight participants (of a total goal of 80) have been enrolled, 15 completed the eight-item Client Satisfaction Questionnaire (CSQ-8), which assessed global satisfaction with treatment and provider, following sessions 1, 4 and 8.

**Results:** When developing content for the MCBT-M protocol two themes emerged: 1) The Migraine Experience, and 2) Treatment Expectations. The Migraine Experience: Since migraine is a chronic disease with episodic attacks and few people have continuous or daily migraine, treatment rationales and educational components that presume continuous symptoms (chronic pain) were modified. Addition of migraine-specific content included 1) migraine phases with prodromal symptoms and 2) modifiable factors/trigger that contribute to migraine onset (reducing emphasis on Gate Control Theory of Pain). Yoga postures that could contribute to neck strain were replaced with the gentle mindful-movement used in MBCT-DR. Since anxiety is highly comorbid with migraine, we highlighted the Recognizing Aversion skills from MBCT-DR to address rumination. Treatment Expectations: Expert feedback agreed that therapy would be more effective if delivered in individual rather than group format. 120 minute weekly group sessions were replaced with 75 minute weekly individual sessions. Each session maintained a 20-30 minute guided mindfulness practice (Mindful eating, Body-Scan Meditation, Breath Meditation, Three-Minute Breathing Space, Mindful Walking, or Mindful Moment).

Of the 18 participants randomized to MBCT-M treatment, 1 (5.6%) discontinued due to changes in preventive medications and of the 20 participants randomized to waitlist/treatment as usual 1 (5%) dropped out prior to follow-up phase. Client satisfaction with treatment has been high across sessions; Session 1 (Mdn = 28.5, IRQ = 25.5-31), Session 4 (Mdn = 28, IRQ = 24.75-32), and Session 8 (Mdn = 31, IRQ = 24.75-32).

**Conclusion:** The Bronx MBCM clinical trial is testing an individual session, migraine-specific adaptation of existing, validated group MBCT protocols for chronic headache pain and recurrent depression. Participants’ satisfaction with MBCT-M demonstrates acceptability of the treatment; feedback has been generally positive and attrition rates have been low and relatively equal across groups thus far.

**Disclosure of Interest**

A. Singer: None Declared, D. Buse Conflict with: Allergan, Amgen, Avanir CoLucid, Dr. Reddy’s Laboratories, Conflict with: Amgen, Eli Lilly, E. Seng Conflict with: National Institute of Neurological Disorders and Stroke (1K23 NS096107-01), International Headache Academy, Conflict with: GlaxoSmithKline, Conflict with: Haymarket Media

**Psychological and Behavioural Factors and Management**

**EP-01-034**

**Effectiveness of a multicomponent intervention on Quality of life of patients with Migraine: A pilot study**

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**Objectives:** Migraine headaches are the third most common medical problem in the world with a global prevalence of 14.7%. Migraine as ranked seventh as the highest cause of disability globally. Migraine is associated with substantial impairment in quality of life. Conventional management of migraine headache is suboptimal and overuse of episodic medication will lead to the development of chronic daily headache. This pilot trial was primarily designed to investigate the effectiveness of a multicomponent intervention in improving the quality of life of patients with migraine.

**Methods:** The study was a prospective, randomized, controlled, single-blinded trial with parallel arms. After obtaining the written informed consent, forty participants were randomized to intervention (n = 20) and control arms (n = 20) using block randomization. The participants randomized to the intervention arm received the multicomponent intervention along with routine pharmacological management. The multicomponent intervention comprised of a behavioral lifestyle modification program and sessions of pranayama (a form of yogic breathing exercise). Participants in the control group received the routine pharmacological management. The subjects were then followed up and the outcomes were assessed at 4th, 12th and 24th week. The primary outcome variable of this pilot study was the quality of life. The Migraine-Specific Quality of Life Questionnaire (MSQ) was used to assess the quality of life of the migraineurs. The outcome assessor was blinded to the allocation status of the study participants. The trial protocol has been reviewed and approved by the institutional ethics committee.

**Results:** Majority of the participants were in the age group of 18-30 years. There was a preponderance of
female participants in the study with 90% of subjects being females in intervention and 75% in control arm. A positive family history was evident in majority of the study participants. The baseline mean (SD) quality of life scores for the subjects in intervention and control group were 29.95 (6.27) and 29.70 (5.20) respectively. However the mean (SD) posttest (at the 24th week) quality of life scores for the subjects in intervention and control group were 77.99(4.11) and 61.30(4.68). Repeated Measures ANOVA was done to evaluate the effectiveness of intervention quality of life of patients with migraine. The F ratio was 566.24 and the associated significance level was 0.001 (<0.05). Hence it is interpreted that the multicomponent intervention was effective in improving the quality of life of patients with migraine. Four paired samples t-tests were used to make post hoc comparisons between conditions, statistically, significant differences were obtained at all the four time points.

**Conclusion:** The research demonstrated that the multicomponent intervention had a positive impact on the quality of life of patients with migraine. The importance of intervention as demonstrated by this research should be considered for use by health professionals working in neurological settings.

**Disclosure of Interest**

V. Renjith Conflict with: Sigma Theta Tau International / Omicron Delta Research Grant, A. Pai: None Declared, A. George: None Declared

**Psychological and Behavioural Factors and Management**

**EP-01-035**

Cognitive beliefs about health and body and illness behavior in patients with chronic headaches

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**Objectives:** Somatosensory amplification, catastrophization and subjective beliefs about bodily weakness as well as illness behavior are considered as factors of functional somatic symptoms especially in patients with somatoform and hypochondriac disorders (Rief et al., 1998, 2003). Different aspects of perception and interpretation of bodily sensations including pain were found to be changed in patients with chronic pain and headaches (Keefe, Lefebvre, 1994, Nicholson, 2010, Yalug et al., 2010) and are considered as targets for cognitive-behavioral therapy with pain (Francis, 1996).

The aim of the study was to compare cognitive beliefs about health and body and illness behavior in patients with chronic headaches and healthy controls and to reveal their relationship with quality of life.

**Methods:** 104 patients (88 females, 18-70 years old) with chronic migraines and tension-type headaches and 41 participants without history of headaches and chronic somatic or mental illnesses (29 females, 18-70 years old) filled a brief version of Quality of Life and Enjoyment Questionnaire (Ritsner et al., 2005), Cognitions About Body and Health Questionnaire (Rief et al., 1998), Scale for the Assessment of Illness Behavior (Rief et al., 2003).

**Results:** Patient with headaches were not only less satisfied with their health, emotions and leisure time activity (but not with communication) than control group ($t = -3.01-6.86$, $p < .01$, $d = .56-26$) but also reported higher somatosensory amplification, more autonomic sensations, higher concentration of their health habits, believed that their body is weak and vulnerable and more frequently catastrophized about bodily sensations ($t = -5.95 - -2.07$, $p < .01$, $d = .38-1.10$). There were two types of illness behavior that were more typical for patients with chronic headaches than for healthy controls: emphasize on availability of medication and medical emergency and changes in life due to symptoms and illnesses ($t = -3.98 - -2.72$, $p < .01$, $d = .50-73$).

Moderation analysis revealed that in both groups higher belief in body weakness ($b = -.32$, $p < .01$) and lower belief in health habits ($b = .14$, $p < .05$) predicted lower satisfaction with health but the effect of belief in bodily weakness was marginally stronger in patients with headaches ($b = .29$, $p < .09$). Satisfaction with emotions was related to more consequences of symptoms for the personal life both in patients and healthy controls ($b = -3.38$, $p < .01$) while satisfaction with leisure time activity was related to less beliefs in bodily weakness ($b = -.30$, $p < .01$) and satisfaction with communication – to higher somatosensory amplification ($b = -.23$, $p < .01$).

**Conclusion:** The level of cognitive beliefs (somatosensory amplification, autonomic sensations, bodily weakness, catastrophization) as well as some aspects of illness behaviour (illness consequences and medication) that are typical for somatoform and hypochondriac disorders (Rief et al., 1998) is high in patients with chronic headaches. However, their effect on the quality of life seems to be common for healthy subjects and patients. Data supports that somatosensory amplification, belief in bodily weakness and negative impact of somatic symptoms on personal life as well as refusal from health habits are related to satisfaction with life domains but these effects are not moderated by headaches. From the cognitive behavioural perspective it could be hypothesized that patients with chronic headaches are more vulnerable to the development of
somatosensory amplification, concentration on health and body as well as illness behaviour that are related to more deterioration of their quality of life.

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Disclosure of Interest

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Psychological and Behavioural Factors and Management

EP-01-036

Utilization of behavioral treatment in migraine patients who visit a Headache Center: A Cross-Sectional Study

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2Barnard College, Barnard College, Columbia University
3NYU Langone Medical Center, 4Ferkauf Graduate School of Psychology, New York, United States

Objectives: Behavioral treatments (biofeedback, cognitive behavioral therapy, progressive muscle relaxation therapy) are level A evidence based treatments for the prevention of migraine. Research has shown that there are barriers for referring to behavioral therapy, and that these therapies are not widely used. As part of an ongoing study, we sought to (1) examine prior healthcare utilization (including treatment by a psychologist) of patients seen by headache specialist, (2) understand migraine patients’ beliefs about their ability to prevent their migraines, and (3) examine migraine patients’ reasons for not undergoing behavioral therapy.

Methods: From July 2016-January 2017, consecutive patients diagnosed with migraine by a fellowship trained Headache Specialist in an academic Headache Center in NYC using the ICHD 3 beta criteria were invited to complete a study questionnaire at the end of the office visit. Questions included information about patient demographics and prior healthcare utilization (including use of behavioral treatment and whether treatment had previously been recommended), and Migraine Disability Assessment (MIDAS) score. Other questions ranked patients’ views on certain headache-related issues, including headache management, patient-doctor relations, and protective headache factors. There were blank spaces for writing reasons for not participating in behavioral therapy. Descriptive analyses were then performed.

Results: 116 eligible patients were seen by the physician in the recruitment period and 67.2% (78/116) took part in the study. 86.5% (N = 64) were female. The average age of headache onset was 16.8 years and of diagnosis was 26.0 years. 84.4% (65/77) of patients reported that they believed that there are things they can do to reduce headache pain. The average MIDAS score was 36.6 (severe disability). The majority of patients (42/72, 58.3%) were referred by the headache specialist for behavioral therapy. Prior to the current visit, patients reported seeking headache care from a variety of other specialists including ophthalmologists (32/78, 41.0%), emergency department/urgent care providers (27/78, 34.6%), chiropractors (15/78, 19.2%), and psychologists (12/78, 15.4%). 32/72 (44.4%) patients reported previously engaging in behavioral headache treatment; of those who had not previously engaged in behavioral headache treatment, fewer than half (17/40, 42.5%) reported having previously received a referral. Expense (13, 76.5%) followed by time (6, 35.3%) were the reasons cited for not participating in behavioral therapy. CBT was the most common behavioral treatment tried (13, 40.6%) followed by biofeedback (12, 37.5%) and progressive muscle relaxation (7, 21.9%).

Conclusion: Most patients presenting to this headache center reported severe migraine disability. Patients reported seeing a wide variety of specialists; however, psychologists were among the least visited specialists. Of those who were previously recommended yet did not access behavioral treatment, they commonly shared that treatment was time consuming, too expensive, or not covered by insurance. More research is needed to determine rates and predictors of successful referral to behavioral treatment options.

Disclosure of Interest

None Declared
Endothelial dysfunction in migraine

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Objectives: We showed different endothelial functions of the anterior and posterior cerebral circulation in healthy subjects, worse vasodilatatory capacity of the posterior cerebral circulation and unimpaired systemic endothelial function in migraine patients without comorbidities. The relationship between cerebral and systemic endothelial function and the anterior and posterior cerebral endothelial function in migraine patients is still not clear.

Methods: We compared cerebral and systemic endothelial function through post-hoc linear regression analysis of cerebrovascular reactivity (CVR) to L-arginine between the middle cerebral artery (MCA) and flow mediated vasodilatation (FMD) of the right brachial artery and posterior cerebral artery (PCA) and FMD in migraine patients without comorbidities and in healthy subjects.

Results: We did not find any significant correlation between CVR to L-arginine in the MCA and FMD and PCA and FMD in migraine patients with aura (p = 0.880 vs. p = 0.682), without aura (p = 0.153 vs. p = 0.179) and healthy subjects (p = 0.869 vs. p = 0.662). On the other hand we found a significant correlation in CVR to L-arginine between the MCA and PCA in migraine patients with aura (p = 0.004), without aura (p = 0.001) and in healthy subjects (p = 0.002).

Conclusion: Our study suggests that the endothelial function of cerebral and systemic circulation might be different in migraine patients without comorbidities, while that of the anterior and posterior cerebral circulation might be coupled with a worse vasodilatatory capacity in the posterior cerebral circulation, which could indicate endothelial dysfunction in this territory.

Disclosure of Interest: None Declared
Variation of the spontaneous blink rate (SBR) in light and dark: comparison between migraine patients and healthy subjects

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²Neurology, CHR Citadelle - CHU, Liège, Belgium

Objectives: The spontaneous blink rate (SBR) is strongly modulated by dopamine (Karson et al., 1982) and by the occipital cortex (Karson et al., 1996) both of which also play a role in migraine pathophysiology (Charbit et al., 2010). Photophobia is a phenotypic hallmark of migraine both during and between attacks. We searched therefore whether the SBR could be increased in migraineurs because of their sensitivity to light.

Methods: We enrolled a total of 38 subjects: 7 healthy subjects (HS), 19 interictal episodic migraineurs (EM) and 10 ictal EM without prophylactic treatment. The SBR was measured in a lit room at a luminance intensity of 145 Lux or in almost total darkness, 12 Lux, using 2 electrodes placed on the orbicularis muscle of the right eye.

Results: We found no difference between groups during lightened sessions. By contrast, in the dark the SBR was reduced in HS and in ictal EM, but not in interictal EM (p = 0.05). The percentage SBR change between light and dark was −36.71 ± 22% in HS, −18.7 ± 34.74% in ictal EM and 1.9 ± 43.98% [SD] in interictal EM. This change was significant in HS (p = 0.017).

Conclusion: We show that in migraine patients between attacks the SBR is not decreased in the dark like in healthy subjects or migraineurs during an attack. This could be due to an abnormal interictal control by dopamine and/or the occipital cortex that normalizes during the attack.

Acknowledgement: this study was supported by FP7-EUROHEADPAIN no. 602633

Disclosure of Interest: None Declared

Cerebral endothelial dysfunction in migraine: a study on the age-specific risk of stroke in patients with migraine

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Objectives: To reveal the mechanisms underlying the age-specific risk for ischemic stroke in migraine patients, we aimed to evaluate cerebral endothelial dysfunction in migraine patients of different age groups.

Methods: We recruited patients with episodic migraine (EM) and normal controls (NC), aged 20–60 years, between October 2015 and August 2016. Cerebral endothelial function was assessed interictally by measuring cerebrovascular reactivity (CVR) using the transcranial Doppler breath-holding test. Breath-holding index of <0.69 was defined as CVR impairment. To compare CVR between EM patients and NCs, both the age- and sex-matched analysis and stratified analysis by age group were performed. A path analysis was used to test the determinants of CVR.

Results: In total, 145 EM patients and 72 NCs were included this study. The age- and sex-matched analysis showed a decreased CVR in all basal arteries in EM patients. The stratified analysis showed that the CVR impairment was most prevalent in the youngest age group (age 20–29 years) and in the posterior circulation, particularly posterior cerebral arteries. In EM patients,
duration (p = 0.020) had a negative impact on the CVR in the posterior cerebral artery, while the effect of current age on the CVR was only indirect via cerebral blood flow velocity.

**Conclusion:** Cerebral endothelial function is impaired in young-age migraineurs and in the posterior circulation, similarly to the characteristics of migraine-related stroke. Age at onset and disease duration, not the current age, may be determinants of cerebral endothelial dysfunction.

**Disclosure of Interest:** None Declared

### Headache Pathophysiology - Imaging and Neurophysiology

**PO-01-005**

**Altered structural & functional connectivity of the ventrolateral PAG in chronic migraine related to migraine frequency**

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**Objectives:** The neurophysiological mechanisms underlying migraine are not yet well understood. Accumulating evidence supports that numerous factors are involved including changes in brain structure, function and the neuro-vasculature. Most of the migraine studies to date have focused on episodic migraine. Consequently, little is known about what drives chronic migraine, which is defined as more than 15 headache days/month and is linked to significantly increased disability compared to episodic migraineurs.

The periaqueductal gray (PAG) is a brainstem region that plays a key role in the perception of pain and its dysfunction is linked to different chronic pain states. For example, it is implicated in migraine pathophysiology, and resting state functional magnetic resonance imaging (fMRI) studies have shown migraine-related allodynia is associated altered functional connectivity between the PAG and both cortical and subcortical pain regions.

The aim of this study was to investigate if changes in PAG physiology are related to features of chronic migraine. We assessed this using a multi-modal imaging approach that included: measuring PAG glutamate concentrations with magnetic resonance spectroscopy (MRS) and assessing PAG structural and functional connectivity with DTI and BOLD-resting state FMRI, respectively. For each imaging modality, we investigated group differences (CM versus controls) as well as relationships with patient’s migraine frequency (MF).

**Methods:** FMRI data was acquired interictally from 12 female chronic migraineurs and 12 female healthy controls using a 3T Siemens Verio and standard fMRI analysis methods. We investigated changes in PAG: i) resting excitability as measured by magnetic resonance spectroscopy (MRS); ii) white-matter tract integrity with DTI/TBSS; and iii) resting-state functional connectivity with the whole brain. For all imaging modalities both simple and multiple regression analyses was performed to investigate group differences and relationships with MF.

**Results:** i) MRS: We found no group differences between patients and chronic migraineurs in combined Glutamate/ Glutamine concentrations (Glx) in the PAG nor a significant correlation between Glx of the PAG and migraine frequency. ii) DTI: We also did not find significant changes in white matter structure between CM patients and controls. We found a significant negative correlation between migraine frequency and fractional anisotropy, a measure of white matter integrity, in the right sagittal stratum and the left anterior corona radiate. These effects were driven by an increase in radial diffusivity. We also found a positive correlation between the concentration of Glx in the PAG and fractional anisotropy in the right anterior corona radiate (t = 3.74, p = 0.048). We also found a significant positive relationship between migraine frequency and functional connectivity between the ventrolateral PAG and bilateral frontal pole, superior and middle frontal gyri.

**Conclusion:** Our results demonstrate a relationship between migraine frequency and altered structural connectivity in chronic migraine, showing a decrease in white matter structure in frontal cortical regions. Conversely, we found an increased functional connectivity between the vlPAG and multiple frontal and prefrontal regions. These regions have been implicated in higher order affective and cognitive pain processing. These results support the notion that increasing migraine frequency is related to altered connectivity between cortical regions and the vlPAG.

**Disclosure of Interest:** None Declared

### Headache Pathophysiology - Imaging and Neurophysiology

**PO-01-006**

**Comparison of the brain structure and resting-state functional connectivity between female patients with trigeminal autonomic cephalalgias and female migraineurs**

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Objectives: To investigate differences in the brain structure and resting-state functional connectivity (RSFC) between female patients with trigeminal autonomic cephalalgias (TACs) and female episodic migraineurs.

Methods: Ten female patients with TACs and 10 sex- and age-matched episodic migraineurs were selected for the study. All patients fulfilled the International Headache Society criteria 3 beta for episodic migraine or TACs. High-resolution structural magnetic resonance imaging (MRI) and resting state functional MRI (RS-fMRI) were performed in both groups.

Results: In comparison with episodic migraineurs, patients with TACs showed significant gray matter decrease in the left angular gyrus, right postcentral gyrus, right angular gyrus, right precuneus, and left precuneus using voxel-based morphometry. Next, these lesions with significantly decreased gray matter were defined as sources (seeds) in RS-fMRI. Seed-to-voxel and region-of-interest (ROI)-to-ROI analyses revealed that only the left angular gyrus showed significant differences in functional connectivity between patients with TACs and migraineurs. In contrast, functional connectivity of the default mode and salience networks showed significant differences between patients with TACs and migraineurs in additional RS-fMRI analysis.

Conclusion: Our study revealed that female patients with TACs and female episodic migraineurs have partly different brain structure and RSFC. Furthermore, structural alteration is not strongly related with RSFC. Alterations in the brain structure and RSFC in TACs and migraine may be caused by different pathophysiological mechanisms.

Disclosure of Interest: None Declared

Headache Pathophysiology - Imaging and Neurophysiology

PO-01-007

Single trial visual evoked potentials in migraine

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Objectives: A large number of studies have reported abnormalities of averaged transient or steady-state visual evoked potentials (VEP) in migraine patients between attacks, but some results are contradictory (see review by Ambrosini et al. 2011). Single trial analysis of VEP in one study (Gantenbein et al. 2013) showed that increases in VEP amplitudes in migraine could be explained by increases in local amplitude (rather than phase synchronization), which is more energy demanding. It is not known whether this is associated with morphological changes of the visual cortex. The aim of this study was to analyse single trial visual evoked potentials (st-VEP) in migraine patients and healthy controls and their anatomical correlates determined by voxel-based morphometry.

Methods: Twenty healthy volunteers (mean age 34.8 ± 11.3, 15F/5M) and 19 interictal migraine without aura patients (ICHD3-beta 1.1) (age: 32.7 ± 12.9, 15F, 4M) participated in the study. For VEP, 600 epochs were uninterruptedly recorded at Oz (Ref Fz) using a pattern reversal stimulus (3.1 Hz, 68°). Artefacted epochs were rejected (<5%). The mean amplitude of st-VEP was extracted for each subject. On a separate day, patients underwent 3T MRI of the brain. Grey matter volume was then correlated with mean st-VEP amplitude, controlling for whole brain size. Statistical analyses and graphs were performed in Prism GraphPad (GraphPad Software). st-VEP and MRIs were processed in EEGLAB and SPM respectively, both running in MATLAB (The MathWorks Inc.).

Results: Mean st-VEP amplitudes were higher in migraine patients (0.7896 μV ± 0.6611) than in healthy controls (0.2523 μV ± 0.6064) (p = 0.012). There was no difference in grey matter volume between the 2 groups of subjects. SPM statistical mapping showed that in migraine patients, but not in healthy controls, mean st-VEP amplitudes were positively correlated with grey matter volume in the primary visual cortex (small volume correction BA 17: 15, −78, 8, pFWE = 0.007, and −14, −78, 9, pFWE = 0.057) and in the right angular gyrus (whole brain analysis: 42, −57, 29 pFWE = 0.007).

Conclusion: This study confirms that migraine patients between attacks have increased amplitudes of mean single trial visual evoked potentials and shows for the first time that this is correlated with grey matter volume in the primary visual cortex.

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Disclosure of Interest: M. Lisicki: None Declared, K. D’Ostilio: None Declared, A. Maertens De Noordhout: None Declared, J. Schoenen Conflict with: Cefaly Technology, D. Magis: None Declared
**Altered brainstem anatomy in migraine**


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**Objectives:** Migraine is a common and debilitating neurological disorder characterised by unilateral throbbing, severe headaches, and often accompanied by nausea and photophobia. The exact mechanisms responsible for migraine remain unknown, although it has been proposed that changes in brainstem anatomy and function, even between attacks, may contribute to the initiation and maintenance of headache during migraine attacks. The aim of this investigation is to use brainstem-specific analyses of anatomical and diffusion weighted images to determine if the trigeminal system displays altered structure in individuals with migraine.

**Methods:** Using a 3 Tesla MRI scanner (Philips) we collected a high resolution T1-weighted anatomical (TR = 5.6 sec., TE = 2.5 ms, raw voxel size 0.9×0.9×0.9 mm) and 2 diffusion tensor images (32 directions, b0, b1000, raw voxel size 2×2×2.5 mm) in 24 migraineurs and 57 control subjects. All migraineurs were scanned during their interictal phase, i.e. at least 72 hours after a migraine and not within 24 hours of a migraine attack. All images were processed using Matlab and SPM12 software. In each individual, mean diffusivity maps were created using the DTI image sets. Using the SUIT toolbox, the brainstem region of the T1-weighted anatomical images and the mean diffusivity (MD) images were isolated and normalized to a brainstem specific template in Montreal Neurological Institute space and smoothed using a 3 mm FWHM Gaussian filter. Significant differences in regional brainstem volume and mean diffusivity were then determined using a random effects procedure (**p < 0.05**, small volume corrected).

**Results:** We found grey matter volume decreases in migraineurs in the region of the spinal trigeminal nucleus and dorsomedial pons. In addition, reduced grey matter volume and increased free water diffusivity occurred in areas of the descending pain modulatory system, including midbrain periaqueductal gray matter, dorsolateral pons, and medullary raphe. These changes were not correlated to migraine frequency, duration, intensity or time to next migraine.

**Conclusion:** This data revealed that when compared to controls, interictal migraineurs show decreased grey matter volume within key brainstem areas know to be activated during migraine attacks in addition to areas involved in endogenous pain modulation. Additionally, increased free water diffusivity occurred in areas of the descending pain modulation system. These data suggest that brainstem anatomy changes may underlie changes in activity that result in activation of the ascending trigeminal pathway and the perception of head pain during a migraine attack.

**Disclosure of Interest:** None Declared

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**Nonlinear visual processing is faster in migraine with aura**

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**Objectives:** Visual system abnormalities in migraine are linked to symptoms like photophobia and the visual aura. Little is known about the mechanisms contributing to these visual system alterations. Processing of visual input by the brain is a highly nonlinear operation, involving complex interactions among cortical and subcortical neuronal networks. Timing of this process can be estimated by analysing the cortical response to external light input at different frequencies. Using a sum-of-sinusoid light signal, instead of the classic pulse train, as input and novel EEG analyses it is possible to assess the time delay and frequency domain response. Here we investigate nonlinear visual processing in subgroups of migraine patients and headache-free participants.

**Methods:** Migraine patients with aura, without aura and healthy participants (N = 10/group) were subjected to sinusoidal light stimulation for 320 1 sec-epochs, while scalp EEG was recorded at the occipital, parietal and frontal lobes. Light stimulus frequencies were chosen to guarantee no overlap of their harmonic and intermodulation frequencies for different orders of nonlinearity. Nonlinear interactions and time delay from stimulus to cortical EEG response were analysed in the frequency domain using novel phase clustering measures and amplitude spectral measures.

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Results: Higher harmonic and intermodulation interactions were detected between visual input and cortical responses. Amplitude spectrum and phase clustering responses differed per order and group. Migraine patients with aura showed a decreased time delay only at the occipital lobe compared to healthy controls and migraine patients without aura.

Conclusion: Visual processing is altered in migraine patients with aura compared to healthy controls and patients without aura. Furthermore, we demonstrated the potential of quantifying nonlinear interactions and temporal dynamics in the visual system using sum-of-sinusoid light stimulation. We are able to uncover alterations in visual processing in the context of neurological disease.

Disclosure of Interest: None Declared

Headache Pathophysiology - Imaging and Neurophysiology

PO-01-010

TRPA1 channel activation by cinnamaldehyde: Are migraine patients more susceptible than healthy subjects?

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Objectives: Previous studies have shown that some known triggers of migraine activate transient receptor potential (TRP) channels, in particular TRP Ankyrin subtype 1 (TRPA1), which makes this an interesting target for migraine therapy. TRPA1 is a nonselective cation channel functioning as a chemical nociceptor which is activated by cinnamaldehyde (CA). Cinnamaldehyde-induced dermal blood flow (CA-DBF) response has been established as a non-invasive, reproducible in vivo human model for TRPA1 activation in healthy volunteers1. The objective of this study is to determine whether the CA-induced DBF and pain response is different between female migraine patients, with and without aura, and healthy volunteers.

Methods: This was a single center, single-blinded, placebo-controlled study in 25 migraine patients (15 without and 10 with aura) and 25 healthy subjects matched for age, sex and BMI. Migraine patients suffered from moderate to severe migraine headache according to criteria from the International Headache Society (IHCD-3). Required migraine headache characteristics included: I) migraine with or without aura, II) one to six migraine attacks a month for at least the last three months prior to the study and III) a history of migraine of at least six months. To exclude influence of hormonal changes, all subjects were tested during their menstrual period. Three 10-mm rubber O-rings (8 mm inner diameter) were placed on the volar surface of the subject’s dominant forearm. Topical doses of 20μL of 10% cinnamaldehyde were applied to the two upper rings and one 20μL placebo dose (i.e. vehicle) was applied to the lower ring. After a 30 minutes acclimatization period in a quiet, temperature controlled (23 ± 1°C) room in a semi-recumbent position, Laser Doppler scans of the subject’s forearms were performed at baseline and at 5, 10, 15, 20, 30, and 40 minutes after CA application. At the same time points, pain scores were recorded using a numerical rating scale (NRS) of 0–10.

Results: Topical application of 10% CA evoked an increase in DBF that did not differ between migraine patients (with and without aura) and healthy controls neither when expressed as Area Under the Curve (AUC0–40 min), nor when measuring the pain scores (table 1). The peak mean DBF response was observed 15 minutes post CA application in all groups.

Conclusion: Although preclinical literature suggests that TRPA1 plays an important role in migraine, we did not find a difference in the peripheral DBF response or pain response to CA-induced activation of TRPA1 between migraineurs and healthy subjects.

Abstract number: PO-01-010

Table

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy volunteers (n = 25)</th>
<th>Migraine patients (n = 25)</th>
<th>p-value (independent t-test)</th>
<th>Migraine with aura (n = 10)</th>
<th>Migraine without aura (n = 15)</th>
<th>p-value (ANOVA with post-hoc Bonferroni)</th>
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<tr>
<td>DBF AUC0–40 min (PU*min)</td>
<td>17,272 ± 1,104</td>
<td>17,943 ± 5,364</td>
<td>0.665</td>
<td>15,918 ± 1,882</td>
<td>19,293 ± 1,202</td>
<td>0.287</td>
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<td>Pain scores AUC0–40 min (NRS-score*min)</td>
<td>8.2 ± 2.3</td>
<td>3.6 ± 1.6</td>
<td>0.104</td>
<td>2.3 ± 1.8</td>
<td>4.5 ± 2.5</td>
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</table>

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Disclosure of Interest: None Declared

Headache Pathophysiology - Imaging and Neurophysiology

PO-01-011

Visual evoked potentials in episodic and chronic migraine – a pilot study

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Objectives: Most studies reported a deficient habituation of visual-evoked potentials (VEPs) interictally in episodic migraine (EM). Chronic migraine (CM), in contrary, exhibits normal habituation, suggesting the presence of persistent ictal-like cortical excitability. Discrepant results, however, exist with regard to VEP amplitudes in migraineurs. In this pilot study, we aimed to confirm these findings by comparing the VEP habituation and amplitudes between EM, CM and healthy controls (HC).

Methods: Pattern-reversal VEPs (6 blocks of 100 sweeps, each for 1 min) were recorded in 10 migraineurs without aura (5 interictal EM and 5 CM with prophylactic treatment) as well as 12 HC. We measured and compared the VEP amplitudes and habituation (slope of the linear regression line of amplitude changes from the 1st to 6th block of 100 sweeps) between the three groups.

Results: In general, both EM and CM exhibited higher VEP amplitudes than HC. CM showed significantly higher first block VEP amplitudes than EM (p = 0.01). Regarding VEP habituation, controls showed a typical VEP habituation where the amplitudes of VEP decreased as time progressed. Thus, the slope was negative in HC (HC slope: -0.52). Yet the VEP slopes in CM and EM were close to zero (CM = -0.11, EM = 0.13, figure 1), in which no obvious VEP habituation was found in both groups. In addition, the slope of VEP in HC was significantly lower than that of EM and CM (EM vs. HC, p = 0.043; CM vs. HC, p = 0.060).

Conclusion: Our findings confirmed the lack of VEP habituation in EM. In contrast to previous studies, however, CM did not exhibit a normal pattern of habituation, suggesting a possible role of prophylaxis in the modulation of cortical excitability. The increased VEP amplitudes in both EM and CM, as compared to HC, were likely to be related to hyper-responsive visual cortical excitability.

Disclosure of Interest: None Declared

Headache Pathophysiology - Imaging and Neurophysiology

PO-01-012

Time-frequency analysis of visual evoked potentials in migraine: getting a better insight into habituation

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Objectives: Visual evoked potentials (VEP) are characterized by a lack of habituation during prolonged stimulation in migraine patients between attacks (Schoenen et al). As this abnormality was not found in some studies (Omland et al.), we decided to assess the habituation phenomenon with time-frequency analysis. In detail, the aim of this study was to perform a time-frequency analysis of VEP and their habituation profile, comparing healthy volunteers and interictal migraine patients.

Methods: Twenty-one healthy volunteers (age 35.5 ± 11.5, 16F/5M) and 21 interictal migraine without aura patients (ICHD3beta 1.1) (age 34.1 ± 13.9, 16F/5M) participated in the study. For VEP, 600 epochs were uninterrupted recorded at Oz (Ref Fz) using a pattern reversal stimulus (3.1 Hz, 68°). Artefacted epochs were rejected (<5%). N1-P1 amplitude, event related spectral perturbations (ERSP) and inter-trial coherence (ITC) were calculated in six successive blocks of 95 epochs. For comparison, data from time-frequency analyses were extracted from a 60–120 ms time window (the range where N1 and P1 occur). VEP were processed in EEGLAB running in

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MATLAB (The MathWorks Inc.). Statistical analyses and graphs were performed in SPSS 20 (IBM Corp.).

**Results:** Throughout the stimulation, a significant reduction in power, i.e. habituation, was found in healthy volunteers but not in migraine patients. Inter-trial coherence progressively diminished in both groups, but to a greater extent in migraineurs. There was no difference between groups in the time domain. The N1-P1 habituation slope positively correlated with the ITC slope.

**Conclusion:** Unlike in healthy volunteers, continuous visual stimulation does not induce habituation in migraine patients as evidenced by ERSP analysis. Because of the major role inter-trial coherence plays in classic evoked potential results, peak-to-peak amplitude itself might not accurately reflect neuronal activation. Indeed, significant modifications in brain dynamics can remain undetected when limiting analyses to the time domain.

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**Headache Pathophysiology - Imaging and Neurophysiology**

**PO-01-013**

**Altered brain functional connectome in migraine with and without comorbid restless legs syndrome: A resting-state functional MRI study**

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**Objectives:** Patients with migraine are frequently comorbid with restless legs syndrome (RLS), although little is known regarding the neurological basis of this association. Both disorders are characterized by distributed functional abnormalities suggesting alterations in the functional connectivity (FC) of multiple brain networks. We investigated functional network changes in migraine patients with and without comorbid RLS to identify common and distinct patterns of functional reorganization associated with these clinically comorbid disorders.

**Methods:** We used resting-state functional magnetic resonance imaging and network-wise analytical approaches to investigate alterations in functional connectomes in 22 migraine patients with RLS, 22 migraine patients without RLS, and 19 healthy controls. Group comparisons and conjunction analyses were used to identify networks wherein the disorders were associated with common and distinct patterns of functional connectomes changes. Additional regression analysis was used to identify associations between alterations in functional connectomes and clinical profiles.

**Results:** Patients with migraine with and those without RLS had lower FC than healthy controls in the dorsal attention, salience, default mode, cingulo-opercular, visual, fronto-parietal, auditory, and sensory/somatomotor networks, which are related to attentional control and sensation. Both migraine groups also shared common patterns of functional connectome changes in sensory/somatomotor, sensory/somatomotor to auditory, and dorsal attention to auditory networks. There was a trend-level significance for functional connectome differences in the salience, default mode to subcortical and fronto-parietal, auditory to salience, and memory retrieval networks between the two migraine groups. Cross-network abnormality in the default mode to subcortical network in particular had a trend-level significance for an association with RLS severity in migraine patients with RLS.

**Conclusion:** We found disruptions of the brain functional connectome in migraine patients with and without comorbid RLS. This may lead to potential insight into the differential neuropathological mechanisms and the design of potential neuroimaging-driven biomarkers for migraine with and without comorbid RLS.

**Disclosure of Interest:** None Declared
Headache Pathophysiology - Imaging and Neurophysiology

PO-01-014

Alterations in regional cerebral blood (rCBF) during nitroglycerin (NTG) triggered migraine headache assessed using arterial spin-labelled (ASL) functional magnetic resonance imaging (fMRI)

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Objectives: Functional imaging in headache research is an increasing area of interest within headache research, because of the insights it can offer in humans into the pathophysiology and neurobiology of the migraine attack. Triggered attacks provide a reproducible and predictable model with which to study migraine. We aimed to study the phenotype and imaging characteristics of the headache stage of migraine using NTG triggered attacks, which have been shown to effectively induce headache attacks in a large proportion of migraineurs. The imaging modality we used was pulsed continuous Arterial Spin Labelling (pCASL), performed on a 3T General Electric MR750 MRI scanner.

Methods: Subjects (n = 18) were recruited following screening and informed consent. Each subject was exposed to either a 0.5 mcg/kg/min NTG infusion over 20 minutes or placebo, depending on randomisation. Each subject received both infusions on two different visits and was blinded to which treatment was being administered. Following the infusion, the timeline and phenotype to development of headache symptoms was documented. A standardised physician administered symptom checklist was used for data collection. Migraine headache was defined as moderate-severe headache which developed after the infusion and was associated with other migraine symptomatology that the subject would usually associate with spontaneous attacks. Imaging (structural T1, T2 and FLAIR, resting state blood oxygen level dependant imaging (rsBOLD) and two six minute pCASL maps) was conducted over 30–40 minutes at baseline and rsBOLD and pCASL during migraine headache. For the placebo visit the imaging was conducted at the same times following infusion in the absence of symptoms. Following scanning, the migraine headache was treated with either 6 mg subcutaneous Sumatriptan or 1 g intravenous aspirin.

Imaging was analysed using SPM 12 (www.fil.ion.ac.uk/SPM). Voxel based analysis of all subjects’ headache scans compared to baseline was carried out.

Results: With whole brain, voxel-wise analysis, significant increases in rCBF were detected in a large cluster that includes anterior frontal, orbito-frontal and parts of the anterior cingulate cortices (p = 0.004 corrected for multiple comparisons at the cluster level). Using a small volume spherical correction, significant increases were also observed in the posterior cingulate cortex (p = 0.031), in the region of the dorsomedial and centromedian thalamic nuclei and in the rostromedial midbrain (p = 0.05). No significant reductions in rCBF were detected.

Conclusion: The headache stage of NTG-triggered migraine is associated with significant areas of increased rCBF compared to baseline, in frontal cortex, anterior cingulate cortex, thalamus and rostral midbrain. The finding of these areas is consistent with previous work suggesting the vital role of the brainstem and other subcortical areas in migraine, as well as other classical pain matrix areas. This study demonstrates the usefulness of ASL in a cohort of migraine patients, as a means of interrogating areas of brain activity changing in response to the headache. The results are consistent with previous studies using blood oxygen level dependant (BOLD) and positron emission tomography (PET) imaging. ASL fMRI is promising non-invasive imaging modality, using rCBF as a correlate of neuronal activity, and could be increasingly used in migraine research.

Disclosure of Interest: N. Karsan Conflict with: Dr Karsan is an Association of British Neurologists/Guarantors of Brain Clinical Research Training Fellow, P. Bose: None Declared, F. Zelaya: None Declared, P. Goadsby Conflict with: Dr. Goadsby reports grants and personal fees from Allergan, Amgen, and Eli-Lilly and Company; and personal fees from Akita Biomedical, Alder Biopharmaceuticals, Autonomic Technologies Inc, Avanir Pharma, Cipla Ltd, Colucid Pharmaceuticals, Ltd, Dr Reddy’s Laboratories, eNeura, Electrocore LLC, Novartis, Pfizer Inc, Promius Pharma, Quest Diagnostics, Scion, Teva Pharmaceuticals, Trigemina Inc., Scion, Conflict with: personal fees from MedicoLegal work, Journal Watch, Up-to-Date, Oxford University Press; and in addition, Dr. Goadsby has a patent Magnetic stimulation for headache pending assigned to eNeura
HEADACHE PATHOPHYSIOLOGY - IMAGING AND NEUROPHYSIOLOGY

PO-01-015

Distinct cerebral metabolic patterns related to trigeminal sensory profiles in migraine patients and healthy volunteers

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Objectives: Episodic migraine patients are thought to be overall hypersensitive to various stimuli between (Ambrosini 2006) and allodynic during (Burstein et al. 2000) attacks, while chronic migraine patients may be permanently allodynic (Bigal et al. 2008). However, there is great variability within patients groups in all studies. It seems thus of interest to identify subgroups of patients with different pain sensitivities and to investigate whether this reflects in distinct brain activity patterns. We decided to analyse thermal perception and pain thresholds in the 1st division of the trigeminal nerve in large cohorts of healthy volunteers (HV), episodic migraine patients between attacks (EM) and chronic migraine patients (CM), and to search for correlations with brain metabolism assessed with FDG-PET.

Methods: A total of 173 subjects (mean age: 35 ± 14 years) underwent quantitative sensory testing (QST): 54 HV (70% fem); 69 EM patients (83% fem), and 50 CM patients (86% fem). Sensory and pain thresholds to cold and warm stimuli were determined using a 1.5 × 1.5 cm thermode (Advanced Thermal Stimulator-Medoc.) placed on the right forehead during three consecutive runs. Additionally, fifty-five subjects underwent an 18-FDG-PET scan (Philips Medical Systems): 20 HV, 21 EM without aura and 14 CM.

Results: QST (n = 173). No significant difference was found between subject groups for Cold Sensory Threshold (CST), Heat Sensory Threshold (HST), Cold Pain Threshold (CPT), and Heat Pain Threshold (HPT) in HV.

A K-means cluster analysis however (Freeman et al. 2014), revealed the existence of 2 distinct sensory profiles within the global population (namely ‘hyper-’ and ‘hyposensitive’), which significantly differed in all QST variables (CST, p < 0.001; HST, p < 0.001; CPT, p < 0.001; HPT, p < 0.001, Fig. 1). Based on k-means cluster pain profiles, both heat and cold pain thresholds were significantly reduced in ‘hypersensitive’ CM compared with ‘hypersensitive’ HV (CPT: p = 0.05; HPT: p = 0.02), indicating that CM patients are hypersensitive to pain.

Conclusion: Overall, we found no difference in trigeminal perception or pain thresholds for cold or warm stimuli between episodic or chronic migraine patients and healthy subjects. Collectively, cluster analysis of QST results disclosed ‘hypersensitive’ and ‘hyposensitive’ subgroups. When compared to their counterparts, ‘hypersensitive’ subjects had decreased metabolism in key pain processing regions of the CNS, but these regions differed between migraine patients (brainstem, thalamus) and healthy volunteers (somatosensory and cingulate cortices). This suggests that individual pain sensitivity is controlled by cortical pain matrix areas in healthy subjects, but that this control shifts to subcortical structures in episodic and chronic migraine patients. Acknowledgements: This work was supported by the EUROHEADPAIN project, FP7-602633


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PO-01-016

A conditioning photic stimulation changes the photic driving amplitude in peri-ictal migraineurs

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A conditioning photic stimulation changes the photic driving amplitude in peri-ictal migraineurs.

FDG-PET (n = 55). In EM, compared to HV, FDG uptake was reduced in left visual cortex, left medial frontal gyrus and bilaterally in the insular, somatosensory and motor cortices. CM had also a reduced metabolism in the orbitofrontal (OFC) and rostral anterior cingulate cortices (rACC). Cerebral metabolism differed between hyper- and hyposensitive individuals with a distinct pattern in each subgroup (Fig. 2). Compared to hyposensitivity, hypersensitivity was associated with reduced metabolism in the brainstem in EM, the thalamus in CM and the somatosensory and anterior cingulate cortices in HV. In addition, SPM-ANOVA contrast modeling the potential gradual effect on brain activity of increasing differences in pain sensitivity between groups showed significant metabolic changes in bilateral thalamus.

Conclusion: Overall, we found no difference in trigeminal perception or pain thresholds for cold or warm stimuli between episodic or chronic migraine patients and healthy subjects. Collectively, cluster analysis of QST results disclosed ‘hypersensitive’ and ‘hyposensitive’ subgroups. When compared to their counterparts, ‘hypersensitive’ subjects had decreased metabolism in key pain processing regions of the CNS, but these regions differed between migraine patients (brainstem, thalamus) and healthy volunteers (somatosensory and cingulate cortices). This suggests that individual pain sensitivity is controlled by cortical pain matrix areas in healthy subjects, but that this control shifts to subcortical structures in episodic and chronic migraine patients. Acknowledgements: This work was supported by the EUROHEADPAIN project, FP7-602633

Objectives: Increased electroencephalographic (EEG) photic driving amplitude (PD) is reported in migraine patients and has been interpreted as a sign of cortical hyper-responsiveness. However PD amplitude may be overestimated and differs throughout the migraine cycle. Hence, increased and decreased PD has been reported during peri-ictal and inter-ictal phases, respectively. The higher discriminating power of PD is usually seen around 20–25 Hz. In this study, we aimed to investigate whether a conditioning photic stimulation influenced the PD power of the following stimuli at different phases of migraine.

Methods: Eighty-one subjects underwent a standard 20-channel EEG (Nicolet, NatusMedical) with intermittent photic stimulation influenced the PD power of the following stimuli at different phases of migraine.

Results: PD to 5 Hz stimuli was similar between HV and all EM subgroups. The conditioning stimulus at 10 or 20 Hz did not change the power of the following PD in HV for the parietal, occipital and temporal electrodes (p = 0.4, p = 0.6, p = 0.9, respectively), nor in EM in ictal or inter-ictal phases. Conversely, in EM peri-ictal phase, PD power significantly decreased after a conditioning stimulus of 10 Hz, but not of 20 Hz. Thus, after the conditioning stimulus at 10 Hz, the values were respectively 0.035 ± 0.012, 0.027 ± 0.016, 0.042 ± 0.010, 0.036 ± 0.015, 0.028 ± 0.013 and 0.027 ± 0.007 V^2. Hz-1 (p = 0.01, p = 0.03, p = 0.004, p = 0.004, p = 0.03, p = 0.002, respectively).

Conclusion: Photic driving can be modulated by a conditioning photic stimulus in proximity of a migraine attack. This preliminary result suggests that visual cortical processing may be differently influenced by external sensory stimulations during this phase of migraine. More patients are being included to confirm these findings, and especially to compare pre-ictal to post-ictal phases.

References

Disclosure of Interest: None Declared

Headache Pathophysiology - Imaging and Neurophysiology

PO-01-017

Whole-brain resting state default mode network connectivity during spontaneous migraine attacks

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Objectives: The default mode network (DMN) is composed by a set of brain regions including medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), and parietal lobe (PL). Disruption of the integrity of DMN connectivity has been previously observed in migraine between attacks. Here we aimed to investigate whole-brain resting state DMN connectivity during spontaneous untreated migraine attacks.

Methods: Thirteen patients with untreated migraine without aura (MI) underwent 3T MRI scans during the initial 6 hours of a spontaneous migraine attack and were compared to the scans of a group composed of 19 healthy volunteers (HV). Using a seed-based approach, we collected resting state data in the abovementioned regions of the DMN. Thereafter, we collected whole-brain connectivity patterns with the seeds representing DMN (conjunction analysis).
Results: There was greater correlation in MI than in HV between regions associated with DMN, including MPFC, PCC, and PL. The conjunction analysis revealed common activation between i) MPFC and left inferior frontal cortex (pars triangularis), left dorsal posterior cingulate cortex, and left associative visual cortex; ii) right PL and bilateral somatosensory association cortices, and left associative visual cortex.

Conclusion: To summarize, we documented associations between DMN and brain regions involved in multimodal brain processing, including visual, somatosensory, and verbal during spontaneous migraine attacks. Whether present findings are related to the ictal migraineurs abnormal sensory perception, such as photophobia and allodynia, and to the ictal drop in verbal fluency remains to be determined.

Disclosure of Interest: None Declared

Headache Pathophysiology - Imaging and Neurophysiology

PO-01-018

White matter lesions in chronic migraine are not associated with changes in pulsatility index

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Objectives: White matter lesions (WML) are more prevalent in migraine; it seems that mainly with a high attack frequency. A vascular etiology has been proposed, but their pathogenesis and clinical significance remains unknown. Pulsatility Index (PI) reflects the vascular resistance and an increase of PI is a marker of structural changes of the small vessels due to lipohyalinosis and microatherosclerosis. White matter lesions (WML) are more prevalent in migraine; it seems that mainly with a high attack frequency. A vascular etiology has been proposed, but their pathogenesis and clinical significance remains unknown. Pulsatility Index (PI) reflects the vascular resistance and an increase of PI is a marker of structural changes of the small vessels due to lipohyalinosis and microatherosclerosis. The aim of this study is to determine whether differences in PI can be used as an indirect marker of an ischemic nature for WML found in cranial MRI studies of chronic migraine (CM) patients.

Methods: This series includes 91 CM women. PI was measured on transcranial Doppler in both middle cerebral arteries (MCA), posterior cerebral arteries (PCA) and in the basilar artery (BA) according to Gosling’s formula. MRIs were acquired on a 1.5T unit following the CAMERA protocol.

Results: A total of 58 CM patients (46.8 ± 10.1 years) had WML, whereas 33 (35.6 ± 12.0 years) did not. Except for age (p < 0.001) the rest of clinical features and comorbidities -including aura, vascular risk factors and acute/preventive treatments- were similar between both groups. PI was within range in all arteries examined. In patients with WML, mean PI was: MCA 0.888 ± 0.141, PCA 0.886 ± 0.143 and BA 0.852 ± 0.144. In patients without WML, mean PI was: MCA 0.912 ± 0.126, PCA 0.938 ± 0.162 and BA 0.876 ± 0.116. There were no differences in mean PI in any of the arteries explored (MCA p = 0.265, PCA p = 0.155, BA p = 0.636) for patients with and without WML.

Conclusion: There were not differences in PI values in the different arteries explored according to the presence or not of WML. These findings argue against an ischemic nature of these lesions in migraine patients.

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Headache Pathophysiology - Imaging and Neurophysiology

PO-01-019

Cerebral metabolism changes measured with PET-FDG in medication overuse headache before and after withdrawal

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Objectives: To evaluate cerebral metabolism in patients with medication overuse headache (MOH) before and after analgesic withdrawal.

Methods: We included adults who fulfilled ICHD-3beta criteria for chronic migraine and MOH who were not
taking any migraine preventive treatment or other neurologic/psychiatric medication. We included control subjects without personal or familiar headache history. We collected clinical data and performed a baseline PET-FDG and 6 weeks after analgesic withdrawal. Images were uploaded to a reference atlas to obtain a mean metabolism value for 30 cerebral regions. We performed statistical analysis comparing controls with MOH patients and a paired sample test to compare values before and after withdrawal.

**Results:** We included 11 women; 9 completed the withdrawal protocol. The mean age was 50.8 ± 6.8 (38–62) and the intake of acute medication was 28.2 ± 2.7 (24–30) days/month and 51.4 ± 26.6 (24–90) pills/month. All subjects did a successful withdrawal with a statistical significant change in the number of headache and acute medication intake days and number of pills/month.

Compared to controls, MOH subjects showed an initial global hypometabolism that was more significant in cerebral anterior areas (right/left): precentral gyrus ($p = 0.002/p = 0.012$), olfactory ($p = 0.015/p = 0.020$), frontal superior ($p = 0.020/p = 0.019$), rectus gyrus ($p = 0.005/p = 0.010$) and insula ($p = 0.009/p = 0.007$). After analgesic withdrawal there was a global trend towards normalization of cerebral metabolism but no individual significant differences were found; the areas that maintain hypometabolism compared to controls were precentral gyrus ($p = 0.011/p = 0.047$), rectus gyrus ($p = 0.009/p = 0.016$) and insula ($p = 0.021/p = 0.017$).

**Conclusion:** Medication overuse is associated with fronto-temporal cerebral hypometabolism which normalizes after 6 weeks of withdrawal except in the precentral, rectus gyrus and insula areas.

**Disclosure of Interest:** None Declared

**Headache Pathophysiology - Imaging and Neurophysiology**

**PO-01-020**

**Nitroglycerin triggering as a human migraine model in clinical research**

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**Objectives:** Exogenous triggering with substances such as nitroglycerin (NTG) has been developed to enable migraine attacks to be studied in a predictable and reproducible fashion. We aimed to study NTG triggering of migraine attacks, with a view to phenotyping these compared to spontaneous attacks and imaging them using functional MRI.

**Methods:** Potentially eligible subjects were telephone screened, invited to a screening appointment and recruited following informed consent, a detailed migraine history, reassessment of eligibility, clinical observations, an electrocardiogram, a pregnancy test if applicable and a physical examination. All subjects were aged 18–50 years of age, with a migraine diagnosis and between 0–22 days of headache a month and no contraindications to NTG or any of the study drugs.

Each eligible subject was exposed to a 0.5 mcg/kg/min NTG infusion over 20 minutes. The phenotype and timeline to development of migraine symptomatology following triggering was documented. Migraine headache was defined as moderate-severe headache occurring after the completion of the NTG infusion with associated symptomatology that the subject would usually associate with a migraine. Migraine headache was treated in all subjects with intravenous aspirin 1 g or subcutaneous Sumatriptan 6 mg.

The association between baseline migraine diagnosis (episodic vs. chronic) and effectiveness of NTG triggering migraine headache was analysed using the Chi-squared test. Binary logistic regression was used to analyse the association between headache days and successfulness of triggering. $P < 0.05$ was considered significant.

**Results:** Forty-nine (9 males) subjects were recruited. The age range was 18–50 years (mean 36 years). MIDAS scores ranged between 0 and 201 (median = 22). The monthly baseline headache frequency ranged from 0–22 days (median = 8). Subjects with more than 22 headache days per month were excluded from the study, due to the high risk of having a spontaneous headache on study visit days. Of the 49 subjects, 25 had episodic migraine with aura (EMA), 19 had episodic migraine without (EMO) and 5 had chronic migraine (CM).

Migraine headache was successfully triggered in 40 subjects (82%). Aura was triggered in 4 subjects. There was a trend towards a statistically significant association ($p = 0.061$) between effective triggering and chronic migraine versus episodic. All 9 subjects who did not trigger a headache with NTG had episodic migraine with monthly headache days ranging from 0–10.

Using binary logistic regression, the model correctly calculated which subjects would trigger in 82% of cases ($p = 0.039$). The relationship between headache days at baseline and the successful triggering of headache using NTG showed a trend (OR = 1.184, 95% CI 0.989–1.147, $p = 0.066$). Inclusion of age of the subjects did not add to this model.
Conclusion: NTG is an effective migraine trigger. Successful triggering may be related to a threshold effect, associated with baseline headache frequency.

Disclosure of Interest: N. Karsan Conflict with: Dr Karsan is an Association of British Neurologists/Guarantors of Brain Clinical Research Training Fellow, P. Bose: None Declared, C. Thompson: None Declared, P. Goadsby Conflict with: Dr. Goadsby reports grants and personal fees from Allergan, Amgen, and Eli-Lilly and Company; and personal fees from Akita Biomedical, Alder Biopharmaceuticals, Autonomic Technologies Inc, Avanir Pharma, Cipla Ltd, Colucid Pharmaceuticals, Ltd, Dr Reddy’s Laboratories, eNeura, Electrocore LLC, Novartis, Pfizer Inc, Promius Pharma, Quest Diagnostics, Scion, Teva Pharmaceuticals, Trigemina Inc., Scion, Conflict with: personal fees from MedicoLegal work, Journal Watch, Up-to-Date, Oxford University Press; and in addition, Dr. Goadsby has a patent Magnetic stimulation for headache pending assigned to eNeura.

Headache Pathophysiology - Imaging and Neurophysiology

PO-01-022

Brain Functional Connectivity Investigation of Patients with Migraine based on Complex Networks Analysis

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Objectives: Using graph theory to construct the resting-state brain complex networks, the topological structure differences of the functional networks between the migraine patients group (MP) and the normal control group (NC) were investigated in this study.

Methods: We firstly acquired the resting-state functional magnetic resonance imaging dataset from 22 migraine patients and 22 normal subjects, respectively. Then, the functional complex networks of the two contrast groups were constructed, and some essential measures such as the average clustering coefficient, characteristic path length, small worldness, assortativity, and betweenness of these two groups were calculated, respectively. Lastly, two sample T test (P = 0.01) on these measures regarding to the two groups were performed to detect the differences statistically.

Results: Compared with NC, the average clustering coefficient of MP group is larger; the topology measures, i.e., small worldness and assortativity, are also changed; the characteristic path length of the nodes such as the caudate nucleus and putamen areas present abnormality; Betweenness centrality as to part of the regions, i.e., the thalamus, inferior occipital gyrus and occipital gyrus, demonstrates obvious increase.

Conclusion: The abnormal brain regions statistically occurred in MP group, were mainly associated with pain processing, visual processing and sensory information.
relay, which contribute to better understanding and interpretation of the related clinical condition of migraine.

**Disclosure of Interest:** None Declared

**Headache Pathophysiology - Imaging and Neurophysiology**

**PO-01-023**

High brain serotonin levels in migraine between attacks: A 5-HT4-receptor binding PET study

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**Objectives:** To investigate brain 5-HT4-receptor binding with positron emission tomography (PET) as a proxy of serotonin (5-hydroxytryptamine, 5-HT) levels in migraine patients between attacks.

**Methods:** Brain 5-HT4-receptor binding, assessed with PET imaging of the specific 5-HT4-receptor radioligand, [11C]SB207145, is inversely related to long-term changes in brain 5-HT-levels. Eighteen migraine patients without aura (≥48 hours migraine free) and 16 age- and sex-matched controls underwent PET-scanning after injection of [11C]SB207145. Patients who reported a migraine attack ≤48 hours after the scan were excluded. The mean neocortical [11C]SB207145 binding potential (BPND) was calculated in a blinded manner.

**Results:** Fifteen patients (age 29.6 ± 10.2 years, 2 men) and 16 controls (28.9 ± 10.2 years, 3 men) completed the study. Migraine patients had significantly lower neocortical 5-HT4-receptor binding than controls (0.62 ± 0.09 vs. 0.68 ± 0.05, p = 0.024). We found no associations between 5-HT4-receptor binding and clinical migraine characteristics.

**Conclusion:** Migraine patients have lower neocortical 5-HT4-receptor binding than controls, which may reflect a chronic or at least episodically high brain 5-HT-level. Our finding is in apparent contrast with the longstanding hypothesis of migraine being a syndrome of chronic low brain 5-HT-levels. We were unable to demonstrate any associations with attack frequency or years with migraine. This suggests that high brain 5-HT-levels may be a trait of the migraine brain rather than a consequence of migraine attacks.

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**Headache Pathophysiology - Imaging and Neurophysiology**

**PO-01-024**

Altered thalamic network connectivity during spontaneous attacks of migraine without aura: a resting-state fMRI study

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**Objectives:** To investigate brain functional connectivity by the resting-state functional magnetic resonance imaging (rsfMRI) during spontaneous migraine attacks

**Methods:** Seventeen migraine without aura patients reported at the hospital for a resting-state functional MRI scan during and outside of a spontaneous migraine attack. Primary endpoint was a difference in functional connectivity between the attack and the headache-free days. Functional connectivity was assessed using seed-based analysis in the FMRIB Software Library. The chosen seeds were located in the thalamus (MNI coordinates x,y,z: right, 22, −24,0 and left, −22,−28,6).

**Results:** We found increased functional connectivity between the right thalamus and several contralateral brain regions (superior parietal lobule, insular cortex, primary motor cortex, supplementary motor area,
orbitofrontal cortex and corticospinal tract). There was decreased functional connectivity between the right thalamus and three ipsilateral brain areas (primary somatosensory cortex, corpus collusum and premotor cortex). We found no change in functional connectivity in the pontine or the cerebellar networks.

**Conclusion:** The study indicates that network connectivity between thalamus and pain modulating as well as pain encoding cortical areas are affected during spontaneous migraine attacks. Thus, the incoming pain signals from the trigeminal afferents during a migraine attack may pass through thalamus without undergoing the normal control mechanisms.

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**Objectives:** Migraine is characterized by abnormal neuronal responsiveness and there is evidence that the brain could have neuronal networks’ properties, hence resilience mechanisms, to avoid attacks. Electroencephalography (EEG) has been widely used and processed to highlight those mechanisms, one of them being a synchrony between areas of the brain. In migraine, it had been shown previously that photic driving, ie the amplitude of the EEG response of the visual cortex to flicker stimuli above 20 Hz, was overall increased, mainly in preictal period. Whereas synchronization between brain areas has been investigated, phase lock within the same electrode has never been applied to EEG.

We hypothesize that higher frequency content (beta) of EEG signal may be less “locked” to lower frequencies (alpha), leading to hyperresponsiveness. This study aims to evaluate the nonlinearities in EEG rhythms and the bicoherence of resting phase EEG in healthy volunteers and episodic migraine patients, towards the identification of a novel electrophysiological biomarker of the migrainous brain.

**Methods:** Twenty-five healthy volunteers (HV, 36.9 ± 14.2 y.o., 88% F) and 41 patients with episodic migraine without aura (ICHD 3 beta 1.1, MO, 33.6 ± 12.2 y.o., 83.6% F) participated to the study. Twenty-three patients were in interictal phase whereas 18 patients were in peri-ictal phase, based on the presence of an attack within 72 hours of the recording. All participants underwent a standard 20 channel EEG (Nicolet, NatusMedical) while resting with eyes closed. EEG data were preprocessed for epoch extraction and artifact rejection. Then bicoherence was calculated on each channel, and its maximum value extracted between 4 Hz and 16 Hz. Ranksum test was used on mean bicoherence over a selection of 5 electrodes between groups and between HV/MO. Classification procedure was based on a polynomial regression (3rd order) on logarithmic transformed bicoherence, trained with 85% of values, and tested with the 15% remaining, with 1000 random selections of training/testing.

**Results:** Mean bicoherence was significantly lower (p = 0.0035) in migraine patients (0.249 ± 0.093) compared to HV (0.345 ± 0.136) but not significantly different between peri-ictal and interictal subgroups (p = 0.76). Bicoherence values successfully sorted out 71% of individuals in both MO and HV groups. Lower bicoherence in MO patients mirrored a deficit of synchronization between alpha band and its double frequency. This diminution of synchronization was able to successfully sort out patients, and could contribute to the subsequent photic driving observed in the literature.

**Conclusion:** This study suggests that spectral bicoherence of the electroencephalogram on resting phase is lower in migraineurs, whatever the migraine phase, and may be an additional interesting electrophysiological biomarker for migraine, besides the habituation of evoked potentials. More studies are warranted to confirm and disentangle this finding, and explore its pathophysiological significance.

**References**
1 Magis et al., 2007. Cephalalgia
We have examined 23 patients with chronic tension-type headache.

Objectives: The purpose of our study was to investigate the hemodynamic disturbances and changes of adaptation possibilities of cerebral vessels in patients with chronic tension-type headache.

Methods: We have examined 23 patients with chronic tension-type headache (CTTH). To evaluate the patients’ hemodynamics we took into consideration the indicators of linear velocity of blood flow (LVF) and indicators of reactivity of vessels in the system of the common carotid arteries. We obtained these data by using the method of Doppler ultrasonography with compression tests.

Results: It was detected that in the patients with CTTH all hemodynamic indicators before compression tests did not differ from healthy subjects. However, in the compression of carotid arteries the elevation of LVF to 49.2% was detected in the state of peace (to 38.4% in the control group, respectively). According to the indicators of changes of LVF in common arteries, the CO was 1.15 ± 0.01 (p < 0.01) and FA was 0.68 ± 0.02, respectively (p < 0.01), in the group of patients with chronic headaches of tension. Even with the minimum of compression time was observed paradoxical reaction of cerebral vessels.

Conclusion: In our opinion, these changes are the results of duration of chronic distress and compensatory muscle spasm which determine the type of headaches in combination with a vessels component.

Disclosure of Interest: None Declared

Headache Pathophysiology - Imaging and Neurophysiology

PO-01-027

Cognitive function performance of migraine in auditory event-related potential and functional magnetic resonance imaging

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Objectives: Migraine is a common and painful condition that affects many people, predominantly from young adulthood to middle age; the years of maximum work and family commitments. Although treatment guidelines were proposed for acute and preventive treatment of migraine, the pathogenesis of migraine was still uncertain. Recent studies showed learning disabilities and attention deficit disorder in children and adolescents with migraine were also noted and adult migraine patients often report cognitive complaints, especially regarding attention and memory. Cognitive function change in migraine patients was highly suspected. Because the migraine without aura (MoA) patients are more common, we selected MoA patients as experimental group. We hope to compare the difference of brain physiologic & cognitive function change between MoA patients and normal people by these non-invasive electrophysiologic & neuroimaging techniques [auditory event-related potential (ERP) and functional magnetic resonance imaging (fMRI)] and cognitive assessments [Mini-Mental State Examination (MMSE) and Wechsler Memory Scale-Third Edition (WES-III)]. This study showed some cognitive impairment in cognitive assessments, especially over recall memory and working memory. These cognitive changes could be compatible with some findings in electrophysiologic & neuroimaging techniques.

Methods: Nineteen migraine subjects (M/F = 5/14, age = 42 ± 10 y/o) and thirteen healthy controls (M/F = 5/8, age = 32 ± 9 y/o) who had no history of neurological disease participated in this study. All participants received MMSE (Folstein et al., 1975) & WES-III (Larrabee, 1999)
mental tests and auditory ERP & fMRI examinations. The auditory ERP and fMRI examination were performed during the ictal phase of the MoA patients. We used an auditory oddball paradigm to analyze target processing using event-related potentials and measured latency and amplitude of P300 target stimulus in P3, Pz and P4 three sites. We also compared the functional connectivity in resting-state fMRI (rsfMRI) between controls and MoA patients and analyzed the data according to Stanford University laboratory. All imaging data were acquired from a 3.0T MR scanner (Skyra, Siemens, Erlangen, Germany).

Results: Our results showed MoA patients have some cognitive impairment in the total score & recall score in MMSE and index scores & percentiles of working memory in WMS-III. More prolonged distal latency and reduced amplitude P300 target stimulus in the MoA patients. There was decreased functional connectivity in rsfMRI in basal ganglion, higher visual and primary visual networks of MoA patients.

Conclusion: These results suggested that patients with migraine might present higher risk of cognitive impairment and the auditory ERP & rsfMRI data provided an evidence of the cognitive dysfunction in these patients.

Disclosure of Interest: None Declared

Headache Pathophysiology - Imaging and Neurophysiology

PO-01-028
The ventilatory threshold is associated with migraine attacks after maximal exercise test in women with episodic migraine

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Objectives: To test the association between cardiopulmonary fitness and migraine attacks following a maximal exercise test in women with episodic migraine.

Methods: Patients with episodic migraine (ICHD-III), and no history of exercise-triggered attacks, were recruited from São Paulo Hospital and/or local community. Patients underwent a maximal cardiopulmonary exercise test on treadmill for determination of peak oxygen uptake (VO2peak), a gold-standard measure of cardiopulmonary fitness, and the ventilatory threshold (VO2VT), a cardiometabolic parameter of anaerobic metabolism and early fatigue. Patients’ cardiopulmonary fitness were categorized as “above fair”/“below fair” categories of the sex- and age-predicted classification of the American College of Sports Medicine for VO2peak, or alternatively, “above”/“below” group’s median for VO2VT. Headaches diaries were tracked for the 72 h after the exercise test, and occurrence of attacks were categorized as “<6 h”, “12 h–24 h”, “24 h–48 h”, “48 h–72 h”, and “No attack”, or “Yes/No”, for having attacks within the 72 h-period. Participants whose attacks were attributed to others triggers were excluded from analyses. UNIFESP’s Research Ethic Committee approved the study’s protocol, and all participants gave signed informed consent.

Results: Twenty-one patients (mean ± SD age: 35.4 ± 11.6 years, BMI: 26.4 ± 5) were included in the analyses. Sixty-seven percent (14/21) of patients had attacks within the 72 h-period. The majority of patients having attacks within the 72 h-period experienced them <6 h after maximal exercise test (38.1%). Most patients (62%) were within the cardiorespiratory fitness category “below fair” for VO2peak. There were no association between cardiorespiratory fitness for VO2peak and whether patients had or not attacks within the 72 h-period [χ2(2) = 1.875, p = 0.39]. However, there was an association between cardiorespiratory fitness related to the VO2VT and whether patients had or not attacks within the 72 h-period [χ2(2) = 8.472, p = 0.014], indicating that patients with below-medium VO2VT values were more likely to experience a migraine attack after maximal exercise test.

Conclusion: Cardiorespiratory fitness, specifically related to lower ventilatory threshold, is associated with migraine attacks after maximal exercise.

Disclosure of Interest: None Declared

Headache Pathophysiology - Imaging and Neurophysiology

PO-01-029
Peripheral vagal nerve stimulation modulates the nociceptive withdrawal reflex in healthy subjects: a cross-over placebo-controlled study

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Objectives: Peripheral non-invasive vagal nerve stimulation (nVNS) has become a target for the treatment of
primary headaches, though its exact mechanisms are unclear. Different studies showed that nVNS modulates both spinal and supra-spinal nociceptive pathways in an inhibitory direction. The nociceptive flexion reflex paradigm is widely used to investigate modulation of nociception and represents a reliable objective measure of the functional activation of the nociceptive network. The aim of our study is to evaluate the effect of nVNS on the nociceptive withdrawal reflex in healthy subjects.

Methods: We enrolled 10 healthy subjects (5 males, age 26.5 ± 2.2 years) in a cross-over placebo-controlled study. Subjects were randomly assigned to: 1) nVNS: one 120-s electrical stimulation on each side of the neck using the gammaCore nVNS device and b) active sham stimulation (SHAM): one 120-s electrical stimulation of the median nerve on each wrist using the same nVNS device. Nociceptive withdrawal reflex was evaluated in the right lower limb according to a standardized paradigm: electrical stimulation delivered at the sural nerve and electromyographic muscular response recorded from the ipsilateral biceps femoris. The reflex threshold following a single stimulus (RT-SS) was the lowest intensity (mA) needed to elicit a stable muscular response. The temporal summation of the nociceptive flexion reflex (RT-TS) was evaluated using a train of 5 stimuli at a frequency of 2 Hz. The other parameters recorded were the area under the curve, the latency of the reflex, and the Visual Analogue Scale (VAS) at RT-SS. Nociceptive withdrawal reflex was investigated at baseline (T0), 5' minute after stimulation (T5) and 30' after stimulation (T30).

Results: At T0 the neurophysiological parameters were comparable between groups. In particular RT-SS was 13.86 ± 3.67 and 16.15 ± 3.53 in nVNS and SHAM groups, respectively (p = 0.086), while RT-TS was 11.0 ± 2.79 in nVNS group and 12.64 ± 3.67 in SHAM group (p = 0.107). nVNS caused a significant increase in the RT-SS at T5 (+14.5% ± 4.2, p = 0.023) and T30 (+25.9% ± 6.6, p = 0.011). Also RT-TS increased following nVSN at T5, but statistical significance was only reached at T30 (+21.7 ± 6.7, p = 0.031). SHAM stimulation did not induce any significant modification on the reflex parameters. When comparing groups, we found that the percentage increase of RT-SS at T5 and T30 was significantly higher in nVNS vs. SHAM (p = 0.008 and p = 0.007 respectively). Accordingly the percentage increase of RT-TS at T30 was significantly higher in the nVNS arm vs. SHAM (p = 0.013). We did not observe any significant modification of the other parameters in either group.

Conclusion: Using a consolidated neurophysiological methodology, we have demonstrated that nVNS induces a rapid onset of analgesia in healthy subjects. Because of its neurophysiological signatures, this analgesic activity is likely related to the inhibition of pain facilitation mechanisms occurring at the spinal and/or supra-spinal level. The mechanistic bases of this activity are yet to be elucidated, but the present observation provides additional evidence for the role of nVNS in the acute and prophylactic treatment of primary headaches.

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Headache Pathophysiology - Imaging and Neurophysiology

PO-01-030
Processing of mechanical and nociceptive trigeminal input at brainstem-level – an fMRI-study

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Objectives: The trigemino-autonomic reflex is a physiological response to trigeminal nociceptive input leading to parasympathetic outflow. The afferent limb of this reflex arc consists of the trigeminal nerve, and the efferent limb comprises the facial/greater superficial petrosal nerve (parasympathetic) dilator pathway. Autonomic symptoms play an important role in cluster headache (CH) and are a hallmark in trigeminal autonomic cephalalgias (TACs). The brainstem plays a major role in processing and the modulation of trigeminal input during attacks of various primary headaches. The question arises which brain regions are involved in processing different types of trigeminal input, generating cranial autonomic output. Therefore we investigated the neural correlates of processing mechanical input into the trigeminal system, using a new stimulation method combined with a well-established brainstem functional magnetic resonance imaging (fMRI-) protocol.

Methods: Kinetic oscillation stimulation (KOS) of the nasal mucosa generates predominantly ipsilateral autonomic symptoms among which lacrimation is quantitatively measurable. The KOS-paradigm was applied to 31 healthy volunteers (12 f, 19 m). For the stimulation-procedure an inflatable catheter was placed into the left nostril, which oscillated during stimulation (85 Hz/80 mbar). Each of the 21 trials consisted of 30 s of stimulation interleaved with resting periods of 90 s duration (jittered +/-10 s). After each trial pain perception and unpleasantness were assessed by a visual analogue scale (VAS). Altogether 23 participants, perceiving no or only moderate pain during the experiment, were included in the General Linear Model based fMRI-analysis. We controlled for...
physiological noise including pulse, respiration, movement and flow of cerebrospinal fluid (CSF).

Results: Lacrimation was significantly generated during stimulation. The fMRI-analysis showed stronger activation \((p < 0.001 \text{ unc; minimum cluster extent of 10 voxel})\) during stimulation compared to rest within the brainstem, the thalamus and bilateral insular cortices. Left and right amygdala as well as the hippocampus were stronger activated during rest compared to stimulation. Some volunteers reported moderate pain for some trials. For pain-trials we observed increased activations in the brainstem, the thalamus, putamen, bilateral insula and in the frontal operculum compared to non-pain trials.

Conclusion: Various brain regions including the brainstem, insula and the thalamus become activated during processing of a non-painful input into the trigeminal system and the generation of parasympathetic output. Furthermore, we observed that processing at brainstem-level of a mechanical input into the trigeminal system differs from processing of a nociceptive input. These findings contribute to the physiological insights of the trigemino-autonomic reflex arc that plays a crucial role in TACs.

Disclosure of Interest: None Declared

Headache Pathophysiology - Imaging and Neurophysiology

PO-01-031

No association between migraine frequency and brain lesions: a study in a series of chronic migraine women

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Objectives: Several 1.5 T MRI studies suggest that silent infarctions (SI) and hyperintense white matter lesions (WML) are more frequent in migraineurs with a high frequency of attacks. Our aim was to study their prevalence in chronic migraine (CM).

Methods: A total of 96 CM women, and as controls 29 episodic migraine (EM) women, underwent a 1.5 T MRI following the CAMERA protocol. Images were evaluated independently by two expert radiologists who were blind to the diagnosis.

Results: WML were found in 59 (61.5%) of CM and in 17 (58.6%) of EM patients. The majority (63% for CM and 71% for EM) were located in the deep white matter. Exclusive periventricular location was exceptional (2 CM cases and none EM). Regarding deep WML, the average was 7.7 (limits 0–177) in CM and 3.2 (0–27) in EM \((p = \text{NS})\), most of of small size. Of the 739 WML found in CM patients, 734 (99.3%) were hemispheric and among these frontal lesions were the most common (81%). Posterior fossa WML were seen, always in the pons, in 5 (0.7%) CM and in 2 (2.1%) EM women. Age >45 was the only vascular risk factor (VRF) correlating with a higher number of WML. We found 7 SI in 6 CM women (6.3%); 4 in the basilar territory with only one in the cerebellum. At least 2 VRFs were seen in 5 of these 6 CM patients.

Conclusion: This study confirms that the prevalence of WML, in most cases small, deep and in the anterior hemisphere, is increased both in CM and EM (61.5% and 58.6% vs. the 10% expected in the population at this age) and does not support an association of such lesions or SI with a higher frequency of attacks, but with the presence of FVRs and mainly age >45.

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Disclosure of Interest: None Declared
beta (12–30 Hz), low–gamma (30–55 Hz), high–gamma (65–90 Hz), ripple (90–200 Hz), high-frequency oscillations (HFOs, 200–1,000 Hz) and very high-frequency oscillations (VHFOs, 1,000–2,000 Hz). Magnetic source power was quantified for each group.

**Results:** Compared with eyes-open, eyes-closed was associated with significant increases of alpha (8–12 Hz) and beta (12–30 Hz) activities, and was also associated with significant decreases of delta (1–4 Hz), theta (4–8 Hz), low-gamma (30–55 Hz) and high-gamma (65–90 Hz) in both the migraine and control groups. Compared with eyes-closed, eyes-open was associated with significant increases of source power in ripples (90–200 Hz), HFOs (200–1,000 Hz) and VHFOs (1,000–2,000 Hz) in the migraine group, but not in the control group.

**Conclusion:** The results demonstrated that migraine subjects had altered brain activities in multiple frequency bands during eyes-open and eyes-closed states as compared with controls. The significant increases of high frequency brain activities at eyes-open status in migraine might be related to migraine headache attacks, which could explain why some migraine subjects like to stay in a dark place to keep eyes-closed. Though the underlying mechanisms remain unknown, it might be associated with an aberrant visual processing or aberrant resting state activation. The findings may facilitate the development of new therapeutic strategies in migraine treatment in the future.

**Disclosure of Interest:** None Declared

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**Objectives:** Primary headache is a common complaint of general population. Both cluster headache (CH) and migraine are considered as disabling primary neurovascular headache disorders which are severe and moderate to severe in intensity accompanied by autonomic symptoms. The pathogenesis of these disorders is not well understood.

**Methods:** Functional MRI plays an important role in revealing headache mechanism. In our studies, the resting-state fMRI was used to investigate the altered functional connectivity in patients of disabling primary headache including CH, episodic migraine (EM), chronic migraine (CM), and medication overuse headache (MOH) so that to reveal possible pathogenesis of these disorders.

**Results:** Our results demonstrate that decreased functional coactivation was detected between bilateral hypothalamus and the salience network (SN) in CH patients of either side headache, altered functional connectivity architecture of marginal division of neostriatum and amygdala in EM, CM and MOH patients.

**Conclusion:** These results suggest that abnormal hypothalamus–SN coactivation may have a role in CH attacks, and altered functional connectivity of affective emotional processing and cognitive processing network may play an important role in development of migraine chronicization.

**Disclosure of Interest:** None Declared

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**Objectives:** To identify the presence of myofascial trigger points in the descending trapezius muscles by MRI.

**Methods:** A cross-sectional analytic study was conducted among 14 women aged between 18 and 28 years (23 ± 1 yrs), divided into two groups (8 migranous and 6 control without headache) carried out between December 2013 and November 2014. The study was approved by the Research Ethics Committee of the Health Sciences Center of the Federal University of Pernambuco (CAAE 23792613.0.0000.5208). The patients underwent a neurological examination for diagnosis of migraine according to ICHD III, beta version. The presence of myofascial trigger points was performed using the Simons’ criteria and subsequently the areas were marked by linolenic acid capsules. MRI was performed with 1.5 T, T1-weighted sequence and T2 in the axial, sagittal and coronal planes. Gadolinium contrast was used.

**Results:** The MRI did not show any signal of alterations in the myofascial trigger points area.

**Conclusion:** The results of previous work show alterations of signals in the areas with trigger points using MRI (Landgraf et al., 2015) as well as in ultrasound imaging (Sikdar et al., 2009). In contrast, in our study MRI did not identify any abnormalities at the sites where the trigger points were palpated.

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**Disclosure of Interest:** None Declared

**Migraine Acute Therapy**

**PO-01-035**

A prospective, randomized, single blind, parallel-group, placebo controlled clinical study to evaluate the short-term effectiveness of combined occipital and supraorbital transcutaneous nerve stimulation (OS-TNS) in treating migraine

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**Objectives:** Combined occipital and supraorbital nerve stimulation (OS-TNS) has previously shown promising results in treating migraine, but this intervention was only available with implanted systems. This study is the first to assess the safety and efficacy of a non-invasive OS-TNS device for acute treatment of migraine.

**Methods:** We undertook a randomized, single-blind, parallel-group, sham-controlled study at the headache clinic of “Meir” general hospital in Israel. Forty (40) adults suffering from episodic migraine, aged 21–62 years, were enrolled. All individuals met the international criteria for migraine. Subjects were randomly allocated keeping 1:1 ratio to receive active (N = 20) or sham occipital and supraorbital stimulation (N = 20) for 45 minutes. Treatment initiated at no more than 90 minutes after the onset of the migraine episode. Ten (10) subjects were excluded from the trial due to protocol exclusion criteria or inability to coordinate an intervention meeting. The primary endpoint was defined based on relative change (%) in VAS pain score from baseline to end of treatment without using pain medication.

**Image:**

![Graph showing relative change in VAS pain score](image)

**Results:** 30 patients treated one acute migraine episode with active OS-TNS device (N = 15). At the end of treatment there was a significant reduction of the average Pain VAS score in the treatment group vs. an increase in Pain VAS score in the control group (−79.2% vs. +14.9%, respectively; P = 0.0002). Pain-free response rates significantly favored the active OS-TNS device at 2 hours (P = 0.0031) and at 24 hours (P < 0.05) post treatment. Superiority of the OS-TNS device was also shown for functional disability (P = 0.0004) and photophobia (P = 0.002). No device-related serious adverse events were recorded.

**Conclusion:** The results of this study demonstrate that combined occipital and supraorbital transcutaneous nerve stimulation (OS-TNS) is a safe and highly effective abortive treatment of episodic migraine and may serve as a superior, fast acting, adverse effects free alternative to medications.

**Disclosure of Interest:** None Declared

**Migraine Acute Therapy**

**PO-01-036**

**Acute Therapy against Migraine with Kanpo Medicine (Japanese Traditional Medicine, derived from natural herbs)**

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**Objectives:** Goreisan (Poria Powder with Five Herbs; GR) and Goshuyuto (Evodia Decoction; GS) are well-known Kanpo medicine against migraine. Kanpo medicine has been derived from natural herbs, so we can apply to any kinds of patients, such as children, adolescents, pregnant women, breast-feeding mothers, elderly patients, and even dialysis patients as well. On the other hand, it is difficult for general practitioners to decide which Kanpo medicine would be suitable for each migraine, besides effectiveness of single dosage of GR or GS alone has been reported around 50%. We have investigated effectiveness of combination therapy of GR and GS for acute splitting headache.

**Methods:** Subjects are patients with acute splitting headache who had visited our clinic in 2015. Cases having focal signs, meningeal signs, frequent vomiting, or high fever were excluded, therefore 139 patients were eligible for this study. Subject age: 5 y. o. – 75 y. o. (31.8 ± 17.6 y. o. median 33). Female/male = 106/33. All patients were given orally GR and GS simultaneously. Numerical Rating Score (NRS) of each headache had been obtained 10 minutes after intervention.

**Results:** GR and GS have shown effective in 119 patients (85.6%) within 10 minutes. NRS 0–3/10; 58 cases. NRS
4–5/10; 47 cases. NRS 6–8/10; 14 cases, who had given another GR and GS 15 minutes later after first intervention, subsequently all NRS of this group had dropped below 3/10 after second intervention. Cases of non-responders (n = 20); Dissection of left vertebral artery found by MRA. Brain tumor found by MRI. 2 cases of Sinusitis found by MRI or CT. Cervical disc herniation found by a plastic surgeon. 6 cases of mental disorders. 7 cases of idiopathic. As to residual 2 cases, one was effective to triptan, the other was effective to second intervention with GR and GS despite of first intervention failure.

Conclusion: Combination therapy of GR and GS is mostly effective against primary headache. This method could triage secondary headache for all generation safely and quickly, suggesting could be very useful for general practitioners but also emergency physicians.

Disclosure of Interest: None Declared

Migraine Acute Therapy

PO-01-037

Emergency care of migraine at a community hospital in Japan

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Objectives: Fifteen years have passed since we became able to use triptan for treating migraine. Subcutaneous injection of sumatriptan is recommended for acute medical treatment of migraine. We give subcutaneous injections of sumatriptan for patients who visit emergency department with severe migraine on holidays or during nighttime. But it is often difficult to make correct diagnosis of migraine at the emergency room by physicians who are not used to diagnosing migraine. In our hospital, emergency medical care of headache patients is conducted by rotating physicians from neurology, neurosurgery and emergency department. In this study, we analyzed patients with migraine who received sumatriptan by subcutaneous injection at our emergency clinic.

Methods: Ota Memorial Hospital is a core hospital accepting emergency patients all day from a medical area with a population of 400,000. In this retrospective study, patients with headache who visited emergency room were extracted from the electronic medical record system during the year of 2016 (January to December). We collected the record of patients with severe migraine who received diagnosis of migraine and received sumatriptan injection. Emergency headache care was performed by mostly by physicians who are not headache specialist. We asked patients if they had visited primary care physicians for their headache before visiting emergency room. We followed the prognosis of patients who were diagnosed as migraine and received injections of sumatriptan for the first time in life at the emergency clinic.

Results: A total of 608 patients visited our emergency room with headache. Subarachnoid hemorrhage (SAH) was 63 (10.4%), migraine 42 (7.0%), meningitis/encephalitis 21 (3.5%), shingles 1, neuralgia 4, headache other than migraine 106 (17.4%) and head injury (head bruise) 372 received emergency medical care at our hospital. Thirty-seven patients with severe migraine, 4 men and 34 women with the mean age of 36.1 years received the diagnosis of migraine by physicians of emergency room. All the patients with severe migraine received subcutaneous injection of sumatriptan. Nineteen patients were diagnosed by neurologist, 11 patients were diagnosed by neurosurgeon, and 7 patients were diagnosed and treated by emergency department physicians. Except for 2 patients, 42 migraine patients had headache improved with sumatriptan subcutaneous injection and returned home. Among patients with migraine, 21 patients visited the emergency room between 5 pm and 0 am. Nine patients visited between 0 am and 9 am. Eight patients visited on Saturdays and holidays. Nine patients came by ambulance. Fifty-nine percent of patients with severe migraine had never visited physician for headache and never diagnosed as migraine before their emergency room visit. Eighty-four percent of patients with severe migraine had no family doctor and had not received medical treatment for headache.

Conclusion: Most of the patients who visited our emergency clinic for severe headache had never consulted primary care physicians for headache before. Diagnosis of such patient was not only SAH (10.4%), but also migraine (as much as 7% of all the headaches at emergency clinic). Making diagnosis of migraine and treating by the injection of sumatriptan were performed properly. We re-realized the importance of headache care at the emergency practice. It is particularly important to educate rotating physicians to the emergency clinic about emergency migraine care. Our study also emphasized the importance of educating patients to consult primary care physicians for headache. Patient should be able to tell the diagnosis of migraine to the physicians of emergency clinic, which will make the emergency headache care more efficient. Our study promoted our community to establish a patient referral system.

Disclosure of Interest: None Declared
Migraine Acute Therapy

PO-01-038
Opioid Use is Related to Headache Frequency and Severity at Follow-Up in Patients with Intractable Migraine
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Objectives: Negative consequences of the overuse of opioids in headache can often include dependence, treatment interference, and the development of medication overuse headache. In addition, some evidence has suggested that opioid use may be related to poorer long-term outcomes in headache sufferers. To further explore this, we examined the relationship between opioid use and headache outcomes in patients with intractable migraine. The aim of this study was to examine the relationship between opioid use and headache frequency and severity over time in patients with intractable migraine.

Methods: The initial sample at baseline assessment included 49 adults presenting to an outpatient specialty headache clinic who reported having experienced headache pain every day within the past month and reported taking opioids on 10 or more days per month for at least three months. At baseline patients were advised to refrain from using opioid medication and adhere to treatment as usual. At three subsequent follow-up points (i.e., 1–3 months; 3–4 months; 6–8 months) current opioid use, headache frequency (i.e., number of headache days within the past month) and severity (i.e., number of headache days with severe pain) were assessed via patient self-report.

Results: At the time of the first follow-up, data was available from 35 patients who had not continued to take opioids on 10 or more days per month for at least three months. At baseline patients were advised to refrain from using opioid medication and adhere to treatment as usual. Future research in this area will benefit from a larger sample size to corroborate these findings. In addition, extraneous factors related to outcome in headache sufferers should be addressed.

Disclosure of Interest: B. Torphy Conflict with: Avanir Pharmaceuticals. J. Babione: None Declared

Migraine Acute Therapy

PO-01-039
Characterization of several adenosine A2A receptor antagonists using an in vivo pharmacological model of migraine
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Objectives: Migraine pathophysiology is associated with activation of the trigeminovascular system and cranial vasodilatation. Adenosine is a potent cerebral vasodilator (through A2A receptors) that increases in plasma during migraine attacks. Blockade of this receptor could represent a new antimigraine target. The present study investigated the role of five adenosine A2A receptor antagonists in relation to neurogenic sensorial vasodilatation.

Methods: A rat closed cranial window was used to study in vivo vasodilatation of the middle meningeal artery in response to exogenous CGS21680 (A2A agonist) or endogenous CGRP (released by periarterial electrical stimulation), in the absence or presence of one of five A2A receptor antagonists JNJ6008A, JNJ1014A, JNJ3791A, JNJ8446A or JNJ5848A (0.3–10 mg/kg) with varying selectivity over the A1 receptor. Experiments were approved by the Erasmus University Medical Centre’s institutional ethics committee, in accordance with National Institute of Health guidelines.

Results: All antagonists tested blocked the in vivo vasodilatation of the middle meningeal artery in response to CGS21680, with the highest potency observed for the antagonists that also display affinity for the A1 receptor.
The antagonists did not affect vasodilatation induced by periarterial electrical stimulation.

**Conclusion:** Whereas the antagonists were effective in blocking A2A and, in certain cases, A1 receptors, as illustrated by the blockade of relaxations to CGS21680, A2A receptors do not appear to be involved in neurogenic sensory CGRP release induced by perivascular electrical stimulation. The therapeutic potential of adenosine receptor antagonists in migraine remains to be determined in clinical trials.


**Migraine Acute Therapy**

**PO-01-040**

**Comparative study on efficacy of a triptan agent alone and combination with anti-epileptic drugs for migraine seizure**

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**Objectives:** Although the guideline recommends administration of no-steroid inflammatory drugs (NSADAs) with a triptan agent at the same time, it was concerned that initiation of gastric ulcer and bronchitis asthma due to use of NSAIDs.

Many cases of serious non-responders to triptan agents in migraine seizures, which inhibits release of neuro-inflammatory protein from trigeminal nerve existed around cerebrovascular and abnormal extension of cerebrovascular, has potentially existed cephalic hypersensitive condition during migraine seizures. For these cases, regular use of anti-epileptic drug(s) as prophylactic medication with onset use of the triptan agent is common for the migraine seizures.

However, effect of only combination use of both the triptan agent and ant-epileptic drug in ongoing seizures in patients with serious migraine is remarkable in practice. Furthermore, use of anti-epileptic drugs which have long-term half-life period and don’t inhibit GABA at post-synaptic site relieves from a seizure experiencing for the following morning.

**Methods:** Under the circumstance, we conducted a small-group comparative study to evaluate clinical efficacy of combination of anti-epileptic drugs with rizatripan (10 mg per dose) at the same time for approximately thirty patients with serious migraine seizure from several kinds of aspect.

**Results:** Use of perampanel hydrate with a triptan agent for seizure at an initial day would avoid onset of further seizures at the following days rather than use of sodium valproate despite of no statistical significance between both groups (p = 0.09). Because it was deemed that there is discrepancy on pharmacokinetics between them. Co-administration of tripatn agent and perampanel 2 mg will be recommended in case of severe migraine attacks, and the efficacy of migraine relief continue over 72 hours.

**Conclusion:** To relief their seizures, our study was definitely demonstrated that combination of perampanel 2 mg with triptan agents would be sufficiently useful in advance.

**Disclosure of Interest:** None Declared

**Migraine Acute Therapy**

**PO-01-041**

**Pharmacological analysis of the inhibitory effects produced by moxonidine and agmatine on the sensory vasodepressor cgrpergic outflow in pithed rats**

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**Objectives:** Resistance blood vessels are innervated by perivascular sympathetic and sensory nerves, which modulate vascular tone. Sensory stimulation results in release of the vasodilator calcitonin gene-related peptide (CGRP). CGRP is also present in the trigemino-vascular system and plays a role in migraine pathophysiology. Currently, CGRP receptor antagonists and monoclonal CGRP antibodies are under clinical evaluation for the acute and prophylactic treatment of migraine. An additional antimigraine strategy could be the inhibition of CGRP release. In this respect, our group has shown that spinal (T9T12) electrical stimulation of the rat perivascular sensory CGRPerergic outflow results in vasodepressor responses that can be inhibited
by activation of prejunctural receptors to several biogenic monoamines.
The aim of this study is to investigate the role of imidazoline I_1 and I_2 receptors in the inhibition by moxonidine and agmatine of the vasodepressor responses produced by stimulation of the perivascular sensory CGRPergic outflow in pithed rats.

**Methods:** Male pithed Wistar rats were prepared for electrical spinal (T_9-T_12, 0.56–5.6 Hz; 50 V, 2 msec) stimulation of the CGRPergic outflow or i.v. bolus injections of α-CGRP (0.1–1 μg/kg) during i.v. continuous infusions of moxonidine (1, 3, 10 or 30 μg/kg-min) or agmatine (1000 or 3000 μg/kg-min). Animals were pretreated with the antagonists AGN192403 (I_1; 3000 μg/kg), BU224 (I_2; 300 μg/kg), rauwolscine (α_2; 300 μg/kg) or AGN192403 + rauwolscine. Experiments were approved by our institutional ethics committee, in accord with National Institutes of Health guidelines.

**Results:** The infusions of moxonidine and agmatine inhibited the vasodepressor responses induced by electrical stimulation, but not by exogenous α-CGRP, implying a prejunctural inhibition. This sensory inhibition was attenuated only by AGN19240, but not by BU224 or rauwolscine.

**Conclusion:** The inhibition of the CGRPergic outflow by moxonidine and agmatine involves prejunctural activation of imidazoline I_1 receptors on perivascular sensory nerves. While our findings should be confirmed in a trigemino-vascular model, our results obtained in a peripheral vascular model suggests the imidazoline I_1 receptors as a target for migraine treatment.

**Disclosure of Interest:** None Declared

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**Migraine Acute Therapy**

**PO-01-042**

**Current status of the primary headache cases in the urban one emergency hospital in Japan**

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**Objectives:** The international classification of headache disorders second edition published in 2004 has been classified a primary headache in four diseases, and the treatment method to satisfy the patients suffering from chronic headache has been proposed in that guidelines. Now, we are going to report the current status of primary headache cases in our hospital responsible for the urban emergency medical care.

**Methods:** We targeted this time for 90 cases of patients diagnosed primary headache after visiting our department with symptoms of headache from April 2014 to June 2015.

**Results:** Their age was 43 ± 18 years, and male was 36 cases, female was 54 cases. Transporting by ambulance was 62 cases (69%), and walk-in was 28 cases (31%). About their consultation day of the week, there are 13 cases in Monday, 17 cases in Tuesday, 17 cases in Wednesday, 14 cases in Thursday, 10 cases in Friday, 12 cases in Saturday, and 7 cases in Sunday. The 13 cases visited our hospital at 0–8 o’clock, 42 cases did at 8–16 o’clock, and 35 cases did at 16–24 o’clock. When they visited, Japan Coma Scale is I-0 in 68 cases, I-1 in 21 cases, I-2 in 1 case and head CT was performed under 69 cases (77%). We diagnosed migraine headache in 36 cases, tension-type headache in 43 cases, cluster and other trigeminal-autonomic headache in 5 cases, and the other primary headache in 6 cases. In 20 cases (22%), we required them hospitalization, and they consisted of migraine 10 cases, tension-type headache 6 cases, 3 cases such as cluster headache, and other in 1 case. Length of hospital stay was 3.8 ± 3.2 days. We performed the treatments by non-steroidal anti-inflammatory drugs in 65 cases, vasoconstrictor in 13 cases (through oral 9 cases, nasal 4 cases, and no subcutaneous injection), an anti-anxiety drugs in 5 cases, Kanpou in 1 case, oxygen in 5 cases, rest only in 19 cases, and other drugs in 7 cases (there were drug combination cases). Their symptoms revealed improvement after visiting our hospital in all cases, and we couldn’t admit death cases. Reconsultation by the same symptoms was seen in 4 cases (4%), and reconsultation cases within 24 hours after visiting hospital were not observed.

**Conclusion:** We reported 90 patients and current status of the primary headache cases in the urban one emergency hospital in Japan. Primary headache is so a disease that impairs extremely quality of the life of patients, accurate diagnosis and treatment are desirable when the symptoms appear. This time, it was relatively satisfactory results in our case.

**Disclosure of Interest:** None Declared

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**Migraine Acute Therapy**

**PO-01-043**

**Role of AMPA receptor phosphorylation in nitroglycerin-induced migraine headache**

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**Objectives:** Migraine is the third most common disease worldwide; however, the mechanisms underlying migraine headache are still not fully understood and current therapies for this type of pain are inadequate. AMPA receptor phosphorylation can promote the receptor trafficking and then enhance the switch from Ca\(^{2+}\)-impermeable to Ca\(^{2+}\)-permeable receptors in the central nervous system, thereby causing activity-dependent changes in synaptic processing of nociceptive information. In the present study, we used an established nitroglycerin (NTG)-induced acute migraine headache mouse model to investigate the effect of blockade of Ca\(^{2+}\)-permeable AMPA receptors in spinal trigeminal nucleus caudalis (Sp5C) on the development of migraine headache.

**Methods:** C57BL/6 male and female mice were used in this study. Intraperitoneal injection of NTG (10 mg/kg, i.p.) was carried out to induce migraine headache. Light-aversive behaviors (immediately following the NTG injection) and mechanical hypersensitivity (120 min after the injection) were measured using a light-dark box and von Frey filaments, respectively. 1-naphthyl acetyl spermine (NASPM), a selective Ca\(^{2+}\)-permeable AMPA receptor channel blocker, was administered to examine whether blockade of Ca\(^{2+}\)-permeable AMPA receptors affects NTG-induced migraine headache. In addition, Ca\(^{2+}\)-imaging was carried out to analyze Ca\(^{2+}\) activities in cultured brainstem neurons following the treatment with NTG and/or NASPM.

**Results:** Injection of NTG (i.p.) induced photophobia and decreased mechanical withdrawal threshold in both male and female mice. The NTG administration also increased AMPA receptor GluA1 phosphorylation at the Ser831 site in the Sp5C. Intra-Sp5C injection of NASPM (3 mM, 0.9 μl) significantly inhibited NTG-produced mechanical hypersensitivity, but had no effect on NTG-induced photophobia. In cultured brainstem neurons, NTG caused a robust Ca\(^{2+}\) influx, and the incubation of NASPM (5 μM) partially blocked the NTG-enhanced Ca\(^{2+}\) activities.

**Conclusion:** Our results suggest that AMPA receptor phosphorylation-enhanced switch from Ca\(^{2+}\)-impermeable to Ca\(^{2+}\)-permeable receptors in the Sp5C contributes to NTG-induced migraine headache.

**Disclosure of Interest:** Y. Tang: None Declared, S. Liu: None Declared, H. Shu: None Declared, Q. Bai: None Declared, Q. Lin: None Declared, F. Tao Conflict with: Supported by NIH/NIDCR Grants (R01 DE022880 and K02 DE023551).

**Migraine Acute Therapy**

**PO-01-044**

**Clinical Profile, Management Trends and Functional disability in Patients with Migraine: A Pan-India Cross-Sectional Study**

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**Objectives:** Migraine is the third most prevalent and seventh leading cause of disability worldwide. Despite high prevalence, there are no population based studies from India. This observational, cross-sectional pan study was conducted to understand the clinical profile, disease burden, and management trends in patients with migraine in India.

**Methods:** Patients (≥18 years) diagnosed with migraine based on clinical diagnosis/ICHD criteria were enrolled across 11 centers in India. Details on demographics, history, clinical pattern, comorbidities, treatment for acute attack and prophylaxis, Migraine Specific Quality of Life (MSQ) and Migraine Disability Assessment Score (MIDAS) were recorded.

**Results:** Of 705 patients enrolled, 81% were females and 19% were males. Mean age of the study population was 35.16 ± 11.09 years. Mean age of onset of migraine was 25.05 ± 8.54 years; mean age of onset was lower in patients in 18–40 years’ group (22.93 ± 6.03 years) compared with patients in 41–60 years (32.70 ± 9.64 years) and >61 years’ group (35.92 ± 14.51 years). Most common trigger for migraine attacks were stress (75%), lack of sleep (67%) and travelling (64%). Nearly half of the patients (54%) had migraine of moderate severity; 38% patients reported severe migraine. Most common drug for acute attacks of migraine was paracetamol (47%) followed by naproxen (13%) and sumatriptan (12%). Propranolol (51%) was the most common medication for prophylaxis of migraine followed by flunarazine (40%). Paracetamol was the most common rescue medication used along with the prophylaxis therapy. Higher proportion of patients had 4h to 72h duration of headache attacks (44%), 1 to 10 attacks per month (70%), pulsating type of headache (76%), and sensory symptoms (negative)
Nausea (65%), photophobia (63%), phonophobia (51%) and vomiting (46%) were the most common symptoms reported to be associated with migraine. Majority of the patients had MSQ score of 3 (some of the time) indicating that the patients sometimes felt that migraine was interfering while dealing with family and close friends (32%); sometimes felt that migraine was interfering while doing leisure time activities, such as reading or exercising (33%); had sometimes difficulty in performing daily activities (35%) and had limitations in concentrating on work or daily activities due to migraine (39%). The comorbidities reported were hypertension (7%), diabetes mellitus (3%), anxiety (2%), asthma (2%), and epilepsy and arthritis (1%).

Majority of patients (46%) had moderate disability with a total MIDAS score ranging from 11–20; severe disability was reported in 37.3% patients, with a total MIDAS score of 21+. Sleep/rest (64%) and meditation (22%) were the most commonly reported relieving factors from migraine associated headache.

**Conclusion:** The present study extends the body of literature characterizing treatment patterns, disorder characteristics, and disability profile in migraineurs in India. Consistent with published literature, this study also highlights a higher prevalence of migraine in women. NSAIDs remain the mainstay acute treatment whereas propranolol was the most commonly prescribed prophylactic drug. Moreover, sleep/rest and meditation were the most commonly reported relieving factors from migraine associated headache. Patients demonstrated restriction in their daily activities, reflected by their MSQ score. Moderate to severe disability was reported in majority of the patients, as assessed by their MIDAS score.

**Disclosure of Interest:** S. Singh Conflict with: The investigator received funding from Abbott India Limited, K. Sarda Conflict with: Is an employee of Abbott, R. Hegde Conflict with: Is an employee of Abbott

**Migraine Acute Therapy**

**PO-01-045**

**Compared to Oral Sumatriptan, AVP-825 Reduces Disability by Relieving Migraine Severity: An Analysis from the COMPASS Study**

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**Objectives:** Migraine presents as a symptom complex, where attacks are defined by a series of correlated symptoms. Pain, nausea, photophobia, and phonophobia are symptoms of migraine which are included in the diagnostic criteria. Drug trials for the treatment of acute migraine attacks often use a narrowly defined efficacy outcome measure based only on improvement of pain. But to those with migraine, all of the symptoms experienced during an attack correlate with their disability in some way. Disability can be conceptualized as an indicator of migraine severity or as a consequence of it. Our previous research measured migraine severity as a latent variable comprising pain, nausea, photophobia, phonophobia and disability as individual indicators. In the current study, we evaluated this competing theoretical model that Migraine Severity (a latent variable defined as a composite of all migraine symptoms, including pain, nausea, photophobia and phonophobia) mediates the relation between treatment and disability using structural equation models (SEMs). Specifically, we tested the hypothesis that, compared to 100 mg oral sumatriptan, AVP-825 (a breath powered intranasal delivery system containing 22 mg sumatriptan powder) reduced disability more because it provided better relief of pain and all migraine-associated symptoms, as measured by Migraine Severity.

**Methods:** The COMPASS Study randomized adults with a diagnosis of migraine to one of two treatment sequences. Participants were instructed to treat up to 5 qualifying migraines within one hour of onset with active study drug (AVP-825 22 mg or oral sumatriptan 100 mg) plus corresponding placebo in each 12-week treatment period. All available data on pain intensity (0 = none to 3 = severe), nausea (0 = no, 1 = yes), photophobia (0 = no, 1 = yes), phonophobia (0 = no, 1 = yes), and associated disability (0 = none to 3 = severe) assessed at pre-dose, 10, 15, 30, 45, 60, 90, and 120 min post-dose were analyzed. SEMs were fitted to test whether the effect of treatment on disability was mediated by the prior Migraine Severity (e.g., Migraine Severity at 10 min predicted disability at 15 min, Migraine Severity at 15 min predicted disability at 30 min, etc.).

**Results:** Our analyses included 259 subjects treating an average of 6.8 attacks each. Participants had a mean age...
of 40 and 84.6% were female. Results showed that the correlational relationship (factor loadings) between each individual migraine symptom and Migraine Severity were statistically significant (pain was most strongly associated with Migraine Severity, then photo/phonophobia, and nausea; data not shown). AVP-825 produced lower levels of Migraine Severity from 10 min through 90 min compared to oral sumatriptan, and increased Migraine Severity predicted increased disability at subsequent time points (p < .01 for all, see Table). Examination of the indirect effect of treatment on disability showed that AVP-825 reduced Migraine Severity from 10 min – 90 min which, in turn, led to lower disability from 15 min – 120 min relative to oral sumatriptan (p < .01; see Table).

**Conclusion:** Findings provided empirical support for the theory that Migraine Severity, a composite variable including pain, nausea, photophobia and phonophobia, predicts subsequent disability. AVP-825 offers greater disability improvement because it treats Migraine Severity better than oral sumatriptan. Our study showed that SEMs can rigorously evaluate clinical theory and measure migraine as a symptom complex. Future studies should be designed to explicitly evaluate the various competing migraine theories (e.g., is disability a measure of Migraine Severity or a consequence of it?) to determine which theoretical model best represents real-world experiences.

**Disclosure of Interest:** J. McGinley Conflict with: Vector Psychometric Group, LLC, R. Wirth Conflict with: Vector Psychometric Group, LLC, D. Buse Conflict with: Allergan, Avanir, and Dr. Reddys, Conflict with: served on scientific advisory board and received compensation from Allergan, Amgen, and Eli Lilly; section editor for Current Pain and Headache Reports, K. Shulman Conflict with: Avanir Pharmaceuticals, Inc., R. Lipton Conflict with: National Institutes of Health, National Headache Foundation, and Migraine Research Fund, Conflict with: serves as consultant, advisory board member, or has received honoraria from Alder, Allergan, American Headache Society, Autonomic Technologies, Boston Scientific, Bristol Myers Squibb, Cognimed, CoLucid, Eli Lilly, eNeura Therapeutics, Merck, Novartis, Pfizer, and Teva, Inc.; receives royalties from Wolff’s Headache, 8th Edition (Oxford University Press, 2009)

**Migraine Acute Therapy**

**PO-01-046**

**Adverse events of sumatriptan and predicting factors: a clinic-based study**

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**Objectives:** Triptans are widely used in migraine acute treatment; however, individual responses and adverse events (AE) vary. Sumatriptan remains the most widely used triptan worldwide. We aimed to investigate factors associated with the development of AE.

**Methods:** We conducted an observational cohort study in a headache clinic in a tertiary medical center. This study is a collaborative study of the original genome-wide association study of migraine. Migraine patients who had been prescribed with sumatriptan were enrolled. Patients were asked of any AE, or triptan sensation after the use of sumatriptan tablet (50mg). Triptan sensation was defined as discomfort, tightness, flushing or paresthesia over the chest, neck, or extending to the face.

**Results:** A total of 1,270 patients were enrolled, of which 1,008 (79.4%) were women, with a mean age of 38.7 ± 11.3 years. Most patients (91.3%) were diagnosed with migraine without aura; while 32.1% fulfilled the diagnosis of chronic migraine, 20.6% the diagnosis of medication over use headache. Any AE was reported in 321 (25.3%) of 1,270 patients, triptan sensation in 115 (9.1%) patients, and most of these AE lasted for 2–3 hours. Compared to those without AE, patients with any AE were more likely to be women (odds ratio [OR]: 1.82, p < 0.001), younger (OR: 0.984 per year, p = 0.006), had a lower depression score (Hospital Anxiety Depression Score – Depression score, 4.8 ± 3.5 vs. 5.5 ± 4.0, p = 0.013). Certain migraineous features were more prominent among patients who developed AE, including lateralized headache (38.4% vs. 21.3%, p = 0.006), pulsating headache (55.1% vs. 62.1%, p = 0.029), photophobia (64.8% vs. 59.2%, p = 0.033), and phonophobia (85.7% vs. 75.0%, p < 0.001). Of note, mense-related headache worsening was more common among those who developed AE than those without (80.5% vs. 69.1%, p < 0.001).

**Predictors for triptan sensation were similar to those with any AE.**

**Conclusion:** In this large cohort, one fourth of migraine patients experienced any AE of sumatriptan and 9.1% reported triptan sensation. Women in overall were more likely to experience any AE. A specific link to certain
migrainous features suggests central sensitization or trigeminovascular activation might be relevant to the development of AE.

**Disclosure of Interest:** None Declared

### Migraine Acute Therapy

**PO-01-047**

**An innovative treatment of chronic migraine and craniofacial neuralgia**

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**Objectives:** A simultaneous treatment of trigeminal and occipital nerves using a combination of dexamethasone, lidocaine, and thiamine never been studied. Migraine headaches or craniofacial neuralgia involving in 90% of cases both trigeminal and greater occipital nerves. Treatment of one nerve without simultaneous treatment of the other did not prove helpful in any of our cases. However, simultaneous treatment of all and both nerves resulted in longest discontinuation of migraine and craniofacial pain. The interaction of genetic signaling with cell surface receptor is a new subject in molecular biochemistry and biology. It is hypothesized that the genetic signals silencing and de-silencing within the autonomic nerve system per se balances the stimulatory effect of the perivascular sympathetic and parasympathetic systems in the peripheral nerves. The objective of this study was the safety and efficacy of simultaneous administration of dexamethasone, lidocaine, and thiamine into the trigeminal nerve branches and the greater and lesser occipital nerves for treatment of chronic migraine and craniofacial neuralgia.

**Methods:** The study is a single-center, randomized, patient-centered pilot study of chronic migraine and craniofacial patients in status migrainous with and without aura. Preparation and administration of a combination of sterile dexamethasone phosphate total dose of 20 mg, 4 mg/ml, lidocaine HCL 1% 40 mg, 10 mg/ml, and thiamin(B1), 200 mg/ml in conducted in a single session into the accessible branches of the trigeminal nerve. The index period (June, 1 2007 – September, 2013). Study follow-ups: one week, 4 weeks, 26 weeks, and 52 weeks. Inclusion Criteria: Patient ages ranged from 12 years old (parental consent was obtained) to 87 years old. Forty patients (10 male and 30 female) participated in the study. Patients were randomly selected from those who approached our clinic seeking treatment for acute exacerbation with status migrainous. All patients exhausted their treatment with abortive and prophylactic medications during the previous 12 months. No medical comorbidity discrimination was specified for this study. Exclusion Criteria: Uncontrolled hypertension, including contraceptive induced. History of stroke, transient ischemic attack, or non-migraine-related seizure. History of brain aneurysm, implantation of any type of neuro-stimulator, trigeminal tractotomy, trigeminal or occipital nerve neuroectomy, or microvascular decompression. Hypersensitivity or allergy to any components of de novo formula.

**Results:** We recruited 52 patients who qualified for the de-novo treatment. Of those, 12 patients showed low or no adherence to post-treatment follow-ups and were excluded from statistical evaluation, and 40 completed planned follow-ups. All patients received the same clinical evaluation and treatment per protocol. Out of 40 patients, 38 (95%) experienced long-term resolution of their migraine or craniofacial neuralgia and 2 (5%) experienced major relief of their complex and chronic migraine with episodic relapse and remission. The average length of migraine free period was 15.24 months. The single longest migraine free period was 65 months until the end of the trial in 2013. One patient did not demonstrate any respond to treatment. An exploratory revision of rt. Temporo-parietal muscle and fascia revealed presence of a neuroma of zygomatico-facial nerve. A Neurectomy resulted in complete resolution of migraine and craniofacial neuralgia.

**Conclusion:** The goal of treatment is to equilibrate and balance autonomous nerve system. Among the multimodal treatment approaches in chronic craniofacial neuralgia and migraines, simultaneous bilateral administration of dexamethasone, lidocaine, and thiamine demonstrated promising results. The de novo treatment is cost effective, safe, and reduces the need for poly-pharmacy.

**Disclosure of Interest:** F. Owiesy Conflict with: employee research

### Migraine Acute Therapy

**PO-01-048**

**Is oral telcagepant a relatively slowly acting drug? a mini-review of 4 rcts**

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**Objectives:** Gepants are a new treatment principle, based on CGRP antagonism, in migraine. Patients want a quick effect and to be pain-free. The onset of action is often forgotten when evaluating oral drugs in migraine. The efficacy of drugs is in most cases compared 2 hours after drug administration.
The aim of this mini-review is by correcting by therapeutic gain (active drug minus placebo) (TG) to evaluate the first part of the time-effect curves up to 2 hours for telcagepant, the best documented CGRP-antagonist.

Methods: Four large randomized, controlled trials (RCTs) with telcagepant were found in PubMed. Data for the early pain-free responses in these RCTs were obtained from Merck Co, US.

Results: In the 4 telcagepant RCTs (280 – 300 mg) the pain-free for the drug at 120 minutes was 26% (369/1377) vs. 10% (143/1394) for placebo. Thus the TG for all studies was 16%. In the large Lancet paper [1] the TG increased 6% (17% to 23%) from 2 to 3 hours; and in a RCTs on combinations of NSAIDs with telcagepant [2] the TG for telcagepant increased 8% (20% to 28%) from 2 to 4 hours.

Conclusion: In 2 placebo-controlled study a statistical significant PF effect vs. placebo after 60 min was demonstrated (Table 1) but the TG was in both studies only 3%. In the other 2 studies (Table 1) telcagepant was first superior to placebo after 90 min. Thus oral telcagepant is relatively slowly acting acute drug in migraine despite the median T_max of 1.5 hours (min. max.: 1 h to 3 h) in blood (n = 19). This is relatively slow onset of action is supported by the additional increases in TGs in 2 RCTs [1,2] beyond 2 h.

The slow onset of action of the CGRP antagonist telcagepant is difficult to explain to be due mainly to a blocking of the drug effect on tissues without blood-brain barrier, e.g. the meningeal artery and extracranial arteries. Alternative mechanisms for the effect of the gepants should be investigated.

References

Disclosure of Interest: None Declared
Objectives: Denmark slower-acting triptans. Tolerated than sumatriptan 100 mg. It is one of the two less effective and has a slower onset of action, but is better. Conflict with: Editor for the British Medical Journal Lindberg: None Declared, A. Langford: None Declared, E. Loder

International Headache Society 2017

Peer Tfelt-Hansen1,*

Objectives: “Naratriptan 2.5 mg has been shown to be less effective and has a slower onset of action, but is better tolerated than sumatriptan 100 mg. It is one of the two slower-acting triptans” [1]. The affinities of naratriptan to the human 5-HT1B and 5-HT1D receptors are similar to those of sumatriptan, and zolmitriptan; in in vitro and in vivo models naratriptan has a pharmacological profile similar to sumatriptan. The oral bioavailability of naratriptan is 74% (Tmax = 2 h) vs. sumatriptan 14% (Tmax = 1½ h). Subcutaneous naratriptan, 10 mg pain free (PF) at 2 h = 88%, is superior to subc. sumatriptan 6 mg (PF at 2 h = 55%) (P < 0.05).

One can thus wonder why naratriptan is “a less effective triptan”, see vignette. This question will be explored in the following.

Methods: The following randomized, trials (RCTs) were reviewed: 2 RCTs with 1 mg, 2.5 mg naratriptan and placebo for up to 4 hours; 2 RCTs comparing naratriptan 1 mg and 10 mg, sumatriptan 100 mg and placebo for up to 4 hours; and 2 RCTs comparing zolmitriptan 2.5 mg with placebo for up to 4 hours.

Results: Therapeutic gain (TG), active drug minus placebo. The combined headache relief for naratriptan 2.5 mg was 46% at 2 h (TG = 19%), and it was 66% at 4 h (TG = 33%). The combined headache relief for zolmitriptan 2.5 mg was 64% at 2 h (TG = 29%), and it was 73% at 4 h (TG = 39%). In addition, in one RCT headache relief for frovatriptan 2.5 mg was 46% at 2 h (TG = 19%), and it was 65% at 4 h (TG = 27%), but the instructions to patients about escape medication was unclear.

Conclusion: 1. The time-curves for triptans can depend on the dose of drugs, confer the results with naratriptan. 2. Tmax in plasma for triptans is 1½ – 2 h. The antimigraine effect of triptans has an increase up to 4 h, and this discrepancy remains unexplained and should be investigated further.

Table 1. Effect of naratriptan, sumatriptan and placebo on headache relief in 2 RCTs in migraine.

<table>
<thead>
<tr>
<th>Drug and doses</th>
<th>Headache relief 2 h (TG)</th>
<th>Headache relief 4 h (TG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 91)</td>
<td>31%</td>
<td>39%</td>
</tr>
<tr>
<td>Naratriptan 10 mg (n = 96)</td>
<td>69% (TG = 38%)</td>
<td>80% (TG = 41%)</td>
</tr>
<tr>
<td>Sumatriptan 100 mg (n = 98)</td>
<td>60% (TG = 29%)</td>
<td>80% (TG = 41%)</td>
</tr>
<tr>
<td>Placebo (n = 107)</td>
<td>22%</td>
<td>27%</td>
</tr>
<tr>
<td>Naratriptan 2.5 mg (n = 209)</td>
<td>50% (TG = 28%)</td>
<td>66% (TG = 39%)</td>
</tr>
<tr>
<td>Sumatriptan 100 mg (n = 240)</td>
<td>59% (TG = 37%)</td>
<td>76% (TG = 49%)</td>
</tr>
</tbody>
</table>

Disclosure of Interest: None Declared

Migraine Acute Therapy

PO-01-051

Remission of Migraine Headache Frequency During Pregnancy

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Objectives: Migraine is one of primary headache which affects about 12% population. It is most common between the ages 20 and 45, with women predominantly. Hormonal
changes, especially during pregnancies is one of the trigger factors. We report a case with migraine attack that dramatically reduce during pregnancy.

**Methods:** Women 43 years old, with recurrent pulsating headache on the left side. It lasted for almost 24 hours without any medication and relieved with either medication or cessation. The headache occurred approximately 15 times a month and worsen with activities, photophobia, and phonophobia. Patients had been experienced nausea and vomiting. Visual loss nor flashing lights phenomenon were not found, neither numbness nor tingling, no weakness of the body neither language disturbance prior to headache. The physical and neurologic examination were normal. Numeric Rating Scale (NRS) was 8 during acute headache attack. MRI and MRA with contrast were performed to exclude intracranial lesion. Patient had been taken paracetamol, diazepam, amitriptyline.

**Results:** The migraine attack's frequencies dramatically reduce 3–4 times a month during pregnancy because the estrogen hormone increased. Estrogen can modulate neurotransmitter system involving serotonin, noradrenaline, γ-aminobutyric acid (GABA). Increasing serotonin concentration is able to increase the activation of 5HT receptor that can block the neuropeptide vasoactive at trigeminal nucleus of brain stem.

**Conclusion:** Increasing estrogen level during pregnancy can reduce the migraine attack frequency.

**Disclosure of Interest:** None Declared

**Migraine Acute Therapy**

**PO-01-052**

**Study of genes involved in Migraine**

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**Objectives:** Migraine is a common brain disorder although the molecular mechanisms involved are poorly understood. Genetic factors essentially contribute to migraine. However approaches to identify genes for common forms of migraine have been of limited success. Genome-wide association (GWA) studies are an important approach used to uncover the genetic susceptibility components of complex diseases such as migraine.

**Methods:** We selected 11 genes from previously published candidate gene association studies and nine additional genes from other studies in migraine.

**Results:** Side-locked unilateral headache and facial pain include a large number of primary and secondary headaches and cranial neuropathies. The SNPs situated within and near the selected identified genes, including those SNPs that were previously thought to be associated with migraine could not confirm with the Bonferroni-corrected significance threshold.

**Conclusion:** The selected genes could not provide any clear evidence for their involvement as a promising candidate genes involved in migraine.

**Disclosure of Interest:** None Declared

**Migraine Preventive Therapy**

**PO-01-053**

**Preventive treatment with lomerizine hydrochloride increases cerebral blood flow during the interictal phase in migraineurs**

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**Objectives:** Migraine is a common, primary, chronic-intermittent neurovascular headache disorder. Previous studies of brain single photon emission tomography (SPECT) showed changes of regional cerebral blood flow (rCBF) in migraineurs during a prodrome, an aura or a headache attack. Sumatriptan (6 mg, sc) did not alter rCBF significantly at a migraine attack (Ferrari et al. Arch Neurol 1995). However, little is known how preventive medication of migraine can influence rCBF. Lomerizine hydrochloride (LH), a calcium channel blocker, has been used widely as a migraine prophylactic drug in Japan. We aimed to analyze brain SPECT findings before and after LH treatment.

**Methods:** Migraine was diagnosed according to the criteria of the International Classification of Headache Disorders, 3rd Edition beta. Migraine was classified into migraine with aura (MA) and migraine without aura (MO). LH (10 mg/day, po) was administered for 3 months. Headache Impact Test-6 (HIT-6) compared before and after LH treatment. Brain SPECT using ⁹⁹ᵐTc-ethyl cysteinate dimer was performed at the headache-free interictal period. Brain SPECT data were analyzed according to revised version of 3-dimensional stereotaxic region of interest (ROI) template (Takeuchi et al. Eur J Nucl Med 2002). A total of 636 ROIs were set in bilateral cerebral cortexes and cerebellar hemispheres. Global CBF was calculated from all data of 636 ROIs in whole brain, including both cerebral hemispheres and cerebellum. SPECT images were divided as regional CBF into 24 symmetrical (right and left) regions per patient: the callosomarginal, the precentral, the central, the parietal, the angular, the temporal, the posterior, the pericallosal, the
lenticular nucleus, the thalamus, the hippocampus and the cerebellar hemisphere. Data of global and regional CBFs were shown in mL/100 g/min. rCBF was compared before and after LH treatment. All data of HIT-6 score and rCBF were analyzed by Wilcoxon singed rank test.

**Results:** A total of 10 migraineurs (4 men and 6 women) were participated in the present study. Mean age (SD) of migraineurs was 55.5 (15.8) years. Mean duration (SD) of migraine was 15.3 (7.7) years. Migraine subtype showed 4 patients with MA and 6 patients with MO.

Mean score (SD) of HIT-6 was 66.3 (11.7) points. LH treatment decreased HIT-6 scores significantly ($P < 0.01$). Compared to rCBF at baseline before LH treatment, LH treatment increased rCBF significantly at 10–20% in the frontal, the parietal and the occipital regions ($P < 0.05$). These changes of brain SPECT findings and HIT-6 score did not differ between MA sufferers and MO sufferers.

**Conclusion:** Previous experimental studies suggested that LH inhibited cerebral hyperperfusion and expression of c-Fos-like immunoreactivity induced by cortical spreading depression via the blockade of Ca$^{2+}$ influx into brain cells in anesthetized rats. (Shimazawa et al. British J Pharmacol 1995). LH had greater effects on CBF than on blood pressure and heart rate in anesthetized rats and beagle dogs. (Hara et al. Exp Pharmacol Physiol 1999). LH blocked 5-hydroxytryptamine (5-HT)$_{2A}$ receptors, and reduced 5-HT-triggered contraction in rat basilar artery (Ishii et al. J Pharmacol Sci 2009). Our study limitation included the small number of patients, rCBF analysis only at interictal phase, and costs and radiation exposure of brain SPECT. Finally, brain SPECT disclosed significant increase of rCBF in the anterior and posterior circulation areas after migraineurs received LH medication for 3 months. The present study indicated that alternation of cerebral circulation during the interictal period could contribute to preventive effects of LH in migraineurs with and without aura.

**Disclosure of Interest:** None Declared

**Migraine Preventive Therapy**

**PO-01-054**

**What happens when chronic migraine patients quit onabotulinumtoxina?**

Pinar Yalıncak Dikmen$^1$, Seda Kosak$^1$, Elif Ilgaz Aydinlar$^1$ and Ayse Sagduyu Kocaman$^1$

$^1$Neurology department, acibadem university school of medicine, istanbul, turkey

**Objectives:** The present study was designed to evaluate the efficacy and rates of quitting Onabotulinumtoxina (OnabotA) and the reasons for doing so among CM patients treated with at least one OnabotA. Our aim was to analyze our 4.5 years’ real-life experience of OnabotA treatment of CM, paying special attention to what happens after 4.5 years. The second objective of this study was to evaluate the latest migraine-related disability and current medication use of CM patients.

**Methods:** 203 patients with CM (40.6 ± 10.1; 177 females, 25 males) were injected with OnabotA as per PREEMPT Protocol between February 2012 and December 2016. The results of a Migraine Disability Assessment Test (MIDAS), duration of migraine and concomitant medication overuse headache were recorded at the first OnabotA treatment. Data were collected by telephone using a standardized interview. The patients were asked about their current MIDAS and the number of analgesic usages and past OnabotA experience.

**Results:** The duration of migraine in CM patients was 10.5 ± 9.1. In total, 513 treatment cycles (n = 1-13) were administered. The mean OnabotA cycles of the patients were 2.5 ± 2.0. At the first injection, the MIDAS scores of the patients were 52.7 ± 25.5 and the mean analgesic usage per month was 26.6 ± 22.7. The subsequent MIDAS scores were significantly lower than the first one; respectively, (17.4 ± 18.6; n = 97); (15.1 ± 15; n = 60); (10.6 ± 11.1; n = 32); (10.5 ± 10.5; n = 21); (10.8 ± 3; n = 12); (11.4 ± 11.8; n = 12); (17.7 ± 20.2; n = 7); (6.0 ± 8.7; n = 5).

Sixty-six percent of the patients (n = 134) answered questions about the benefit of the treatment, their reasons for quitting OnabotA treatment, and their current headache features. Fifty-five patients could not be reached and fourteen patients refused to take part in the study. Seventy-six percent of the patients (n = 102) thought they had benefited from OnabotA; however, 24 percent of the CM patients (n = 32) did not respond to OnabotA. 134 patients gave a number (from 0 to 10) to represent the efficacy of their treatment; 83 percent of the patients (n = 111) gave a score of 5 or above 5 for its usefulness (6.8 ± 2.8).

The reasons for quitting OnabotA among CM patients (n = 107) were as follows: no benefit (n = 31; 29%); no need any more/significant improvement of headache (n = 30; 28%); expensiveness/economic reasons (n = 27; 25%); distance to hospital/location (n = 5; 5%); painful needles (n = 4; 4%); side effects/cosmetic reasons (n = 4; 4%); busy schedule (n = 6; 5%). Six of the 134 patients continued to receive OnabotA treatment at different center now.

The current MIDAS scores of the patients were 16.6 ± 16.5 and the mean number of analgesics per month was 9.0 ± 14.6. Comparing the current and the first MIDAS scores ($p < 0.001$) and the number of analgesic usages ($p < 0.001$) now and at first showed a statistically significant decline in both.

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Conclusion: The most important reasons of the quitters were no benefit from OnabotA, significant improvement of headache and economic difficulty. Our results confirm the usefulness of OnabotA treatment in 76% of patients. Moreover, the migraine-related disabilities of the patients were greatly reduced after only one OnabotA injection and remained the same for several years. Real-life experience with OnabotA showed that the CM patients, even though they had not completed four cycles of the treatment, had extremely diminished migraine-related disability and medication overuse, even after 4.5 years, compared with their condition at first.

Disclosure of Interest: None Declared

Migraine Preventive Therapy

PO-01-055

Chiropractic spinal manipulative therapy for migraine. A three-armed, single-blinded, placebo, randomized controlled trial

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2Head and Neck Research Group
3HØKH, Research Centre, Akershus University Hospital, Oslo, Norway
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Objectives: To investigate the efficacy of chiropractic spinal manipulative therapy (CSMT) for migraineurs.

Methods: Prospective three-armed, single-blinded, placebo, randomized controlled trial (RCT) of 17 months duration including 104 migraineurs with at least one migraine attack per month. The RCT was conducted at Akershus University Hospital Oslo, Norway. Active treatment consisted of CSMT, while placebo was a sham push manoeuvre of the lateral edge of the scapula and/or the gluteal region. The control group continued their usual pharmacological management. The RCT consisted of one month run-in, three months intervention and outcome measures at the end of the intervention and at three, six and 12 months follow-up. Primary end-point was number of migraine days per month, while secondary end-points were migraine duration, migraine intensity and headache index (HI) and medicine consumption.

Results: Migraine days were significantly reduced within all three groups from baseline to post-treatment (p < 0.001). The effect continued in the CSMT and placebo group at all follow-up time points, while the control group returned to baseline. The reduction in migraine days was not significantly different between the groups (p > 0.025 for interaction). Migraine duration and headache index were significantly more reduced in the CSMT than the control group towards the end of follow-up (p = 0.02 and p = 0.04 for interaction, respectively). Adverse events were few, mild and transient. Blinding was concealed throughout the RCT.

Conclusion: It is possible to conduct a manual-therapy RCT with concealed placebo. The effect of CSMT observed in our study is likely due to a placebo response.

Disclosure of Interest: None Declared

Migraine Preventive Therapy

PO-01-056

Adverse events in a chiropractic spinal manipulative therapy single-blinded, placebo, randomized controlled trial for migraineurs

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Objectives: Unlike pharmacological randomized controlled trials (RCTs), manual-therapy RCTs do not always report adverse events (AEs). The few manual-therapy RCTs that provide information on AEs are frequently without details, such as the type and-, severity of the AE and reason for withdrawal. Thus, we prospectively reported all AEs in a chiropractic spinal manipulative therapy (CSMT) RCT in a prospective 3-armed, single-blinded, placebo, RCT.

Methods: Seventy migraineurs were randomized to the CSMT or a placebo, with 12 intervention sessions over three months. The recommendations by CONSORT and the International Headache Society’s Task Force on AEs in migraine RCTs were followed. A standardized reporting scheme designed for pharmacological RCTs was used, and the AEs were described as frequencies and percentages within each group. The 95% confidence intervals (CIs) for the percentages (absolute risk) of AEs in each group were calculated when possible. Attributable risk (%) and relative risk were calculated with the corresponding 95% CIs.

Results: AEs were assessed in 703 sessions, with 355 in the CSMT group and 348 in the placebo group. Local tenderness was the most common AE, reported by 11.3% and 6.9% of the CSMT group and the placebo group, respectively. Adverse events were few, mild and transient. Blinding was concealed throughout the RCT.

Conclusion: It is possible to conduct a manual-therapy RCT with concealed placebo. The effect of CSMT observed in our study is likely due to a placebo response.

Disclosure of Interest: None Declared
group, respectively, and tiredness on the intervention day was reported by 8.5% and 1.4% of CSMT group and the placebo group, respectively. The highest attributable risk was for tiredness on the treatment day, 7.0% (CI 3.9–10.2%) which presented a relative risk of 5.9 (CI 2.3–15.0).

Conclusion: AEs were few, mild and transient, and severe or serious AEs were not observed.

Disclosure of Interest: None Declared

Migraine Preventive Therapy

PO-01-057

Sustained Reduction in Chronic Migraine following Occipital Nerve Decompression Surgery: Further Implications for Extracranial Origin of Headache

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Objectives: We aimed to determine if Nerve Decompression Surgery (NDS) of the bilateral lesser and greater occipital nerves (bLON/GON) would reduce the burden of chronic migraine (CM). CM affects nearly 5% of the 36 million Americans with migraine. A subset of individuals with CM experience chronic occipital headache with chronic tenderness of suboccipital neck muscles and soft tissue. Recently a subset of these patients who underwent NDS for alleviation of their daily headaches also underwent biopsy of the occipital periosteum, and these biopsies were characterized by upregulation of proinflammatory genes. As animal studies have demonstrated that compression of peripheral nerves can cause local inflammatory changes, we hypothesized that compression of bLON/GON and may be the cause of the observed inflammation, and that NDS may reduce inflammation and associated CM.

Methods: Eighteens patients with CM and predominantly occipital pain underwent NDS of the bLON/GON. Twenty-three patients identified in a similar time frame with similar headaches who were referred for NDS but unable to undergo the procedure served as a control group. Log recordings of headache frequency and intensity were obtained for three months prior to surgery and for the first six months post-operatively. NDS included removal of compressive portions of trapezius and semispinalis capitis muscles and their fascial attachments, as well as perineural inflammatory tissue.

Results: No adverse events were associated with the outpatient surgical procedure. At study entry, the number of predominantly occipital CM days per month was 30 for subjects assigned to the control group, and 29.17 for subjects in the surgical group. A comparison between the control group and the surgical group at follow-up was also statistically significant (p < 0.001). More than 50% of surgical subjects experienced a 50% reduction in headache days.

Conclusion: Decompression of bLON/GON reduces headache burden in some patients with CM, most likely through a mechanism of reducing inflammation in the molecular environment surrounding periosteal pain fibers. This study provides further benefit for localized extracranial pathophysiology in CM, and also reports an effective treatment option for some patients with predominantly occipital CM.


Migraine Preventive Therapy

PO-01-058

Cognitive Tolerability with Once-Daily Trokendi XR® (extended-release topiramate) vs. Immediate-Release Topiramate

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Objectives: In studies of immediate-release topiramate (TPM-IR) dosed BID, migraineurs demonstrated greater susceptibility to TPM-related adverse events (AEs), particularly cognitive dysfunction, vs. patients with epilepsy. Trokendi XR® (extended-release topiramate, Supernus Pharmaceuticals, Inc.) is a novel, extended-release formulation producing more constant steady-state TPM plasma concentration-time profiles with QD dosing than TPM-IR BID. We report a series of studies suggesting the potential for better cognitive outcomes with Trokendi XR vs. TPM-IR.

Methods: Prospective Comparison in Healthy Adults (Bioequivalence Study). Prospective, single-blind, randomized-sequence, crossover study in healthy adults.
adults comparing relative bioavailability of 200 mg/day QD Trokendi XR vs. Q12hr TPM-IR (Topamax®). This study also included neuropsychometric tests (verbal fluency; mental processing speed) at steady state (50, 100, 150, 200 mg/day) as secondary endpoints. Retrospective Comparison with Previous TPM-IR Treatment (Chart Review). Multi-site analysis of medical chart data for patients prescribed Trokendi XR, including subset of patients previously treated with TPM-IR. Treatment-emergent adverse event (TEAE) occurrences during Trokendi XR and previous TPM-IR treatment were compared. Retrospective Parallel Comparison (Claims Analysis). Analysis of medical and pharmacy administrative claims data for patients with first-time pharmacy claim for Trokendi XR or TPM-IR (Topamax or generic) in same 14-month period and ICD-9 code for migraine. Persistence based on refills served as composite measure of effectiveness and tolerability. Claims for medical care suggesting TPM-related complications were proxies for TEAEs.

Results: Prospective Comparison in Healthy Volunteers (Bioequivalence Study). Despite bioequivalence and same mean trough TPM concentrations (n=33), verbal fluency change scores significantly favored Trokendi XR for overall exposure period (p=0.02) and 100 mg/day (p=0.0002). Mental processing speed: similar trends in change score patterns without statistical significance. Occurrence of any cognitive symptom as TEAE: Trokendi XR, 24% (B/34) vs. TPM-IR, 34% (13/38).

Retrospective Comparison with Previous TPM-IR Treatment (Chart Review). Of 285 patients with primary diagnosis of migraine with/without epilepsy treated with Trokendi XR, 124 patients were previously treated with TPM-IR. Subset’s characteristics similar to overall migraine population. Significantly (p<0.05) lower TEAE incidence favoring Trokendi XR vs. previous TPM-IR: overall TEAEs, 23% vs. 48%; any cognitive effect: 6% vs. 28%.

Retrospective Parallel Comparison (Claims Analysis). TPM-IR cohort: n=8596; Trokendi XR cohort, n=468. Trokendi XR was associated with significantly (p<0.001) longer persistence vs. TPM-IR; the difference emerged within first 2 months and was sustained throughout observation period. Trokendi XR associated with numerically lower rate of claims suggestive of cognitive effects as treatment-related complications.

Conclusion: Multiple datasets comparing Trokendi XR and TPM-IR suggest the potential for improved cognitive tolerability of Trokendi XR vs. TPM-IR, which may positively impact persistence. Additional prospective studies and analyses of additional datasets are needed to confirm these observations. Studies funded by Supernus Pharmaceuticals, Inc.
Trokendi XR was 7.7 (0.36) months compared to TPM-IR, 6.4 (0.08) months (p < 0.001). Difference between Trokendi XR and TPM-IR emerged within the first 2 months and persisted throughout the observation period. Medication possession ratio (MPR) and adherence (≥80% MPR) were significantly (p < 0.001) higher in the Trokendi XR cohort. In patients treated continuously for ≥6 months (TPM-IR, n = 3118; Trokendi XR, n = 217), the mean change in average monthly migraine events per patient significantly favored Trokendi XR over TPM-IR (p = 0.01 with pre-index count as covariate), as did healthcare utilization measured as outpatient visits (p < 0.001) and prescription drug use (p < 0.001). Occurrence rates for cognitive effects and paresthesia resulting in medical care were lower in the Trokendi XR cohort.

Conclusion: In this claims-based study, Trokendi XR was associated with significantly better outcomes vs. TPM-IR, manifested as significantly higher persistence – a composite measure of effectiveness, tolerability, and adherence. A key advantage of Trokendi XR may be in the early phase of treatment – as TPM therapy is initiated – producing a more favorable trajectory for persistence with TPM therapy. Analyses of larger datasets are needed to confirm these findings. Study funded by Supernus Pharmaceuticals, Inc.


Migraine Preventive Therapy

PO-01-060

GAS (Group A Streptococcus) induces migraine

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Objectives: GAS infection sometimes induces severe splitting headache. Especially in adults, strong headache would be more recognized than sore throat or any other symptoms. Goreisan (GR) and Goshuyuto (GS) are famous Kanpo medicine (Japanese traditional medicine derived from natural herbs) against migraine, then we have reported combination therapy with GS and GS are mostly effective to primary headache within 10 minutes.

Methods: We have already noticed this intervention could be effective to headache accompanied by GAS infection, but not effective to headache accompanied by influenza at all. We have speculated different mechanisms which trigger headache between GAS infection and influenza. Characteristics of headache induced by GAS infection resemble migraine well. On the other hand, first attack of migraine would be occurred around 5 years old. GAS infection would also be firstly encountered at the same age. Susceptible age for both migraine and GAS infection is similar; besides interestingly, as to migraine patients less than 10 years old, boys are slightly predominant over girls, which is also the same gender difference of GAS infection.

Results: We would present two typical cases below.

Case 1. 4 year - 10 month - male
Past History; infantile colic, had been treated with Kanpo medicine (Kanbakutaisoutou)
Family History; mother, two elder brothers and one elder sister have had migraine.
Present illness;
4 years 1 month; First GAS infection
4 years 3 months; First attack of splitting headache treated with Kanpo medicine. Since then headache attack with nausea occurred several times, which had been diagnosed migraine.
4 years 10 months; He had high fever (39.1°C), abdominal pain, nausea and migraine attack. Since his Strep test was positive, he was given antibiotics and Kanpo medicine simultaneously. His headache successfully disappeared within 10 minutes after intervention.

Case 2. 41-year-old female
At age of 12, she had been diagnosed migraine with aura. Up to 24 years old, she had suffered from migraine attack frequently. Especially taking red wine and cheese had triggered migraine attack within a few minutes. Since age of 30 she had never taken wine or cheese, as a result she has been free from migraine attack.
At age of 41, she had visited our clinic with strong splitting headache, sore throat and slight fever (37.5°C). Her Strep test was positive. GR and GS had been given to her, 10 minutes later her headache had been completely disappeared. She has recognized her headache was migraine later, because she had not experienced migraine attack for more than 10 years.

Conclusion: GAS infection induces migraine. If we could get vaccine against GAS infection, it could reduce morbidity of migraine.

Disclosure of Interest: None Declared
Clinical characteristics of the patients with migraine in whom Goshuyutou is effective

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Objectives: Goshuyutou is a traditional Chinese medicine that is effective for the management of chronic headache. However, no large clinical scientific study of goshuyutou has yet been reported. We use Western medicines as the first choice for treating migraine at present; however, for many patients, their headache is uncontrollable with typical Western medicines. We prescribed goshuyutou for such patients with chronic migraine. The purpose of this study is to investigate the clinical characteristics of the migraine patients in whom goshuyutou is effective.

Methods: We examined 20 patients (5 men and 15 women) who were diagnosed with migraine and prescribed goshuyutou at our headache clinic. The patient age ranged from 14 to 63 years old. The migraine diagnosis was based on the International Classification of Headache Disorders 3β and was made by a single physician (author) on the Board of the Japanese Headache Society and certified as a headache master by the International Headache Society. Secondary headache was missed in most patients, even with appropriate examinations, including computed tomography (CT) or magnetic resonance imaging (MRI). Several patients had accompanying disease, but the cause of headache was diagnosed as migraine.

We prescribed triptan for all patients. In Japan, five brands of triptan are available, so if one triptan was not effective, another brand was prescribed. For patients with frequent migraine attack (more than four times per month), preventive medication was also prescribed. Our first choice of preventive medication is 10 mg of lomerizine hydrochloride (Migsis1), because no major side effects have been observed. If this prescription was not effective, we increased the dose of lomerizine hydrochloride or added 5–10 mg of amitriptyline (Tryptanol2). The clinical effects of these preventive medications were evaluated for several months. For patients with intractable migraine attack, we added 5–7.5 g of goshuyutou. Western medications were basically continued at the same doses. At one month after the start of goshuyutou, the clinical effects of goshuyutou were evaluated by the patients themselves. We interviewed the patients who did not visit our clinic by telephone. The clinical effects were classified as very effective (headache disappeared), effective (frequency or intensity of headache decreased) and no effect (no change).

Results: The headache did not disappear after one month of goshuyutou medication in any patients. However, the intensity or frequency of the headache improved in 13 patients. No effect was observed in 4 patients. Three patients did not visit the clinic after the medication or could not be contacted by phone. Therefore, the final effective rate was 76%. All patients continued to take preventive drugs and triptan.

There were no marked differences in the age or sex between the effective and ineffective groups. Neck pain, shoulder stiffness, nausea, photo sensitivity, phono sensitivity, family history of migraine, medication overuse headache and coldness of extremities were observed in both groups.

The effective group tended to have low migraine frequency and a long migraine history; however, because of the small number of patients, Mann Whitney test demonstrated no significant differences (p < 0.05). Five patients in the effective group had aura; however, no patients in the ineffective group had aura. Menses-related migraine was observed in 1 of 3 female patients in the ineffective group and 6 of 10 female patients in the effective group.

Conclusion: Goshuyutou was effective for the patients with aura and menses-related migraine.

Disclosure of Interest: None Declared

Migraine Preventive Therapy

PO-01-062

Onabotulinumtoxin A for Chronic Migraine with Medication Overuse: clinical results of a long-term treatment

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2University of Memphis, Memphis, United States

Objectives: The use of OnaBotulinumtoxin A (BonTA) as treatment of different neurological conditions is always more common in the last decades; its application has been consolidated on the basis of the significant results according to the results of the PREEMPT studies. The possibility for patients to be treated with a second cycle of therapy after the first year of treatment is under discussion, in particular for patients who obtained significant clinical benefit from the first period of treatment. In this report a group of patients, treated with BonTA for one year according to the PREEMPT, has been retreated for one more year in order to confirm the clinical benefit obtained after the first year of treatment.
Methods: A first group of 50 patients, 8 male; 42 females, mean age 51.2 ± 9.0; onset of migraine 18.2 ± 8.3, suffering from Chronic Migraine with Medication Overuse (CM) according to HIS criteria, was treated by BonTA for a period of one year at the Headache Center of the Neurological Institute C. Besta in Milan. All patients underwent to a withdrawal program in a day hospital regimen for 5 days in order to stop the overuse of symptomatic medications. After one year of treatment with the application of therapy every three months, 16/50 patients asked to continue the treatment as they recorded a significant clinical improvement. Patients were treated by a second period of therapy according to PREEMPT, with the same treatment schedule previously applied: 5 sessions, one session every three months, at the dosage of 155 UI per 31 sites. Clinical indexes, number of headache days per month, symptomatic medications per month were recorded by using a headache daily diary during both periods of treatment.

Results: 16 patients, 15 females, 1 male, (mean age 52.5 ± 9.9; onset of migraine 15.4 ± 3.9) were submitted to a second period of treatment for one more year, are encouraging: they evidenced a significant decrease of days of headache per month at one year and the results were confirmed after 2 years of treatment: (25.3 ± 6.1 baseline vs 15.1 ± 7.8 at one year vs 15.5 ± 8.7 at 2 years) and also a significant decrease of medication intake per month (23.8 ± 6.8 baseline vs 13.8 ± 7.68 at one year vs 15.8 ± 8.48 at 2 years). Patients did not report any side effect and they considered the treatment safe and well tolerated, although we did not record these indexes specifically.

Conclusion: In preceding studies it has been demonstrated the efficacy and safety of BonTA in CM over a period of 24 months and also at different dosages, higher than 155 U well tolerated. In terms of mean reduction of days of migraine and medication consumption, our clinical experience, show significant results even if the dosage was limited to 155 U and the results were confirmed over a period of 24 months. The treatment was safe and well tolerated. Patients adherence to treatment was high, no missed appointments and side effects (usually reported from oral prophylaxis as weight gain, somnolence, fatigue, hypotension) were not recorded during the course of treatment. All patients were able to manage the medication intake, without relapses of medication overuse in absence of other prophylaxis for their migraine. BonTA seems to be effective for patients with CM, in particular the long duration of action and favourable adverse events make it a suitable therapeutic alternative for those patients not compliant with oral preventive medications. The application of BonTA is indicated also in the early stage of the disease and this may result in better treatment outcome. Although our results are preliminary, as the limited group of patients retreated, they led to intense efforts to evaluate analgesic properties of BonTA and to assess its clinical applicability for period longer than one year.

Disclosure of Interest: None Declared

Migraine Preventive Therapy

PO-01-063

Effects of high-intensity interval training versus moderate continuous aerobic exercise training on attack frequency and microcirculation in episodic migraine: A randomized controlled trial (RCT)

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3Department of Neurology, University Hospital Basel, Basel, Switzerland

Objectives: Migraine is a highly prevalent and disabling neurological disease. The objective of this study was to elucidate whether different aerobic exercise programs at high vs. moderate exercise intensities distinctly affect migraine frequency and retinal vessel parameters using a three-armed RCT. Effects of different exercise modalities on migraine and retinal vessel diameters have not been systematically studied.

Methods: 24 migraineurs were enrolled in the present RCT (20 female, 4 male, age: 36.4 (11.0), BMI: 22.9 (4.0), migraine days: 4.6 (2.6)). Participants were randomly assigned to either high intensity interval training (HIT), moderate continuous training (MCT) or the control group (CON). Both intervention groups trained twice a week during a 12 week intervention period. HIT followed a 4×4 interval program alternating between 4 minutes at 90% followed by 3 minutes at 70% HRmax while MCT ran at 70% HRmax for 45 minutes. Both training regimen were equicalorically adjusted. In total, 24 training sessions were conducted. CON received no exercise intervention. The primary outcome was the number of migraine days recorded during the last 4 weeks of the training intervention compared to the 4-week run in period. Moreover, Static Vessel Analysis was performed during pre- and post- measurements to obtain baseline central retinal arterial (CRAE) and venular (CRVE) diameters to calculate the arteriolar-to-venular diameter ratio (AVR). Maximal ramp exercise testing on a treadmill was employed to assess maximal (VO₂max) and submaximal (velocity at the individual anaerobic threshold) fitness parameters. Headache and migraine frequency and physical
Abstract number: PO-01-063

Table

<table>
<thead>
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<th>HIT</th>
<th>MCT</th>
<th>CON</th>
<th>ANCOVA</th>
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<td>n = 8</td>
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<td><strong>Pre/Post mean (SD)</strong></td>
<td><strong>SMD</strong></td>
<td><strong>Pre/Post mean (SD)</strong></td>
<td><strong>SMD</strong></td>
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<td><strong>Migraine Days</strong></td>
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<td><strong>1.94</strong></td>
<td>4.6 (2.3)/3.6 (2.7)</td>
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<td><strong>VO₂ peak [ml/min/kgBW]</strong></td>
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<td>0.80</td>
<td>36.7 (6.1)/38.4 (7.6)</td>
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<td><strong>IAT [km/h]</strong></td>
<td>8.2 (0.8)/8.8 (0.5)</td>
<td>0.90</td>
<td>8.1 (1.0)/8.2 (1.0)</td>
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</tbody>
</table>

activity diaries were kept 4 weeks prior to the start of the intervention and during the intervention period.

**Results:** Large effects of both interventions on migraine days with more pronounced effects in favor of HIT compared to MCT were observed (see Table). Retinal AVR improved with a large time × group interaction ($\eta^2_p = 0.14$) in favor of HIT vs. MCT (HIT: pre: 0.89 (0.06), post: 0.92 (0.07), SMD = 0.46; MCT: pre: 0.85 (0.07), post: 0.86 (0.07), SMD = 0.25), whereby the increase of AVR in HIT is attributed to a pronounced increase in arteriolar diameters (CRAE pre: 188.0 (17.2), post: 192.8 (20.0), SMD = −0.26) while MCT revealed a constriction of venules (CRVE pre: 234.7 (8.5), post: 230.0 (9.6), SMD = 0.52).

**Conclusion:** Both exercise intensity modalities resulted in significant reductions of migraine days and headache days in migraineurs. HIT is a safe training modality for migraineurs showing more pronounced effects on migraine attack reduction, cerebrovascular health indices and maximal oxygen uptake compared to MCT. Thus, supervised aerobic exercise should be considered a complementary preventive and treatment strategy for migraineurs.

**Disclosure of Interest:** None Declared

**Migraine Preventive Therapy**

**PO-01-064**

**Improved efficiency of a nurse–led Migraine Botox service by implementation of a ‘lean’ management approach**

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2ProcEx Solutions Ltd, Wales, United Kingdom

**Objectives:** Demand for Botox treatment for chronic migraine is increasing, resulting in pressure on the service. In 2015 we had an increasing waiting list of 35 patients with a wait time of approximately 4–6 months. Botox was administered by several consultants and a clinical nurse specialist, often in ad-hoc clinics. Appointment time-slots were 30 minutes per patient. The challenge faced in 2016 was to substantially increase the number of patients receiving Botox without additional resources. The main objective was to develop a standardised approach for Botox clinics enabling the highest level of efficiency resulting in an increased number of patients treated without increasing clinical staff, shifting the patient load from consultants to specialist nurse led service.

**Methods:** A 4-day assessment by a management-efficiency company [ProcEx Solutions Ltd] scrutinised every part of the patient pathway and consultation, and identified many opportunities for improvement. A few months later we participated in a 4-day kaizen (rapid improvement) event where we implemented the recommendations identified in the assessment. We were able to standardise the configuration of our clinic set up utilising lean techniques. We categorised patients as ‘runners’ (uncomplicated), ‘repeaters’ (more time-consuming, complex) and ‘strangers’ (new patients), which enabled implementation of a standardised patient pathway with fixed appointment times. The time allocated depended on the type of patient and

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whether the patient could be treated in a 15 minute or a 30 minute time slot. The table below illustrates the patient categorisation.

This standardised approach gave us the potential to increase our capacity from 791 treatments in 2015 to 1,530 treatments in 2016 resulting in a 93% increase in patient treatments.

**Results:** There was an actual increase from 55 treatments per month in the first half of 2015 to 91 treatments per month in the second half of 2016. In 2015 we were able to treat a total of 28 new patients and this increased to a total of 63 new patients in 2016.

**Conclusion:** Implementation of these standardised practices has improved clinic efficiency, treating significantly more patients in the unit with the same number of staff. Furthermore, it facilitated a shift from consultant to nurse-led treatment, making it more cost effective. As a result of this, the waiting list has been eliminated and the wait time for treatment reduced from 4 months to 6 weeks. We continue to see an upward trend in treatment numbers.


**Migraine Preventive Therapy**

**PO-01-065**

**Long-Term Safety and Tolerability of OnabotulinumtoxinA Treatment in Chronic Migraine Patients: COMPEL Analysis by Treatment Cycle**

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**Objectives:** The COMPEL study was a 108-week multicenter, open-label study designed to evaluate the efficacy and safety of onabotulinumtoxinA in adults with chronic migraine (CM). This analysis of the COMPEL data examines the safety and tolerability of onabotulinumtoxinA after each treatment cycle over a total of 9 cycles (108 weeks).

**Methods:** The COMPEL Study enrolled adults with CM. OnabotulinumtoxinA 155 U was administered every 12 weeks as 31 fixed site, fixed dose injections. The primary outcome was the reduction in headache day frequency per 28-day period at week 108 (after 9 cycles) compared to baseline. Safety and tolerability, overall and by treatment cycle, were assessed through the collection of data on the incidence and nature of adverse events (AEs), including serious AEs and those that occurred in patients who withdrew. AEs were based on patient reports at each follow-up visit, and physical examination, including vital signs, at screening, week 48 and 108. Patients were withdrawn from the study if suicidal ideation was identified or if pregnancy occurred. Any AE with a start day or an increase in severity in the period between successive treatments was attributed to the preceding treatment. The safety population consisted of all patients who received ≥1 dose of onabotulinumtoxinA.

**Results:** Of 716 patients enrolled in the study, the majority were Caucasian (81%), women (84.8%), and had a mean (SD) age of 43 (11.3) years. Patients typically had a family history of migraine (62.7%) and a mean (SD) time since onset of 10.6 (11.0) years. 373 patients (52.1%) completed the study and 343 (47.9%) withdrew. The primary reasons for discontinuation were withdrawal of consent (n = 92, 12.8%), loss to follow-up (n = 82, 11.5%) and protocol violation (n = 60, 8.4%). Overall, 481 patients (67.2%) received 60 weeks of treatment; 402 (56.1%) received 108 weeks. OnabotulinumtoxinA met the primary endpoint of significantly reducing headache day frequency (n = 715) by 10.7 (6.4) days, P < 0.0001 at week 108 from a baseline mean (SD) of 22 (4.8) days. AEs were reported by 436 patients (60.9%), most of which were mild to moderate in severity. 32 patients (4.5%) discontinued the study after experiencing AEs. 6 women became pregnant and discontinued from the study. The incidence of AEs tended to decrease with repeated onabotulinumtoxinA treatment; 24.2% after the first cycle, 18.4% after the fourth and 12.2% after the ninth (last). Neck pain (2.7%), eyelid ptosis (1.8%), musculoskeletal stiffness (1.4%), injection-site pain (1.3%), and headache (1.3%) were the most common AEs after the first cycle. The incidence of these AEs tended to decrease with each subsequent onabotulinumtoxinA treatment cycle. Neck pain reduced from 2.7% to 0.2% after the last cycle; eyelid ptosis: 1.8% to 0.0%; musculoskeletal stiffness: 1.4% to 0.2%; injection site pain: 1.3% to 0.0%; and headache: 1.3% to 0.5%. 75 (10.5%) patients reported serious AEs. Treatment-related AEs were reported by 131 patients (18.3%), 1 of which was considered serious; 13(1.8%) withdrew.

**Conclusion:** The COMPEL study results demonstrated that when administered using a fixed dose, fixed-site paradigm over 108 weeks, onabotulinumtoxinA was well tolerated and no new safety signals were identified. The incidence of overall AEs and the most common
Among 644 patients enrolled in the REPOSE study, safety and tolerability of onabotulinumtoxinA was also assessed. In the REPOSE study, which aims to investigate the long-term real-life use of onabotulinumtoxinA for the treatment of chronic migraine, The Repose Study, a prospective, non-interventional, observational, open-label study conducted among 7 European countries, demonstrates that preventive treatment of CM with onabotulinumtoxinA in a longer-term (24-month) real-world setting sustains a reduction in the frequency of headache days and significantly improves quality of life relative to baseline. No new safety concerns were identified.

**Disclosure of Interest:** F. Ahmed Conflict with: Received honorarium for consultancy and lecturing from Allergan, Eneura, Electrocore and Novartis, which is paid to the British Association for the Study of Headache and the Migraine Trust, Conflict with: Allergan, C. Gaul Conflict with: Allergan Pharma, Ratiopharm, Boehringer Ingelheim Pharma, Lilly, Novartis Pharma, Desitin Arzneimittel, Cerbotec, Bayer vital, Hormosan Pharma, electroCore und Grünenthal, Reckitt Benckiser, Ratiopharm, TEVA. Employee: Migraine and Headache Clinic Königstein, Germany, P. Martelletti Conflict with: Allergan, Teva, Bayer, Conflict with: Allergan, Teva, Bayer, J. C. Garcia-Monco Conflict with: Allergan, A. Manack Adams Conflict with: Allergan.
Migraine Preventive Therapy

PO-01-067

Burden of illness among treated migraine patients with ≥4 headache days in the past month

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Objectives: To determine the burden of illness among patients treated for migraine with ≥4 headache days in the past month.

Methods: The data source was the 2016 US National Health and Wellness Survey (NHWS; N=97,503), a self-administered, nationally representative sample of adults (≥18 years). Respondents were included in this analysis if they self-reported a diagnosis of migraine, experienced ≥4 headache days in the past 30 days, and were currently using a prescription treatment for migraine. Using propensity score matching to reduce bias, respondents meeting the above criteria were matched with people without migraine on age, gender, comorbidities (Charlson Comorbidity Index), annual household income, education, insurance status, body mass index (BMI), and smoking status. Outcomes included mental health comorbidities, work productivity and activity impairment as measured by the Work Productivity and Activity Impairment Questionnaire (WPAI), health utilization (emergency room visits, and hospitalizations), and estimated annual indirect and direct costs. Post-match, groups were compared using One-Way ANOVAs and chi-square tests on outcomes.

Results: There were 197 respondents in each cohort. A statistically significantly greater proportion of treated migraine patients reported being diagnosed with depression than non-migraine controls (58.4% vs. 27.9%, p < 0.001). A greater portion of treated patients also reported being on long-term disability compared to non-migraine controls (13.7% vs. 5.6%, p < 0.001). Treated migraine patients reported greater losses in work productivity and increases in activity impairment. Compared to non-migraine controls, treated patients experienced greater absenteeism (11.8% vs. 6.3%, p = 0.03), presenteeism (36.0% vs. 17.5%, p < 0.001), overall work impairment (40.9% vs. 20.9%, p < 0.001), and activity impairment (45.4% vs. 25.4%, p < 0.001). These patients also reported more HCP visits (7.55 vs. 4.43, p < 0.001) and ER visits (0.48 vs. 0.25, p = 0.030) compared to non-migraine controls in the previous 6 months. Greater work productivity loss among treated migraine patients resulted in higher estimated annual indirect costs ($14,770.57 vs. $5,764.93, p < 0.001) compared to non-migraine patient controls. Treated migraine patients utilized more healthcare services than non-migraine patients ($24,499.90 vs. $15,318.91, p = 0.013).

Conclusion: The overall burden associated with migraine is substantial despite the availability of treatment options. Migraine patients in this survey reported a higher percentage of depression, long-term disability, work productivity loss, absenteeism, presenteeism, activity impairment, and use more health care services compared to people without migraine. As a result, patients treated for migraine incurred substantially greater direct and indirect costs compared to non-migraine controls.

Disclosure of Interest: L. Lee Conflict with: Kantar Health, J. Bell Conflict with: Teva Pharmaceuticals, T. Fitzgerald Conflict with: Teva Pharmaceuticals

Migraine Preventive Therapy

PO-01-068

The impact of headache free days on quality of life and costs among people with migraine with ≥4 headache days in the past month

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Objectives: To determine the relationship between quality of life measures and headache free days (HFDs) among patients with ≥4 headache days in the past month. This patient population is at risk of progressing to chronic migraine, which is defined as ≥15 headache days per month. Increasing the number of HFDs may substantially improve a patient’s quality of life

Methods: The data were drawn from the 2016 US National Health and Wellness Survey (NHWS; N=97,503), a self-administered, nationally representative sample of adults (≥18 years). Patients who indicated they were diagnosed with migraine and reported experiencing ≥4 headache days a month were considered at risk for progressing to chronic migraine. Multivariable analyses were conducted in this subgroup of patients. The primary independent variable was the number of HFDs as both a continuous (30 minus number of HFDs in the past 30 days) and categorical (0–10, 11–20, and 21–26 HFDs) measure. Each measure was used as a predictor in separate generalized linear models (GLMs).

Outcomes included patient reported number of days absent from work and days of household activities
Results: Using HFDs as a continuous variable in the multivariable regression, each HFD was found to be associated with a 0.15 (regression coefficient) point reduction in HIT-6 scores. As a categorical variable, each 10 day increase in HFDs was associated with significantly lower HIT-6 total scores (adjusted means = 66.59 [0–10 HFDs], 65.66 [11–20], 63.91 [21–30], all p < 0.02).

Increasing the number of HFDs from 0–10 to 21–26 (adjusted means = 4.44 vs. 1.46, p = 0.002) and from 11–20 to 21–26 (3.36 vs 1.46, p = 0.009) categories was associated with significantly fewer work days missed due to migraines. Similarly, increasing the number of HFDs from 0–10 to 11–20 (adjusted means = 22.99 vs. 9.72, p < 0.001) and from 0–10 to 21–26 (22.99 vs. 7.34, p = 0.001) categories was associated with significantly fewer days of household activity missed due to migraines. In other words, each HFD reduces both number of work days missed and number of days of household activities missed by 5%.

Conclusion: Increasing the number of HFDs is associated with an increase in quality of life among patients suffering from migraine and at risk for developing chronic migraine. Patients reported significant incremental improvement in multiple quality of life measures as the number of HFDs increased. Migraine also places a substantial indirect cost burden on this patient population and increasing total indirect costs (adjusted means = $16,975 vs. $6,919, p = 0.025).

Disclosure of Interest: L. Lee Conflict with: Kantar Health, J. Bell Conflict with: Teva Pharmaceuticals, T. Fitzgerald Conflict with: Teva Pharmaceuticals
Conclusion: The drop in average peak βHB blood levels after 1–2 weeks of ingestion is likely to be a consequence of adaptation, enabling a quicker uptake and usage of βHB. While it is too early to draw any conclusions from this case series, these preliminary results might warrant the conduction of a randomised, placebo-controlled, double-blind efficacy and safety trial to assess the potential of exogenous ketogenic substances in migraine prevention.

Disclosure of Interest: None Declared

Migraine Preventive Therapy

PO-01-070

A randomized controlled clinical trial on the efficacy of acupuncture for migraine prophylaxis: the ACUMIGRAN study

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Objectives: The efficacy of acupuncture for migraine prophylaxis still remains controversy [1–3]. The aim of our study was to evaluate the non-inferiority of acupuncture compared to that of pharmacological treatment as prophylaxis for migraine with and without aura.

Methods: This is a randomized controlled clinical study. Patient suffering from migraine without preventive treatment in the past three months were recruited. After the run-in period episodic migraineurs were assigned randomly to two groups: the acupuncture group (A) was treated with 12 sessions of acupuncture and the pharmacological group (B) was treated with the most appropriate medication for each patient. Headache frequency was compared at baseline and at the end of treatment.

Results: A total of 105 patients (19 males and 86 females) were enrolled in this study. Out of these, 52 were randomized at A and 53 at B. At baseline no significantly differences were found between the two groups. Of the overall sample 74 patients completed the protocol. After 4 months, the migraine frequency decreased from $9.19 \pm 2.99$ to $4.36 \pm 2.66$ in A and from $8.25 \pm 2.53$ to $4.44 \pm 2.37$ in B. Headache frequency decreased significantly after treatment without differences between the two groups (time-effect: $p < 0.001$; group effect: $p = 0.332$; interaction time-group effects: $p = 0.556$). Responders (migraineurs with a reduction of headache days by at least 50%) were 35.71% in A and 31.25% in B ($p = 0.687$).

Conclusion: Our preliminary data suggest that acupuncture was as effective as pharmacological treatment in decreasing migraine frequency. This study was funded by II Programma sperimentale regionale per l’integrazione delle MNC nel servizio sanitario dell’Emilia-Romagna.

References

Disclosure of Interest: None Declared

Migraine Preventive Therapy

PO-01-071

Magnesium in migraine prophylaxis – is there an evidence-based rationale? A systematic review

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Objectives: Magnesium plays a decisive role in intracellular energy production and neuronal excitability, which are critical factors in the pathophysiology of migraine. Experimental studies indicate reduced intracellular levels of magnesium in migraineurs. We performed a systematic review of randomized controlled trials investigating magnesium for migraine prevention.

Methods: Clinical trials published from 1990–2016 were sorted and analyzed in a structured selection procedure with regard to evidence and under consideration of the guidelines for controlled trials for drugs in migraine by the International Headache Society. The number of migraine
days and number of migraine attacks were chosen as efficacy parameters.

**Results:** Out of 205 search results, 5 clinical trials fulfilling the selection procedure were found. One out of two Class I evidence trials showed a significant reduction of the number of migraine attacks compared to placebo, while two out of three Class III trials evinced a statistically significant reduction of the primary efficacy parameters compared to placebo.

**Conclusion:** This systematic review provides Grade C evidence for treatment of migraine with magnesium. Prophylactic treatment of migraine by means of high levels of magnesium dicitrate (600 mg) seems to be a safe and cost efficient strategy in clinical use.

**Disclosure of Interest:** None Declared

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**Migraine Preventive Therapy**

**PO-01-072**

**Sustained Reduction in Days Using Acute Medications with Fremanezumab (TEV-48125)**

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**Objectives:** Fremanezumab, (formerly known as TEV-48125), a fully humanized monoclonal antibody that selectively binds to both isoforms of the CGRP ligand and prevents CGRP from binding to the CGRP receptor, has been shown to be effective for high-frequency episodic migraine (HFEM) and chronic migraine (CM) prevention. The sustained effect on acute medication use, which is a marker of migraine-related disability and a risk factor for migraine chronification, has not been previously reported.

**Methods:** Fremanezumab was evaluated in randomized, double-blind, placebo-controlled 12-week phase 2 studies in patients with HFEM and CM. Participants allocated to fremanezumab received one of two dosing strategies: HFEM participants were randomized to receive monthly injections of 225 mg or 675 mg for 3 months; CM participants were randomized to receive either monthly injections of 900 mg, or an initial loading dose of 675 mg and subsequent injections of 225 mg for 3 months. An electronic headache diary captured headache-related data. Using post-hoc analyses, we determined the percentage of patients with at least a 50% and 75% reduction in the number of days requiring acute medication use at month 1 that continued to sustain this 50% or 75% reduction over 3 months.

**Results:** Figure 1 illustrates sustained 3-month response results in HFEM patients. Figure 2 illustrates sustained 3-month response results in CM patients.

**Conclusion:** As these findings are from post-hoc analyses, they must be interpreted with caution; nonetheless, significant percentages of patients on fremanezumab were able to demonstrate a sustained 3-month 50% and 75% reduction respectively in the use of abortive migraine medications. Given the importance of acute medication usage on disability and the risk of future progression, future trials should prospectively collect and report the percentage of study participants who are able to sustain a reduction in acute medication use over a meaningful period of time.
Disclosure of Interest: R. Halker: None Declared, E. Aycardi Conflict with: Dr. Aycardi is employed by Teva, M. Bigal Conflict with: Employed by Teva, P. Loupe Conflict with: Dr. Loupe is employed by Teva, D. Dodick: None Declared

Migraine Preventive Therapy

PO-01-073

The validity of wireless sensors for measurement of surface electromyography and skin temperature: Basis for a novel preventive headache treatment

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Objectives: Delivery of preventive biofeedback treatment to young migraineurs is a tedious and time-consuming undertaking, and it is unavailable to the majority of those in need, despite its effectiveness [1]. The aim of the present study was to assess the validity of Bluetooth compatible sensors for measurement of surface electromyography (SEMG) and peripheral skin temperature, in combination with a mobile phone application (app), as a basis for a novel, innovative mHealth delivery of biofeedback self-treatment for young persons with primary headache. This abstract presents data from the ongoing study.

Methods: Sensors fulfilling the three criteria (1) wireless setup, (2) small size and (3) low cost were identified. An iOS compatible application was programmed to communicate with the biosensors. Twenty healthy volunteers were recruited to use the biosensors through the app with simultaneous control measurements made with stationary neurophysiological equipment. SEMG sensors were attached to the right trapezius muscle and temperature sensors were attached to the right distal index finger. Investigations were made to assess agreement in change values for SEMG and temperature. Agreement between wireless and stationary SEMG sensors was assessed through the following activities: maximal voluntary contraction (MVC) of the trapezius muscle followed by submaximal voluntary contractions at 50% (VC50%) and 25% (VC25%) force. Similarly, agreement between wireless and stationary temperature sensors was investigated for the difference between room temperature and finger temperature.

Results: The app was programmed as a minimal viable product (MVP) to receive data from the wireless biosensors, to process this data and feed it back to the user through a simple interface. The app also allowed for viewing previous recorded sessions and extraction of data for analysis. Results from twelve participants (age 18–29 years) showed convincing visual agreement of muscle activation patterns. Root mean square (RMS) values were calculated for contraction periods. Table 1 shows ratio of RMS values between VC50% and VC25% for the stationary and wireless setup, indicating good consistency of agreement between stationary and wireless equipment. Table 1 also shows difference from room temperature to finger temperature in degrees Celsius for both temperature sensors.

Conclusion: Results indicate that wireless sensors may be suited to use as an integrated part of an app to monitor physiological parameters with the intention of biofeedback-treatment. The results also emphasize the general concept of using wireless sensors and apps to measure physiological parameters as useful and feasible.

Disclosure of Interest: None Declared

Migraine Preventive Therapy

PO-01-074

Effects of OnabotulinumtoxinA Treatment on Disability and Quality of Life in Patients with Chronic Migraine with Baseline Headache Every Day: A COMPEL Subanalysis

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Objectives: Chronic migraine (CM) is a disease with varied attack frequency and pain symptoms. The objective
of this subanalysis of the 108-week, multicenter, open-label COMPEL study addresses the efficacy and safety of onabotulinumtoxinA in CM patients with baseline compared with no baseline headache every day (HED).

**Methods:** Patients received onabotulinumtoxinA 155 U with/without concomitant prophylaxis. A subpopulation with baseline HED was assessed, which was defined as a diary entry of HED with an entry during the 28-day screening period. The primary outcome was the reduction in headache frequency per 28-day period at 108 weeks (9 treatments). Exploratory outcomes included, but were not limited to, scores for the Migraine Disability Questionnaire (MIDAS), with higher scores indicating greater disability; Migraine-Specific Quality of Life (MSQ), consisting of 3 subscales, Role Function Preventive, Role Function Restrictive, and Emotional Function, with higher scores indicating greater quality of life; and Patient Global Assessment of Treatment (PGAT), which assesses patient satisfaction with their treatment. Adverse events and their relatedness were recorded.

**Results:** In patients with baseline HED (N = 153) and without baseline HED (N = 562), onabotulinumtoxinA reduced 28-day headache frequency relative to baseline (week 60: HED, −7.9 ± 8.6; no HED, −10.7 ± 6.5; week 108: HED, −10.5 ± 9.4; no HED, −12.0 ± 6.8; between-group comparison for both timepoints P < 0.001). MIDAS scores were significantly decreased (improved) at week 60 (HED, −36.3 ± 69.4; no HED, −44.8 ± 51.4) and week 108 (HED, −44.8 ± 73.7; no HED, −44.0 ± 46.3; between-group comparison for both timepoints P < 0.001). Similarly, MSQ subscale scores improved from baseline at weeks 48, 96, and 108 (Role Function Preventive subscale scores: week 48, HED = 16.9 ± 23.1, no HED = 19.0 ± 20.1; week 96, HED = 16.3 ± 25.2, no HED = 19.7 ± 21.8; and week 108, HED = 15.0 ± 27.0, no HED = 19.2 ± 19.7, P < 0.001; Role Function Restrictive subscale scores: week 48, HED = 21.1 ± 25.6, no HED = 24.4 ± 21.4, P < 0.05; week 96, HED = 24.2 ± 25.7, no HED = 27.0 ± 23.8; and week 108, HED = 25.5 ± 25.3, no HED = 26.3 ± 22.4; and Emotional Function subscale scores: week 48, HED = 22.1 ± 27.3, no HED = 24.9 ± 25.5; week 96, HED = 25.7 ± 29.6, no HED = 26.8 ± 26.0; and week 108, HED = 27.2 ± 28.2, no HED = 25.7 ± 25.8). Similarly in both groups, the proportions of patients who were extremely satisfied/satisfied (by PGAT) typically increased, and the proportions dissatisfied decreased. 3.3% HED and 1.4% non-HED patients who discontinued reported a treatment-related adverse event.

**Conclusion:** These results support the efficacy of onabotulinumtoxinA for reducing headache days and disability and improving quality of life for up to 108 weeks in CM patients with or without HED. Both groups had similar beneficial treatment effects, with a slightly greater benefit observed in patients without HED. No new concerns regarding safety were identified.

**Disclosure of Interest:** J. I. Lopez Conflict with: Dr. Lopez and his parent institution, Renown Health, have received clinical research funding from Allergan plc, Conflict with: Has served on the advisory boards for Alder, Allergan, Cipla, Lilly, and Supernus, A. Blumenfeld Conflict with: Allergan, Pernix, Teva, Avanir, Depomed, and Supernus, Conflict with: Received funding for travel, speaking, and/or royalty payments from Allergan, W. Young Conflict with: AGA, Alder, Allergan, Amgen, Autonomic Technology, Cumberland, Dr. Reddy Laboratories, Eli Lilly, Eneura Inc, Merz, and St. Jude Medical Consultant: Allergan and Supernus, A. Manack Adams Conflict with: Allergan, Conflict with: Allergan, J. Rothrock Conflict with: His parent institution has received funding from Allergan plc for clinical research he has conducted, Conflict with: has received honoraria from Allergan plc for participating as a speaker and preceptor at Allergan-sponsored educational programs

**Migraine Preventive Therapy**

PO-01-075

**Effects of OnabotulinumtoxinA Treatment on Disability and Quality of Life in Patients with Chronic Migraine with Baseline Alldynia:**

A COMPEL Subanalysis

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**Objectives:** Alldynia is common in the chronic migraine (CM) population. The presence of alldynia has been reported to reduce the likelihood of a positive response to migraine therapies. The objective of this subanalysis of the 108-week, multicenter, open-label COMPEL study is to evaluate the efficacy and safety of onabotulinumtoxinA in CM patients with baseline compared with no baseline alldynia.

**Methods:** Patients received onabotulinumtoxinA 155 U with/without concomitant prophylaxis. Based on the Alldynia Screening Questionnaire, a subpopulation with baseline alldynia was identified during the 28-day screening period. The primary outcome was the reduction in headache frequency per 28-day period at 108 weeks (9 treatments). Exploratory outcomes included but were not limited to scores for the Migraine Disability Questionnaire (MIDAS), with higher scores indicating greater disability; Migraine-Specific Quality of Life (MSQ).
Results: In patients with baseline allodynia (N = 289) and without baseline allodynia (N = 426), onabotulinumtoxinA reduced 28-day headache frequency relative to baseline (week 60: allodynia, −9.9 ± 6.7; no allodynia, −10.3 ± 7.3; week 108: allodynia, −10.8 ± 7.1; no allodynia, −12.5 ± 7.4). MIDAS scores were significantly decreased (improved) at week 60 (allodynia, −48.6 ± 60.3; no allodynia, −38.9 ± 51.5; P < 0.05 between-group comparison) and week 108 (allodynia, −53.0 ± 50.3; no allodynia, −37.7 ± 53.0). Similarly, MSQ subscale scores improved from baseline at weeks 48, 96, and 108 (Role Function Preventive subscale scores: week 48, allodynia = 19.8 ± 20.9, no allodynia = 17.6 ± 20.6; week 96, allodynia = 20.8 ± 23.1, no allodynia = 17.8 ± 22.0; and week 108, allodynia = 20.6 ± 21.9, no allodynia = 16.9 ± 20.7; Role Function Restrictive subscale scores: week 48, allodynia = 26.5 ± 22.3, no allodynia = 21.6 ± 22.1; week 96, allodynia = 28.9 ± 25.0, no allodynia = 24.6 ± 23.4; and week 108, allodynia = 28.0 ± 23.3, no allodynia = 24.7 ± 22.7; and Emotional Function subscale scores: week 48, allodynia = 26.7 ± 26.4, no allodynia = 22.5 ± 25.3; week 96, allodynia = 28.3 ± 27.0, no allodynia = 25.3 ± 26.5; and week 108, allodynia = 27.6 ± 26.5, no allodynia = 24.9 ± 26.1). Similarly in both groups, the proportions of patients who were extremely satisfied/satisfied (by PGAT) typically increased, and the proportions dissatisfied decreased. 2.1% allodynic and 1.6% non-allodynic patients who discontinued reported a treatment-related adverse event.

Conclusion: These results support the efficacy of onabotulinumtoxinA for reducing headache days and disability and improving quality of life for up to 108 weeks in CM patients with or without allodynia. Both groups had similar beneficial treatment effects, with a slightly greater benefit commonly observed in patients with allodynia despite its reported treatment-resistant phenotype. No new concerns regarding safety were identified.

Disclosure of Interest: W. Young Conflict with: AGA, Alder, Allergan, Amgen, Autonomic Technology, Cumberland, Dr. Reddy Laboratories, Eli Lilly, Eneura Inc, Merz, and St. Jude Medical Consultant: Allergan and Supernus, Conflict with: Has served on the advisory boards for Alder, Allergan, Cipla, Lilly, and Supernus, J. I. Lopez Conflict with: Dr. Lopez and his parent institution, Renown Health, have received clinical research funding from Allergan plc, J. Rothrock Conflict with: His parent institution has received funding from Allergan plc for clinical research he has conducted, Conflict with: has received honoraria from Allergan plc for participating as a speaker and preceptor at Allergan-sponsored educational programs, A. Manack Adams Conflict with: Allergan, Conflict with: Allergan, A. Blumenfeld Conflict with: Allergan, Perrinex, Teva, Avanir, Depomed, and Supernus, Conflict with: Received funding for travel, speaking, and/or royalty payments from Allergan

Migraine Preventive Therapy

PO-01-076

Evaluation of the Effects of an Organic Light Emitting Diode Lighting Environment for Patients with Migraine

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Objectives: This study aims to reduce migraine attacks for migraine patients caused by the uniform emitting surface of Organic Light Emitting Diode (OLED) lighting in their lives. We also sampled hair at the time of OLED lighting, identified the expression rhythm of the human clock gene (Per3), and investigated the correlation between headaches and the number of days’ drug is taken.

Methods: Subjects of the study were seven migraine patients residing in a room installed with OLED (3000K) and Light Emitting Diode (LED) (3000K) lighting. Ages were 20 to 22 years old. The study was first performed for a period of four weeks with LED lighting followed by another four weeks with OLED lighting. The method used to investigate were headache conditions of the subjects (headaches, number of days taking drug), Beck Depression Inventory (BDI), Profile of Mood States (POMS), and Pittsburgh Sleep Quality Index (PSQI). The Unified Glare Rating (UGR) was calculated using a Luminance & Color Environment Photometric Tool (L-CEPT). The human clock gene (Per3) was measured by sampling hair four times a day every six hours, purifying the RNA from the attached hair follicle cells, and analyzing it with the real-time PCR method.

Results: The average number of days with a headache throughout the four weeks’ period with LED for the seven migraine patients was eight days, which was reduced to 6.9 days with OLED. The average number of days’ drug was taken throughout the four week periods was 2.1 days with LED and 2 days with LED, showing no variation. The BDI average showed improvement for depression, from 3 with LED to 1.1 with OLED. The average Total Mood Disturbance score for POMS also showed improvement for mood, from 18.2 with LED to 16.4 with LED. The average of the total score for the PSQI showed an
Efficacy of migraine prophylaxis is typically measured by its ability to reduce the frequency of migraine attacks. A previous economic model of migraine prophylaxis stratified migraine patients into health states based on their headache day frequency per 28 days (0–3, 4–9, 10–14, 15–19, 20–23, 24–28). The aim of this analysis is to explore the performance of parametric distributions to model MD frequency continuously, in contrast to the traditional health state approach, based on the headache day definitions used previously.

Methods: Patient level data from a phase 2 study (NCT01952574) of erenumab 70 mg as prophylaxis in episodic migraine (EM) were used to compare the distribution of patients by MD frequency at each time point during the study double-blind phase and open-label extension up to 52 weeks, using three approaches: 1) the distribution of individual patients as observed in the study, 2) the split of patients across the six health states defined above, and 3) a beta-binomial distribution fit to the study observations.

The observed and beta-binomial distributions were used to generate a weighted average MD frequency for patients within each health state. The health state approach assumed that patients were uniformly distributed, and that the mean MD frequency in each health state was the midpoint of the defining range. Bootstrapped confidence intervals were generated to identify any significant differences between approaches.

The three approaches were used to estimate the mean MD frequency per 28 days for each health state and the overall mean frequency across 1 year of study follow-up.

Results: Data from 103 EM patients treated with 70 mg erenumab were available for at least one study visit, with 73 patients followed up to 52 weeks. A total of 83.4 patient-years of treatment were included in the analysis. Over 1 year, the mean frequency of MD observed was 56.6 (Bootstrap 95% CIs: 54.1–59.3). The health state and beta-binomial approaches estimated 61.7 (59.1–64.3) and 56.7 (54.1–59.5) MD, respectively.

Observed mean MD frequencies for patients in the “0–3”, “4–9” and “10–14” MD health states were numerically lower than the health state midpoints; 1.4 (0.9–2.0), 5.9 (5.3–6.5) and 11.3 (10.0–12.4), respectively. Reliable estimates for the health states with 15+ MD could not be generated, as these were not well represented in the EM study population.

Conclusion: The results of this analysis suggest that the use of a parametric distribution is able to provide accurate approximations of the MD frequency observed in the EM study dataset analyzed.

Modeling MD frequency as a continuous outcome, rather than as a series of categories, retains all of the observed information on the distribution of patients by MD frequency, and does not require arbitrary health states to be defined. Furthermore, it is possible to use the parametric distribution to populate health states, but the reverse is not true.

The continuous distribution approach may also offer additional advantages for economic evaluation. Firstly, it more readily allows for indirect comparisons based on study primary endpoints (e.g. change in MD frequency per 28 days). Secondly, the number of MDs and associated...
events (e.g. emergency room visits) can be directly quantified. Based on the numerical error observed in this analysis, it does not appear that this estimation is possible to do accurately using the health state approach.


**Migraine Preventive Therapy**

**PO-01-078**

**Botulinum toxin A and acute detoxification in chronic migraine and medication overuse: a randomised, double-blind, placebo-controlled trial**

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1Neurology
2Radiology
3Psychiatry
4Medical Statistics, LUMC (Leiden University Medical Centre), Leiden, Netherlands

**Objectives:** Results from two randomised controlled studies suggest efficacy of botulinum toxin A in chronic migraine. However, many of the patients in these studies also had medication overuse. In such patients, acute detoxification alone might also be effective, but is often hampered by severe withdrawal symptoms. Here we assessed whether botulinum toxin A affords additional benefit in addition to acute detoxification.

**Methods:** We conducted an investigator-initiated, randomised, double-blind, placebo-controlled trial at the Leiden University Medical Centre Headache Clinic. Patients aged 18–65, with chronic migraine and medication overuse, were randomly assigned (1:1) to receive botulinum toxin A (155 units) or placebo (saline and 17.5 units botulinum toxin A only administered in the forehead, to prevent unblinding by facial relaxation). Participants in both groups were instructed to acutely refrain from using any acute anti-headache medication and to taper off any prophylactic agent they were using. Primary outcome was the relative change in number of headache days per month at 12 weeks. Secondary outcomes were: (A) Quality of Life during detoxification; (B) proportion of participants who succeeded to refrain from medication for at least three months; (C) change at 12, 24, 36 and 48 weeks of (i) cumulative headache duration; (ii) number of days with (moderate/severe) headache, migraine, or use of acute anti-headache medication. This trial was registered at the Netherlands Trial Register (NTR3440).

**Results:** According to a 90% power calculation to detect a 20% treatment difference, we included 179 participants (n = 90 botulinum toxin A; n = 89 placebo). The results are currently being analysed and will be presented at the meeting.

**Conclusion:** The study was successfully completed and results will be presented at the meeting.

**Disclosure of Interest:** None Declared

**Migraine Preventive Therapy**

**PO-01-079**

**Cognitive Behavioral Therapy and Greater Occipital Nerve Blockade Combination in The Treatment of Chronic Migraine**

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2Algology, Ankara Research and Training Hospital
3Algology, Gazi University School of Medicine, Ankara, Turkey

**Objectives:** Cognitive behavioral therapy (CBT) and greater occipital nerve (GON) block with local anesthetic effectiveness have been shown in the treatment of migraine separately. We are applying CBT and GON blockade together in chronic migraine. We decided to present the results of two chronic migraine patients.

**Methods:** Patients with the diagnosis of chronic migraine according to the IHC 2013 had been followed with headache diary. CBT and GON blocks with bupivacaine had been done weekly.

**Results:** First patient’s headache frequency was 17 headache days in 30 days, mean VAS score: 7.08, mean headache duration: 8.6 hours, Beck depression score (BDS): 7 and Beck anxiety score (BAS): 11 at baseline. At the end of four month. Headache frequency was 9 headache days in 30 days, mean VAS score: 5.9, mean headache duration: 7.7 hours, (BDS): 0 and (BAS): 0.
Second patient's headache frequency was 17 days in 30 days, VAS score:5.8, mean headache duration:7.7 hours, BDS: 17 and BAS: 25 at baseline after three months treatment headache frequency:0 in 30 days, BDS: 10 and BAS: 11.

**Conclusion:** As these results show combination of CBT and GON blockade with local anesthetics decreased headache frequency, VAS score, headache duration, BDS and BAS.

**Disclosure of Interest:** None Declared

**Migraine Preventive Therapy**

**PO-01-080**

**Treatment-Induced Improvement in Migraine Classification in the Fremanezumab HFEM Study**

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2Clinical Development, Teva Global Research and Development, Frazer PA
3Academic Affairs and Network, Teva Global Research and Development, Overland Park KS, United States

**Objectives:** Fremanezumab (formerly TEV-48125) is a fully humanized monoclonal antibody targeting the calcitonin-gene related peptide (CGRP) ligand, a validated target for migraine preventive therapy. Fremanezumab was found to be effective and well-tolerated as a preventive treatment for migraine in a high frequency episodic migraine (HFEM) phase 2 study. Study participants included patients with migraine with and without aura who were classified as having episodic migraine (EM) as per the International Classification of Headache Disorders (ICHD III beta). Herein, we determined whether there was a treatment induced shift in the number of patients who met the criteria for classification as having high frequency episodic migraine (HFEM) to moderate frequency episodic migraine (MFEM) and low frequency episodic migraine (LFEM) during the HFEM phase 2 study.

**Methods:** Patients were randomized to receive either fremanezumab doses (225 mg or 675 mg) or placebo as subcutaneous injections every 28 days for 12 weeks. Headache information was captured daily using an electronic headache diary. For the post-hoc analysis, the frequency of headache days (days of headaches lasting >4 hours) and migraine days (days with headaches classified as migraine, probable migraine or treated with triptan or ergot compounds) per month were categorized into four types of migraine classification: Chronic migraine (CM) as having ≥15 headache days with 8 migraine days; HFEM 8 to 14 headache days with 8 migraine days; Moderate frequency EM (MFEM) 4 to 7 headache days and 4–7 migraine days; Low frequency EM (LFEM) 0 to 3 headache days and 0–3 migraine days. Analyses on the shifts for migraine classification from baseline to month 3 were performed to determine the percent of patients who showed improvement (HFEM to MFEM or LFEM), worsening (HFEM to CM), and those who remained classified as HFEM.

**Results:** Overall, the percent of patients in the fremanezumab arms showed significant improvement in migraine classification compared to placebo patients at month 3 (those on 225 mg 73% vs 49% for placebo, 95% CI: 0.098 to 0.358 and those on 675 mg 71% vs 49% placebo, 95% CI: 0.079 to 0.341, Table 1A). Chi square analyses indicated that the shift of migraine classification during the study was not independent of treatment, $X^2 = 1.91E-05$, $p = 0.91E-05$. As shown in Table 1B, 45% and 52% of patients on fremanezumab 225 mg and 675 mg showed a shift in migraine category from HFEM to LFEM in 3 months as compared to 20% of placebo patients.

**Conclusion:** As patients with migraine have more frequent migraine attacks, a central sensitization is facilitated, and a vicious cycle is created with a consequent increase on the frequency of migraine attacks. As treated patients were more likely to improve and less likely to worsen compared to those on placebo, this study suggests that fremanezumab may potentially prevent the progression of migraine to more chronic forms. Fremanezumab HFEM Study supported by Teva Pharmaceutical Industries Global Research and Development, Netanya Israel

<p>| Table 1. Patient classification in migraine categories during the HFEM study. |
|------------------|------------------|------------------|
| Overall shift in migraine categorya | Placebo | Fremanezumab 225 mg | Fremanezumab 675 mg |</p>
<table>
<thead>
<tr>
<th>Num (%) patients in 3rd month</th>
<th>n = 104</th>
<th>n = 95</th>
<th>n = 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsen</td>
<td>7 (7%)</td>
<td>2 (2%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Stable</td>
<td>42 (40%)</td>
<td>14 (15%)</td>
<td>17 (18%)</td>
</tr>
<tr>
<td>Improve</td>
<td>51 (49%)</td>
<td>69 (73%)</td>
<td>68 (71%)</td>
</tr>
<tr>
<td>Discontinued</td>
<td>4 (4%)</td>
<td>10 (11%)</td>
<td>8 (8%)</td>
</tr>
</tbody>
</table>

*aShift in migraine category, worse = HFEM to CM, stable = HFEM to HFEM, improve = HFEM to MFEM or HFEM to LFEM, discontinued = left study*  

<table>
<thead>
<tr>
<th>Table 1B. Migraine Categories</th>
<th>Placebo</th>
<th>Fremanezumab 225 mg</th>
<th>Fremanezumab 675 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Num (%) patients</td>
<td>n = 98b</td>
<td>n = 88</td>
<td>n = 91</td>
</tr>
<tr>
<td>HFEM</td>
<td>41 (42%)</td>
<td>14 (16%)</td>
<td>17 (19%)</td>
</tr>
<tr>
<td>MFEM</td>
<td>28 (29%)</td>
<td>22 (25%)</td>
<td>21 (23%)</td>
</tr>
<tr>
<td>LFEM</td>
<td>20 (20%)</td>
<td>40 (45%)</td>
<td>47 (52%)</td>
</tr>
</tbody>
</table>

Migraine Preventive Therapy

PO-01-081
Impact of Chronic Migraine on Health Resource Utilization, Quality of Life, and Work Productivity: Baseline Results from a Prospective, Observational Study (PREDICT)

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5600 Hys Centre, Edmonton
6Allergan plc, Ontario, Canada

Objectives: The PREDICT study aims to examine the long-term health-related quality of life (QoL) in patients being treated with onabotulinumtoxinA for chronic migraine (CM).

Methods: This is a multicenter, prospective, observational study in adult patients with CM naïve to onabotulinumtoxinA treatment (NCT02502123). Seven treatments of onabotulinumtoxinA are to be administered as described in the Canadian onabotulinumtoxinA product monograph (version July 7, 2014). The primary endpoint is the mean change at treatment 4 from baseline in the Migraine-Specific Quality of Life (MSQ). Secondary endpoints include healthcare resource utilization and work productivity. Data as of December 31, 2016 are summarized descriptively.

Results: Patients included in this analysis (N = 191) were on average 45 years of age (range = 19–72, n = 187); majority were female (85.1%, n = 160/188) and Caucasian (94.1%, n = 176/187). Average age at CM diagnosis was 39 years (range = 7–73, n = 178). The mean age at which the patient started experiencing headache on >15 days a month was 34 years (range = 4–69, n = 177). Patients reported an average 23.1 headache days per month (range = 12.0–30.6, n = 184) in the past 3 months and the majority (60.4%, n = 110/182) indicated a family history of CM. Majority of patients (95.1%, n = 176/185) had taken abortive medications for CM in the past 3 months; most commonly reported were simple analgesics (70.7%, n = 135/191) and triptans (67.0%, n = 128/191). Patients also indicated use of opioid combination analgesics (14.7%, 28/191) and/or opioids (2.6%, 5/191) in the past 3 months (patients taking opioid-containing products on more than 8 days per month were excluded from the study). Majority of patients (80.4%, n = 148/184) had taken a prophylactic medication for CM in the past 2 years; most commonly reported were antidepressants (47.1%, n = 90/191) and anticonvulsants (41.4%, n = 79/191). A total of 176 patients (96.7%) had visited a healthcare professional for treatment/evaluation of their headache and 32 patients (17.7%) indicated visiting an emergency room or urgent care clinic in the past 6 months; many (33.9%, n = 61/180) had received headache-related diagnostic testing. MSQ scores (lower scores indicate decreased QoL) revealed that migraine had the biggest impact on limiting the performance of daily activities (mean[SD] = 36.7[17.6], n = 185) and the lowest impact on preventing the performance of daily activities (mean[SD] = 51.1[22.6], n = 185). Patients employed at the time of screening (73.9%, n = 136/184) worked an average 27.4 hours (SD = 15.5) during the past 7 days and on average missed an additional 6.0 hours (SD = 9.7) of work due to problems associated with their headache. On average, patients indicated that their work productivity was 54% impaired and regular daily activities were 61% impaired due to headaches during the past 7 days.

Conclusion: Baseline data continue to demonstrate the social and economic burden of CM through the increased health-related costs and impairment in work productivity and regular daily activities. In addition, the observed gap in CM diagnosis, impact of headache on QoL, as well as the numerous medications prescribed, many of which have been shown to be ineffective, are all evidence of the unmet need. The PREDICT study may help to provide data on the longer-term impact of onabotulinumtoxinA on QoL in patients with CM.


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Migraine Preventive Therapy

PO-01-082

Fremanezumab (formerly TEV-48125) decreases migraine symptoms such as nausea, vomiting, photophobia and phonophobia and reduces the need for acute medications in the first week of treatment in the HFEM study.

Marcelo Bigal¹, Mirna McDonald², Ernesto Aycardi¹-*, Pippa Loupe³, Robert Noble⁴ and Investigators of the Fremanezumab (TEV-48125) HFEM Study

Objectives: Migraines have a substantial impact on daily living, affecting productivity and impacting the quality of life for patients and their families. Patients frequently take acute medications to relieve migraine pain and reduce associated symptoms. Fremanezumab (formerly TEV-
48125) was found to be effective and well-tolerated as a preventive treatment for migraine in a 3 month phase 2 high frequency episodic migraine (HFEM) study. The present analyses evaluated the efficacy of two doses of subcutaneous fremanezumab (225 mg and 675 mg) during the first three weeks of therapy in patients with high frequency episodic migraine (HFEM) to relieve symptoms associated with migraine pain such as nausea, vomiting, photophobia and phonophobia and the use of acute medications.

**Methods:** In this multicenter, placebo-controlled, parallel-group study, patients with HFEM were first screened and trained to use an electronic headache diary during a 28 day run-in period. After the run-in period, participants who met inclusion criteria and were 80% compliant with daily diary intake were randomized, and treated once every 28 days for three months with either placebo, fremanezumab 225 mg or 675 mg. Compared to placebo, both doses of fremanezumab significantly reduced the primary endpoint of the HFEM study, change in the number of migraine days in month 3 relative to baseline; herein we performed post-hoc analyses to assess the efficacy of each dose during the first 3 weeks of treatment to reduce migraine symptoms of nausea, vomiting, photophobia and phonophobia. We also determined whether in the first 3 weeks of therapy patients taking fremanezumab were able to reduce their consumption of acute medications for migraine relative to patients taking placebo.

**Results:** The sample consisted of 296 study participants. Compared to placebo, decreases in days with nausea or vomiting occurred within 1 week of therapy for fremanezumab 225 mg and 675 mg doses (both p < 0.01), a benefit that was maintained through the second and third weeks of therapy (Fig. 1 Panel A). Both doses decreased the number of days with photophobia and phonophobia at 1 week (p < 0.0001; Figure 1 Panel B), two weeks (p = 0.0003 and p = 0.0004) and 3 weeks (p = 0.0044 and p = 0.0047). For the weekly number of days taking acute medications, there were decreases for both fremanezumab doses compared to placebo during week 1 (p < 0.0001), week 2 (p < 0.0001) and week 3 (p < 0.0001 and p = 0.0002), shown in Fig. 1, Panel C.

**Conclusion:** In post-hoc analyses, fremanezumab treatment resulted in a rapid preventive response in patients with HFEM, with improvements seen in reducing migraine symptoms such as nausea, vomiting, photophobia and phonophobia within the first week of fremanezumab therapy. Patients also were able to rapidly reduce their use of acute medications to treat migraine attacks. The HFEM study was supported by Teva Pharmaceutical Industries Netanya Israel.


**Migraine Preventive Therapy**

PO-01-083

Body fat was associated to migraine in a sample of young university students of são paulo, brazil

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2Neurology, Universidade Federal de São Paulo, São Paulo, Brazil

**Objectives:** This study aimed to evaluate the association between nutritional status and the occurrence of migraine in University students from São Paulo-Brazil.

**Methods:** Cross-sectional study carried out with 46 students, men and women, over 18 years old, enrolled in different undergraduate courses of a private University. The students were invited to the nutritional status assessment consisted by the measurement of the following variables: weight, height and abdominal circumference. Body Mass Index (BMI) was calculated and the results were classified according to the cut-off points of World Health Organization (WHO) (1998). Cardiovascular risk, according to the abdominal circumference (AC) measurement, was either evaluated according to WHO (2000) cut-off points. To determine participants’ body composition, specially body fat percentage, and hydration status, bioelectrical impedance was performed. Body fat values were categorized by Lohman et al (1988) recommendations. Then the students answered a questionnaire about headache occurrence, for medical diagnosis, being the results evaluated by an experimented neurologist, according to the International Headache Society (2013) criteria for classification of migraine types. Statistical analyzes were performed using SPSS software, version 21. To investigate the associations between the occurrence of migraine and BMI categories, cardiovascular risk according to AC, fat percentage categories and hydration level chi-square test was used and to study differences in means between individuals with or without migraine, Student’s t-test was performed, considering a 5% significance level. The Ethics Committee of the University approved this research (n.50839915.9.0000.0084).

**Results:** Sixty-one percent of the students were female (n = 28) and the mean age was 22.2 years old (min. 18;
max. 32). Most of the students, 95.7%, reported at least one headache episode in the last 12 months, and 71.7% of the university students met the criteria for migraine, with a higher prevalence of migraine without aura (63.6%). Twenty-nine percent of the women were overweight according to BMI classification, and only 3.6% had a body fat percentage considered adequate. Half of male students presented body fat percentage above the average values reported by Lohman et al. Twenty-five percent of the women presented an increased risk of cardiovascular diseases, and of these, 7.1% presented a very high risk for metabolic diseases. The majority of the students, 80.4%, were well hydrated according to bioelectrical impedance. No associations were found between BMI and AC categories and migraine. This study showed a statistically significant association between body fat percentage and occurrence of migraine (p = 0.008), and individuals with migraine had mean values 6.22% higher than those without the condition (20.91% versus 14.69%). No differences in mean values of body hydration between students with or without migraine diagnosis were found (p = 0.070).

**Conclusion:** The results suggested that body fat percentage, but not hydration status, BMI or AC, was related to the occurrence of migraine in a Brazilian sample of University students.

**Disclosure of Interest:** None Declared

**Migraine Preventive Therapy**

**PO-01-084**

**Migraine prevalence and environmental triggers in university students of são paulo-brazil**

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1Health and Biological Sciences Center, Mackenzie Presbyterian University
2Neurology, Universidade Federal de São Paulo, São Paulo, Brazil

**Objectives:** This study evaluated the migraine prevalence and the triggers to this condition in young adults, students of a private University of São Paulo-Brazil.

**Methods:** A cross-sectional study was carried out with 197 students, men and women, enrolled in several courses of the University, with age above 18 years old. The students answered two questionnaires, one evaluating the presence of diagnostic criteria for migraine, recommended by the International Headache Society (2013) and the other on environment factors triggering migraine attacks, used by Rockett (2010), in southern Brazil. An experimented neurologist made the definitive diagnosis of migraine, using the questionnaire answers. Statistical analyzes were performed using SPSS software, version 21. For the investigation of associations between possible triggers and migraine, the chi-square test was used, and to study differences in triggering factors among individuals with migraine with aura or without aura, Student’s t-test was used at a significance level of p < 0.05. All the participants were volunteers and this research was conducted based on the ethics in human research guidelines, with approval of the Ethics Committee of the University, under the number 51061015.0.0000.0084.

**Results:** The mean age of participants was 21.75 years old (SD = 4.82), most of them being women (70.7%). Among the participants, 35.6% reported that they were simultaneously students and workers. Fifty-six percent of the students reported that they usually practice physical activity, being 67 (50.4%) females. Ninety-five percent of the participants reported at least one headache episode in the last 12 months, and 72.3% met the diagnostic criteria for migraine. The prevalence of migraine with aura was higher, affecting 52.2% of the students. Female students had a significantly higher prevalence of migraine (79.4% versus 20.6%, p < 0.001). In addition, the prevalence of migraine was higher among the students who did not work (p = 0.010). It was also possible to observe that individuals with aura have vestibular migraine (56.3% versus 41.5%, p < 0.001). There was no association between physical activity or sleep hours and migraine. Some triggers of migraine attacks were statically significant, such as fasting or omitting meals (p < 0.001), smelling strong odours (p < 0.001), menstrual period (p < 0.023) and cola soft drinks intake (p = 0.04). Menstrual period showed a strong association to attacks in the female students who had migraine with aura (61.1% against 31.5%, p < 0.002).

**Conclusion:** The results showed that the prevalence of migraine in the University students of the present research was higher than the results observed in other Brazilian studies. This is a preoccupant fact, because the attacks could impair the student performance in University, and reduce their quality of life. Young women seem to be more affected by migraine, and besides all the environmental triggers found in this study, menstrual period appeared to be an important additional factor for female participants.

**Disclosure of Interest:** None Declared
Migraine Preventive Therapy

PO-01-085
Rational Design of a Monoclonal Antibody Inhibiting Calcitonin Gene-Related Peptide, ALD403 (Eptinezumab), to Provide Early Onset, High Efficacy, Extended Duration of Action, and Desired Safety for the Prevention of Migraine

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Objectives: To describe the rational design objectives and clinical trial results supporting the efficacy, safety, and durability of action for ALD403 (eptinezumab), a genetically engineered humanized anti-CGRP antibody, for migraine prevention. Therapeutic mAbs currently in development that target the CGRP pathway may be differentiated by their unique characteristics relating to target selection, affinity, immunogenic recognition (Fcγ activity), route and schedule of administration, clearance mechanisms (FcRn activity and glycosylation pattern), formulation solubility, and bioavailability. Each of these characteristics was evaluated and intentionally selected during the ALD403 (eptinezumab) design process to achieve objectives for high efficacy, desirable safety profile, and patient adherence including optimal dose levels, a convenient treatment schedule (30 minutes intravenous [IV] infusion once every 12 weeks), early onset of migraine prevention, and a 12-week duration of activity.

Methods: The binding affinity for ALD403 to α-CGRP was evaluated by surface plasmon resonance. The pharmacokinetics, efficacy, and safety for ALD403 administration were evaluated in two Phase 2 clinical trials following single IV administration in patients with frequent episodic (FEM) or chronic migraine (CM), and one Phase 3 multi-dose trial in patients with FEM (PROMISE 1).

Results: ALD403 achieved high in vitro binding affinity, KD(M) = 1.5E−11, for the antagonism of soluble α-CGRP ligand, and a low concentration for the inhibition of capsaicin induced dermal vasodilation, IC50 = 0.5 μg/mL, in a Phase 1 trial following a single IV administration of 1,000 mg ALD403 in FEM patients, the mean maximum concentration, Cmax, 336.4 μg/mL, was observed 4.8 hours, Tmax, after the start of the 1-hour infusion. The mean elimination half-life, T1/2, was 27.9 days and ranged from 19.9 to 46.5 days. The mean plasma concentration, Cmin, observed at Week 12 was 25.6 μg/mL. Significant differences from placebo were observed for reductions in mean migraine days from baseline over Weeks 1–4, 1.7 days (p < 0.001), and Weeks 5–8, 0.9 days (p = 0.033). In CM patients, following IV infusion of 10, 30, 100, or 300 mg, exposure to ALD403 increased proportionally as indicated by respective area under the curve, AUCinf, values of 3,000, 7,884, 26,395, or 80,980 μg·hr/mL and Cmax values of 4.3, 11.0, 37.3, or 108.7 μg/mL. Mean concentrations of ALD403 Cmin at 12-weeks post-infusion of 10, 30, 100, or 300 mg were 0.3, 0.7, 2.4, or 7.7 μg/mL, respectively. Aggregate migraine hours/day were decreased 24 hours following administration and significant differences from placebo were observed for reductions in mean migraine days from baseline over Weeks 1–12 following 300 mg, 2.9 days (p < 0.001); 100 mg, 2.4 days (p = 0.003); or 30 mg, 2.8 days (p < 0.001).

Conclusion: The rational design of mAbs enables selection of attributes important for achieving a desired clinical efficacy and safety profile. ALD403 (eptinezumab) was designed in this way and has demonstrated 100% bioavailability, early onset of migraine preventative action, high efficacy in reducing migraine frequency, and a 12-week duration of action following a single IV infusion. These observations suggest ALD403 (eptinezumab) has the potential to be an important new treatment option for migraine prophylaxis in patients with FEM and CM.


Migraine Preventive Therapy

PO-01-086
Comparison of Propranolol versus Placebo Use in Reduction of Migraine Days by Frequency of Migraine Episodes, Systematic Review and Individual Patient Level Data Meta-Analysis

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Objectives: Propranolol is one of the medications considered efficacious in episodic migraine prophylaxis. However, there are no randomized controlled trials of propranolol in chronic migraine prophylaxis. It is becoming more widely recognized that chronic migraine patients suffer from a different disease process, but recent data indicates that frequent episodic migraine patients (> = 10 headache days/month) are more alike to chronic
migraine patients and as such may respond to similar medications.

We have undertaken a systematic review and individual patient level meta-analysis of trials that include a population of infrequent and frequent migraneurs to determine if the response to propranolol seen in episodic migraine is independent of frequency of attacks.

**Methods:** MEDLINE, EMBASE, Pubmed, were searched through to December 2016. Publications were also sought through a hand-search of journals and of the American Headache Society (AHS) and International Headache Society (IHS) conference proceedings and the references lists of identified trials were also reviewed to identify additional articles.

Studies were included if they were randomized controlled trials comparing propranolol with placebo or an active comparator in adult migraineurs and had available individual patient level data. Trials were assessed independently by two reviewers. The pooled headache frequency on propranolol was the outcome measure, varying this by headache frequency on placebo to determine if there was an effect of headache frequency at baseline with response to propranolol.

**Results:** Three randomized controlled trials (RCT) were included in the individual patient level meta-analysis, they were class III trials. The analysis was done by subgroups in each trial of infrequent and frequent episodic migraneurs as defined by headache days on placebo (likely an underestimate of headache frequency). Our analysis shows that there is a treatment effect in reduction of mean headache frequency in each of these respective populations compared to placebo.

**Conclusion:** Propranolol is shown efficacious in reducing the headache frequency in frequent episodic migraneurs, a population that likely overlaps with chronic migraine patients. Although this analysis is limited by a small number of patients in the frequent migraine group, it raises the possibility that propranolol is useful in chronic migraine patients for migraine prophylaxis, and provides justification for a study looking at this question.

**Disclosure of Interest:** None Declared

**Migraine Preventive Therapy**

**PO-01-087**

**Effect of anti-CGRP receptor antibody AA58 on CGRP receptor internalization and trafficking**

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2Neuroscience
32Medical Sciences
4Therapeutic Discovery, Amgen Inc., Boston, United States

**Objectives:** Therapeutic antibodies that block the CGRP signaling pathway are a promising new drug class for migraine prevention. An anti-CGRP receptor antibody has demonstrated efficacy in clinical studies for the treatment of episodic and chronic migraines. To further understand the mechanism of action of the antagonist antibody, we measured the effects of anti-CGRP receptor antibody AA58 on the CGRP receptor internalization and trafficking in engineered cells.

**Methods:** We engineered a CHO cell line, which does not endogenously express CLR or RAMP1, by co-expressing His-tagged RAMP1 and myc/FAP-tagged CLR. The...
cells were used to directly measure both functional responses and receptor internalization after exposure to agonist alpha-CGRP (CGRP) alone or in combination with CGRP receptor antagonist antibody AA58. CGRP receptor signaling was measured by a cAMP accumulation assay and receptor internalization was monitored with a flow cytometric fluorogen-activating protein (FAP) assay. Immunofluorescence (IF) confocal microscopy was also used to visualize CGRP receptor internalization and trafficking in cells processed at fixed time points. cAMP responses and receptor internalization were compared to those in CHO cells expressing un-tagged CGRP receptor components. Functional cAMP responses were also measured in SK-N-MC cells expressing native CGRP receptors to confirm receptor pharmacology.

**Results:** Exposure to AA58 alone induced neither cAMP accumulation nor internalization of the CGRP receptor. Exposure to agonist CGRP led to comparable dose-dependent cAMP accumulation in CHO cell lines expressing tagged or un-tagged CGRP receptors. In all cell lines tested, responses to agonist CGRP were blocked by co-incubation with an antagonist peptide CGRP8–37 or with AA58.

Prior to the application of agonist or antagonist, CGRP receptor immunoreactivity was confined to the cell membrane. As measured by flow cytometry, CGRP induced internalization of the receptors within minutes of application. IF confocal microscopy visually confirmed immunoreactivity of CGRP receptor on both membrane and intracellular vesicles 5 minute after CGRP application. Following 10 min of agonist application, most of the CGRP receptor immunoreactivity was localized to the intracellular compartment. At the 30 min time point, immunoreactivity was observed in perinuclear bodies that colocalized with LAMP2 immunostaining (a marker of lysosomal membrane protein) suggesting that CGRP receptor was targeted for lysosomal degradation. Coincubation with AA58 blocked CGRP induced internalization of the CGRP receptors.

There was no indication of apoptosis based on nuclear morphology indicating that AA58 blockade is not detrimental to cell health.

**Conclusion:** Using an engineered CHO cell line expressing tagged, functional CGRP receptors, we demonstrate that exposure to anti-CGRP receptor antibody AA58 alone did not induce any cAMP response and the internalization of the receptor. However AA58 inhibits agonist-induced cAMP accumulation and receptor internalization. These findings suggest that therapeutic antibodies act by inhibiting the CGRP-induced functional cAMP response and delaying receptor internalization and trafficking.


**Migraine Preventive Therapy**

**PO-01-088**

**Postural correction and orthopedic massage decrease migraine episodes and reduce headache attributed lost time**

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**Objectives:** Due to controversial information about the effect of different physiotherapy methods used in the treatment of migraine patients, the aim of the study was to assess postural correction and the effect of orthopedic massage to upper body posture; the frequency of migraine attacks; headache attributed lost time; head, neck and shoulder girdle muscles tone and active range of cervical motion in migraine patients before and after five week therapy program.

**Methods:** The purpose of the postural correction therapy program was to instruct and guide subjects to maintain good upper body alignment during sitting, standing or walking in everyday activities. The program consisted of five sessions administered once a week. The duration of each therapy session was one hour. Every session included postural correction and the orthopedic massage, lasting 55 minutes.

Upper body alignment from anterior, posterior and lateral view was assessed with observation (New York Posture Rating Chart). Score of posture was formed of the head, shoulders and thoracic spine evaluation results (free evaluable structures in free view, 0–3 indicating poor, 4–7 fair and 8–10 good posture). Based on the subjects headache diary and the question “On how many days in the last month did you have a headache” from The Headache Under-Response to Treatment (HURT) Questionnaire migraine episodes during the past months were recorded. Headache attributed lost time was assessed with HALT questionnaire. Muscles tone was assessed bilaterally using the Total Tenderness Score (TTS) in subject’s supine and prone position for m. trapezius pars descedens, m. splenius capitis, linea nuchalis superior, m. levator scapulae, m. sternocleidomastoideus, m. masseter, m. temporalis, m. deltoideus pars anterior. Active range of cervical motion (caROM) was assessed in six directions by cervical goniometry.
This study was approved by the Research Ethics Committee of the University of Tartu.

**Results:** Ten consented patients (9 women, 1 man) with migraine diagnosis (2 with aura and 8 without aura) were included in a five-week postural correction and orthopedic massage therapy. The patients’ mean age was 41.6 years (SD 10.78 years, range 23–58 years) and the mean body mass index 24 kg/cm² (SD 3.8 kg/cm², range 18–30 kg/cm²). The average period of migraine symptoms was 14.6 years (SD 12.1 years, range 2–36 years). Before therapy, during the past month migraine episodes were reported on 10.3 days (SD 5.59, range 3–16).

After the therapy subjects' upper body posture was 10.4% more correct in every three assessed views than before therapy (respectively before therapy 25.1 and after therapy 9.5% in flexion (53.7 and 59.3 degrees; p < 0.01), 12.8% in extension (61.1 and 70.1 degrees; p < 0.05), 13.8% in rotations to the right (67.3 and 78.1 degrees; p < 0.05) and 11.5% to the left (72.8 and 82.3 degrees; p < 0.05). Lateral flexion to the right (35.3 and 39.7 degrees) and to the left (40.3 and 45.3 degrees) were also increased (both 11.1%), but not significantly (p > 0.05). Migraine days per month decreased 35.9% (10.3 and 6.6 days; p < 0.05). HALT and Total Tenderness scores were significantly lower compared to the baseline (51.3%, 24.2 and 11.8 HALT score; p < 0.01, and 49.9%, 24.5 and 12.4 TTS score p < 0.001 respectfully).

**Conclusion:** Postural correction and orthopedic massage are effective in decreasing migraine days, probably leading to an improved quality of migraine patients’ life. Physiotherapy methods used in current study were effective also in improving upper body functionality related with upper body posture, head, neck and shoulder girdle muscles tone and cervical mobility.

**Disclosure of Interest:** None Declared

### Migraine Preventive Therapy

**PO-01-089**

**Hull Prospective Analysis of OnabotulinumtoxinA (Botox) in the treatment of Chronic Migraine; a real-life data in 742 patients; updated results on over six years of experience**

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**Objectives:** To evaluate the efficacy and safety of OnabotulinumtoxinA in adult patients with Chronic Migraine (CM) in real-life settings.

**Methods:** Adult patients with CM attending the Hull Migraine Clinic were treated with OnabotulinumtoxinA based on clinical needs. Patients were treated as per PREEMPT protocol. Patients were asked to maintain a headache diary for at least 30 days prior to and continuously after treatment. Patients with medication overuse were included based on the expert opinion. Data were extracted for headache days, migraine days, crystal clear days (headache-free) as primary outcome; also analgesic consumption, adverse events and quality of life using HIT-6. Responder was defined as per Hull criteria (50% reduction in either headache or migraine days or increment on headache free days twice the baseline) for treatment in the first cycle.

**Results:** Of a series of 742 patients (July 2010 – February 2017) full data were available on 626 patients (112 male, median age 48 years; range 19–77 years, 514 female, median age 45 years; range 18–91 years). A total of 3368 cycles were given. 611 (97.6%) had failed three preventive treatments. 363 (57.9%) patients were overusing analgesics. Patients had CM for a median of 4 years (Range 0.5–67 years). 363 (58.4%) responded based on Hull Criteria and reported improved health related quality of life outcome. 82 (13.0%) reported adverse events mainly stiffness in the neck with 50 (7.9%) reporting mild ptosis.

**Conclusion:** We report on a large cohort of real life patients receiving OnabotulinumtoxinA for chronic migraine.

**Disclosure of Interest:** F. Ahmed Conflict with: Allergan, Eneura, Electrocore, Novartis as Advisory Board member paid to British Association for the Study of Headache and the Migraine Trust, Conflict with: Educational Officer for British Association for the Study of Headache, Trustee of Migraine Trust, IHS Board Member, A. Ghabeli: None Declared, A. Buture: None Declared, M. Khalil: None Declared

### Migraine Preventive Therapy

**PO-01-090**

**Does Medication overuse matter? Response to OnabotulinumtoxinA in Chronic Migraine (CM) patients with or without medication overuse; update from real-life data**

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**Objectives:** Introduction: CM affects 2% of the general population with substantial impact on quality of life.
Medication overuse in CM is seen in around two third of patients in specialist headache clinics. There is lack of consensus on whether preventive treatment be initiated before or after the analgesic withdrawal. We analysed the response to OnabotulinumtoxinA in patients with CM with or without analgesic overuse treated at the Hull Migraine Clinic.

**Objectives:** To compare the efficacy of OnabotulinumtoxinA in adults with Chronic Migraine with or without medication overuse.

**Methods:** Adult patients with CM were offered OnabotulinumtoxinA based on clinical need and were injected based on the PREEMPT treatment paradigm. Headache diaries were maintained for 30 days prior to and continuously after treatment. Data were extracted for headache, migraine and headache-free days and responders were defined based on Hull Criteria (50% reduction of either headache or migraine days or increment in headache free days twice that of the baseline).

**Results:** Of 742 patients, full data for the first cycle was available on 626 patients [363 (57.9%) with analgesic overuse and 263 (42.1%) without overuse]. The responder rate based on Hull criteria was 59.8% in patients with analgesic overuse compared to 56.8% in patients without overuse. 50% reduction in Migraine days was 41% and 44% respectively. There was significant reduction in days with analgesic consumption in both groups.

**Conclusion:** Patients with CM respond equally well to OnabotulinumtoxinA irrespective of analgesic consumption at baseline.

**Disclosure of Interest:** M. Khalil: None Declared, A. Buture: None Declared, A. Ghabeli: None Declared, F. Ahmed Conflict with: Allergan, Eneura, Electrocore, Novartis as Advisory Board member paid to British Association for the Study of Headache and the Migraine Trust, Conflict with: Educational Officer for British Association for the Study of Headache, Trustee of Migraine Trust, IHS Board Member

**Migraine Preventive Therapy**

**PO-01-091**

Long term outcome for OnabotulinumtoxinA therapy in Chronic Migraine; a two year follow up of 403 patients from the Hull Migraine Clinic

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**Objectives:** Introduction: The long-term outcome for patients with CM treated with OnabotulinumtoxinA remains uncertain. The National Institute for Health and Care Excellence (NICE) recommends discontinuing treatment if there is no response to two consecutive cycles (negative stopping rule) or when the migraine becomes episodic (positive stopping rule). However, this is based on consensus only.

**Objectives:** To determine the long term outcome of patients with CM treated with OnabotulinumtoxinA.

**Methods:** Methods: All patients treated with OnabotulinumtoxinA at the Hull Migraine Clinic were prospectively followed. Treatment was delivered as per the PREEMPT paradigm. Responders were defined as per NICE or Hull criteria. Treatment was stopped if there was no response to two consecutive cycles or until the headache days were less than 10 for three consecutive months (modified positive stopping rule).

**Results:** Results: Of a series of 742 patients treated between July 2010 and February 2017 and received 3368 cycles, full data was available on 626 patients. Treatment data for at least two years (range 24–54 months) was available on 403. 234 (58.06%) patients fulfilled either NICE (48%) or Hull criteria for responder at cycle 2 and continued treatment. 169 patients (41.9%) stopped treatment at cycle two. Of the 234 patients 94 (40.17%) patients continued treatment for two years or more and 140 (59.8%) were able to stop the treatment within two years; 32/140 (22.8%) relapsed after stopping, 15/140 (10.7%) got resistant after initial response and 88/140 (62.85%) remained episodic.

**Conclusion:** Conclusion: At two years, 40% of initial cohort of responders will still require therapy with OnabotulinumtoxinA.

**Disclosure of Interest:** A. Buture: None Declared, A. Ghabeli: None Declared, M. Khalil: None Declared, F. Ahmed Conflict with: Allergan, Eneura, Electrocore, Novartis as Advisory Board member paid to British Association for the Study of Headache and the Migraine Trust, Conflict with: Educational Officer for British Association for the Study of Headache, Trustee of Migraine Trust, IHS Board Member

**Migraine Preventive Therapy**

**PO-01-092**

Analysis of patterns of response to OnabotulinumtoxinA in Chronic Migraine in predicting long-term outcome

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**Objectives:** Introduction: The efficacy of OnabotulinumtoxinA for Chronic Migraine (CM) is
established; however, long term outcome data is limited and need for ongoing treatment remains uncertain.

Objectives: The study aims to identify patterns of response to OnabotulinumtoxinA that predict successful conversion to episodic migraine.

Methods: Adult patients receiving OnabotulinumtoxinA for CM at the Hull Migraine Clinic were prospectively followed. All patients maintained headache diary continuously during treatment. Data was extracted on headache and migraine days to identify patterns of response and need for ongoing treatment at two years.

Results: Of 403 patients followed up for at least two years 234 fulfilled NICE or Hull Criteria for responder and continued treatment beyond cycle 2. Of the 234 responders, 94 patients were still obtaining positive response at year 2 and 88 were successfully converted to episodic migraine. Others were either lost to follow up, relapsed, became resistant or stopped treatment for other reasons. Our study analysed patterns of response and outcome in the cohort of 182 responders. We found two distinct patterns of response with 100 (54.9%) patients having a fluctuating ‘wearing off’ pattern with an increase in headache frequency prior to their next treatment; 82 (45.05%) having a steady decline on headache days without significant fluctuation between treatments. We found that the ‘wearing off’ pattern predicted those patients who would remain in chronic migraine with only 12/100 (12%) patients converting to episodic migraine compared to 63/82 (76.8%) with stable non-fluctuating response.

Conclusion: We observed two distinct patterns of response that help to predict long-term outcome.

Disclosure of Interest: A. Buture: None Declared, A. Ghabeli: None Declared, M. Khalil: None Declared, F. Ahmed Conflict with: Allergan, Eneura, Electrocore, Novartis as Advisory Board member paid to British Association for the Study of Headache and the Migraine Trust, Conflict with: Educational Officer for British Association for the Study of Headache, Trustee of Migraine Trust, IHS Board Member

Migraine Preventive Therapy

PO-01-093

OnabotulinumtoxinA in Chronic Migraine; Predicting response to treatment based on headache days at baseline

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Objectives: OnabotulinumtoxinA is an established preventive treatment for Chronic Migraine (CM). Predicting response to treatment is unknown, although potentially duration of CM, frequency of headache or migraine days may have some bearing on the response rate. To establish whether the number of headache days at the baseline predict response to treatment with Botox in adult patients with CM.

Methods: Patients receiving OnabotulinumtoxinA at the Hull Migraine Clinic were prospectively followed. The treatment was delivered as per PREEMPT protocol and patients were asked to maintain a headache diary at least four weeks before and continuously after treatment. Data was extracted for headache and migraine days and headache free days before and after treatment. Patients were divided into three frequency groups based on the number of headache days pre-treatment as low frequency (15–20), moderate frequency (21–25) or high frequency (26–30). The response to treatment in the three groups were compared.

Results: Of a series of 742 patients treated between July 2010 and February 2017, full data was available on 626 patients receiving 3368 cycles in total. 125 (19.9%) had low frequency, 144 (23%) had moderate frequency and 357 (57%) had high frequency headache days. Patients with low or moderate frequency of headache days at baseline tend to respond better than those with high frequency headache days before treatment. However, the improvement in severity (migraine days) was similar in the three groups. Achievement of headache free days was more in those with high frequency at baseline. Applying Hull Criteria that considers headache, migraine and headache free days to identify response, patients with moderate frequency seem to respond better.

Conclusion: Patients with low or medium frequency of headache days at baseline seem to respond better than those with high frequency headache days before treatment.

Disclosure of Interest: A. Buture: None Declared, A. Ghabeli: None Declared, M. Khalil: None Declared, F. Ahmed Conflict with: Allergan, Eneura, Electrocore, Novartis as Advisory Board member paid to British Association for the Study of Headache and the Migraine Trust, Conflict with: Educational Officer for British Association for the Study of Headache, Trustee of Migraine Trust, IHS Board Member

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Migraine Preventive Therapy

PO-01-094

A Multicenter, Prospective, Single Arm, Open Label, Post-Market, Observational Study to evaluate the use of sTMS in reduction of Migraine Headache (ESPOUSE Study)

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Objectives: Single pulse transcranial magnetic stimulation (sTMS) is an FDA-approved acute treatment for migraine with aura. Open label patient experience in the United Kingdom has suggested a possible preventive benefit in migraine. The objective of this clinical trial was to evaluate the efficacy and tolerability of sTMS for the treatment of migraine.

Methods: The ESPOUSE Study was a multicenter, prospective, single-arm, open label, observational study to evaluate sTMS for the preventive treatment of migraine with or without aura. From December 2014 to March 2016, 263 patients with migraine were consented to complete a 1-month baseline headache diary followed by 3 months of treatment. The full analysis set (FAS) included patients who completed the baseline headache diary, met the inclusion criteria including 5-25 headache days per month, and used the device at least once. The treatment protocol consisted of both preventive (4 pulses twice daily) and acute treatment (3 pulses at 15 minute intervals repeated up to 3-times for each attack). The primary effectiveness endpoint (PEE), mean reduction of headache days compared to baseline, was measured over the 28-day period ending at 12 weeks. In the absence of a placebo control group, the PEE was compared to the performance goal, which is a statistically-derived, estimated placebo effect size, based on historical controls, of -0.6 day reduction of headache days from baseline.

Results: A total of 263 subjects were consented, 229 completed a baseline diary, 220 subjects were found to be eligible based on the number of headache days, and 217 were assigned a device (safety data set). 132 subjects met the strict inclusion criteria based on the protocol definition of a headache day (4 or more hours of headache reaching moderate to severe pain), comprising the FAS. FAS baseline characteristics include: mean age of 42.8 years; 80.3% female; 85.6% Caucasian, 8.3% African American, 5.3% Hispanic, and 0.8% other. The PEE analysis was assessed in the FAS dataset. The mean reduction of headache days from baseline compared to the performance goal was statistically significant. There was -2.8 ± 0.4 mean reduction of headache days from baseline (9.1 days) in the FAS compared to the performance goal of -0.6 days (p < 0.0001). 19.4% of subjects reported adverse events that were determined as “definitely”, “probably”, or “possibly” device-related. There were no serious adverse events. The top three adverse events were lightheadedness (4.5%), tingling (3.9%), and tinnitus (3.9%). 9 patients withdrew from the study because of adverse events.

Conclusion: This open label study suggests that sTMS may be an effective, well-tolerated treatment option for migraine prevention.

The ESPOUSE Study was supported by eNeura Inc.

Disclosed of Interest: A. Starling Conflict with: Amgen, Lily, eNeura, S. Tepper Conflict with: ATI, Conflict with: Alder, Allergan, Amgen, ATI, Avanir, Electrocore, eNeura, Scion Neurostim, Teva, Kosano, Conflict with: Acorda, Alder, Allergan, Amgen, ATI, Avanir, BioVision, Dr. Reddy’s, Electrocore, Eli Lily, eNeura, Kimberly-Clark, Perini, Pfizer, Scion Neurostim, Teva, Kosano, M. Marmura Conflict with: Teva, eNeura, Conflict with: Teva, Supernus, E. Shamim Conflict with: kinetics Foundation, CD PROBE (Allergan), COMPEN(Allergan), Myorisk (NIEHS), eSPOUSE (eNeura), NIH intramural support NINDS and NIHMS, Mid-Atlantic Permanente Research Institute. I have not received any personal compensation from Allergan but have received research funding, M. Robbins Conflict with: eNeura, N. Hindiyeh: None Declared, A. Charles: None Declared, P. Goadsby Conflict with: Grants and personal fees from Allegan, Amgen and Eli Lilly and company. Personal fees from Akita Biomedical, Alder Biopharmaceuticals, Autonomic Technologies Inc, Avanir Pharma, Cipla Ltd, Colucid Pharmacueticals Ltd, Dr Reddy’s Laboratories, eNeura, Electrocore LLC, Novartis, Pfizer Inc, Promius Pharma, Quest Diagnostics, Scion, Teva Pharmaceuticals, Trigemina Inc., Scion; and personal fees from MedicoLegal work, Journal Watch, Up-to-Date, Oxford University Press and in addition, Dr Goadsby has a patent Magnetic stimulation for headache pending assigned to eNeura., R. Lipton Conflict with: He receives research support from the NIH: 2PO1 AG003949 (Program Director), 5U10 NS077308 (PI), 1RO1 AG042595 (Investigator), RO1 NS082432 (Investigator), K23 NS09610 (Mentor), K23AG049466 (Mentor). He also receives support from the Migraine Research Foundation and the National Headache Foundation. He serves on the editorial board of Neurology and as senior advisor to Headache. He has reviewed

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Objectives:
Sporadic hemiplegic migraine (SHM) is a rare form of migraine with aura associated with motor weakness defined by its absence in the first or second degree relatives of the probands. Treatment is based on case reports only and the young age of onset in women complicates treatment during child bearing years. This case report adds to the evidence for prophylaxis and acute treatment in women of childbearing age with SHM and the young age of onset in women complicates treatment during child bearing years. This case report adds to evidence for treatment of SHM which has largely been limited to case reports of prophylaxis and acute medication which are contraindicated in pregnancy. The treatment continued throughout her pregnancy and breastfeeding with good effect.

Methods:
A 32 year old doctor presented with a two year history of SHM. She had episodes of unilateral hemisensory progressing to hemiplegic aura lasting up to 48 hours. She continued to have regular migraines without aura. Imaging and investigations were normal on multiple admissions. Triptans were unsuccessful in treating the attacks. Pizotifen which she used previously was not controlling her symptoms. Due to the severe functional impact of the motor aura and headache were causing on her work and family and her wish to conceive, Propranolol 80 mg bd was used. Acute treatment was changed to nVNS at the onset of sensory aura with headache along with simple analgesics. nVNS was used twice daily for one month and then acutely for sensory attacks. She was able to abort hemisensory attacks including those progressing distally into her limbs which would previously have resulted in motor aura, by using nVNS acutely along with the low dose simple analgesics. She noticed that 30 minutes after using her acute treatment her symptoms would start to resolve in a way that she had not previously experienced. She became pregnant 6 months later and continued with the Propranolol and nVNS/ Paracetamol. The dose of Propranolol was lowered to 40 mg bd through her late pregnancy without change to her migraine symptoms.

Results:
A pragmatic approach to treatment using several interventions was tried due to the severity of her symptoms. The combination of Propranolol with nVNS/simple analgesia reduced her total MIDAS score from 104 to 22 before her pregnancy, with the HIT6 reducing from 66 to 60. nVNS and low dose simple analgesia was successfully used acutely and stopped the patient’s normal progression of symptoms to motor aura from the initiation of prophylaxis and through the subsequent months. The initiation of nVNS improved the effectiveness of her acute treatment with the result that this combination was sufficient through pregnancy. The treatment continued throughout her pregnancy and breastfeeding with good effect.

Conclusion:
There is only one case report to our knowledge of Propranolol being used as prophylaxis for hemiplegic migraine. This case report adds to evidence for treatment of SHM which has largely been limited to case reports of prophylaxis and acute medicine which are contraindicated in pregnancy. The treatment was well tolerated and enhanced the patient’s quality of life as shown in the improvements in quality of life measures. The difference in improvement between the MIDAS and HIT6 highlights the improvement in the work related impact of the hemiplegic migraine which was more identifiable in the MIDAS scale. We suggest that Propranolol should be considered for treatment in women of childbearing age with SHM and further work should be undertaken into the use of nVNS for acute treatment of hemiplegic migraine.

Disclosure of Interest: None Declared

Migraine Preventive Therapy

PO-01-095

Case report: treatment of sporadic hemiplegic migraine with propranolol and non invasive vagal nerve stimulation (nVNS) in a young woman through pregnancy

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Objectives: Sporadic hemiplegic migraine (SHM) is a rare form of migraine with aura associated with motor weakness defined by its absence in the first or second degree relatives of the probands. Treatment is based on case reports only and the young age of onset in women complicates treatment during child bearing years. This case report adds to the evidence for prophylaxis and acute treatment for hemiplegic migraine.

Methods: A 32 year old doctor presented with a two year history of SHM. She had episodes of unilateral hemisensory progressing to hemiplegic aura lasting up to 48 hours. She continued to have regular migraines without aura. Imaging and investigations were normal on multiple admissions. Triptans were unsuccessful in treating the attacks. Pizotifen which she used previously was not controlling her symptoms. Due to the severe functional impact...
**Migraine Preventive Therapy**

**PO-01-096**

**OnabotulinumtoxinA for Chronic Migraine during pregnancy: experience from Hull Headache Clinic, United Kingdom**

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**Objectives:** The use of OnabotulinumtoxinA during pregnancy is restricted due to the lack of adequate and well-controlled studies. While women who are pregnant, nursing or planning a pregnancy are excluded from clinical trials, many women treated with OnabotulinumtoxinA for axillary hyperhidrosis, chronic migraine and cosmetic indications are of reproductive age. A 24-year retrospective review of the Allergan safety database on 574 pregnancies demonstrated that the prevalence of fetal defects in OnabotulinumtoxinA-exposed mothers to be comparable to background rates in the general population. Most of these patients were treated for cosmetic reasons or movement disorders. There are no reports regarding patients with Chronic Migraine exposed to OnabotulinumtoxinA therapy during pregnancy.

**Objective:** We report pregnancy outcomes on 15 patients with Chronic Migraine exposed to OnabotulinumtoxinA.

**Methods:** Adult patients treated with OnabotulinumtoxinA for prophylaxis of Chronic Migraine at the Hull Headache Clinic received prospective follow-up. Female patients of reproductive age were asked to report on pregnancy before each treatment. Pregnant patients were advised against further treatment unless they chose to continue following an informed discussion about the uncertain impact of treatment on the fetus.

**Results:** Of the 15 patients who reported pregnancy (8–16 weeks), 12 wished to continue with further treatment at three-monthly intervals. 3 patients did not continue further treatment. All 15 patients had normal vaginal delivery, live births and no fetal malformations were reported.

**Conclusion:** We report no adverse outcome in 15 pregnant patients with CM exposed to OnabotulinumtoxinA. There is need to collect further data before establishing its safety.

**Disclosure of Interest:** A. Ghabeli: None Declared, K. Peddada: None Declared, F. Cheng: None Declared, A. Buture: None Declared, M. Khalil: None Declared, F. Ahmed Conflict with: Allergan, Enura, Electrocore, Novartis as Advisory Board member paid to British Association for the Study of Headache and the Migraine Trust, Conflict with: Educational Officer for British Association for the Study of Headache, Trustee of Migraine Trust, IHS Board Member

**Migraine Preventive Therapy**

**PO-01-097**

**Novel formulation of nasal oxytocin for the treatment of migraine**

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2Trigemina, Moraga, United States

**Objectives:** Objective: We have shown that nasal administration of oxytocin (OT) in rats produced a clear craniofacial limited analgesic effect that is mediated through transport along trigeminal nerve to act at OT receptors on trigeminal neurons. Mg++ has been shown to enhance binding affinity of OT for its receptor. This aim of this study was to test whether formulations of OT which include a magnesium (Mg) salt would enhance the effect of nasal OT on trigeminal nerve associated pain.

**Methods:** Methods: We have previously shown that craniofacial inflammation induced by electrocutaneous (EC) stimulation of the face of anesthetized rats produces an 5–10 fold upregulation of oxytocin (OT) receptors on trigeminal ganglia neurons. Thus, we pretreated rats with EC 24 hours prior to testing for nociceptive withdrawal responses to noxious heating of the face. We then nasally administered either OT, Mg, or one of a series of concentration combinations of 1 of 3 Mg salts and OT in solution. We then measured the effects of this administration on withdrawal latencies over the next 3 hours.

In separate studies, rats were given CFA injection in the cheek in order to induced inflammation and receptor upregulation. 24-48 hours thereafter, rats were euthanized and trigeminal ganglia removed, dissociated and neurons prepared for whole-cell patch clamp electrophysiology. The effects of OT and OT plus Mg solutions on excitability of neurons was then tested by current injection. Action potential current thresholds, suprathreshold action potential number, and effects on sodium and potassium currents were determined.

**Results:** Results: Both OT delivered alone as well as any of the Mg salts produced significant elevation of the withdrawal latency in response to noxious heat. The combination of the two produced a clear supraadditive effect at many dose ratios, demonstrating pharmacologic synergy between OT and Mg. The superiority of OT formulation with Mg++ was confirmed in the electrophysiologic study, in that it produced distinctly greater inhibition of TG neuron excitability, AP generation and sodium current.

**Conclusion:** Conclusion: Addition of Mg++ via Mg salt synergistically enhanced the analgesic effect of oxytocin when applied nasally to rats. This effect appears to be
meditated, at least in part, through an enhanced direct inhibition of the excitability of trigeminal ganglia neurons, likely through enhancing binding of OT to its trigeminal ganglia OT receptors.


Migraine Preventive Therapy

PO-01-098

Efficacy of diet restriction on migraine

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Objectives: Migraine type headache is a very common headache, but its pathogenesis is still not fully understood. It varies from person to person, and there are many factors that trigger a migraine. Foods take an important place among these factors. In this study, the efficacy of food limitations triggering migraine in the prevention of migraine attacks was investigated

Methods: Patients diagnosed with a migraine without aura according to International Classification of Headache were included in the study. 50 migraine patients stating that migraine attack started after the intake of certain foods were evaluated. The patients were divided into 2 groups randomly. The foods triggering migraine identified for patients were excluded from the diet of the patients both in group 1 (N=25) and group 2 (N=25). Attack frequency in a month, attack duration and attack severity (by using the Visual Analogue Scale) were recorded before starting the diet restriction and 2 months after the diet restriction. Diet restriction was removed in the patients in group 1 after the second month; however, diet restriction continued in group 2, and in the fourth month, attack frequency in a month, attack duration and attack severity (using the Visual Analogue Scale) were determined in both groups

Results: A total of 50 patients consisting of 9 males and 41 females were evaluated in this study. In both groups, in the 2nd month after the diet application, attack frequency in a month, attack duration and attack severity were detected to be statistically lower to a significant extent compared to the period before diet implementation (p < 0.05). In the evaluation in the fourth month, it was observed that this significance continued only in group 2

Conclusion: The results of the study reveal that if the foods triggering migraine attacks are identified in migraine patients, restricting these foods from the diet can be an effective and reliable treatment method to reduce migraine attacks

Disclosure of Interest: None Declared

Migraine Preventive Therapy

PO-01-099

The clinical efficacy of short-lasting ketogenic diet in migraine is due to a general normalization of cortical hyperresponsivity rather than to a direct modulation of the brainstem activity

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Objectives: We previously reported that a short-lasting period of ketogenic diet (KD) regimen can help to prevent migraine and can normalize its interictal abnormal cortical hyperresponsivity. Here, we aimed to verify whether cerebral cortex is the primary site of KD-related changes or if the latter are the expression of ketones ability to modulate brainstem subcortical structures.

Methods: We simultaneously recorded the nociceptive specific blink (nBR, a marker of the brainstem trigeminal activity) and cortical pain-related evoked potentials (PREP) elicited by the stimulation of right the supraorbital division of the trigeminal nerve in 18 migraine without aura patients before and after 1-month of KD, during ketogenesis. We measured nBR R2 component as well as PREP amplitude habituations over 2 blocks of 5 averaged responses.

Results: We confirmed the ability of 1-month KD of significantly decreasing mean attack frequency and duration. KD significantly induced normalization of the interictally reduced PREP habituation (pre: +1.8, post: −9.1), while nBR habituation remained unchanged.

Conclusion: The results of the present study suggest that the clinical efficacy of a short-lasting KD regimen in migraine can be primarily due to a general normalization of the interictal cortical dysfunction, and not to a direct modulation of the subcortical brainstem activation.
Migraine Preventive Therapy

PO-01-100

75% responder rate provides greater improvement in domain scores of the SF-36 than the historically accepted 50% responder rate

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2 Michigan Head Pain & Neurological Institute, Ann Arbor
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Objectives: Historically, successful prophylactic therapy in migraine is defined as a 50% reduction in migraine days, paralleling the efficacy of many available preventive medications. Patients with chronic migraine (CM) experiencing a 50% reduction of migraine often continue with frequent migraines and potential impairment of quality of life (QOL). The Short-Form Health Survey (SF-36) questionnaire is a widely used validated measure of disease burden. ALD403 (eptinezumab) is a genetically engineered humanized anti-CGRP antibody, for migraine prevention. In a Phase 2b clinical trial in patients with CM, a single intravenous (IV) administration of ALD403 (eptinezumab) demonstrated a reduction in migraine days with efficacy maintained from week 1 through 12 weeks. We compare the impact of different responder rates for weeks 1–12 on SF-36 scores following infusion of 300 mg and 100 mg of ALD403 or placebo in that trial.

Methods: Patients with CM aged 18 to 55 years were randomized to receive a single IV infusion of ALD403 300 mg (n = 114) or 100 mg (n = 118) or placebo (n = 116) in this Phase 2b parallel group, double-blind study. The primary endpoint was ≥75% response rate (RR) for reduction in migraine days over Weeks 1–12. The SF-36 was completed by each patient during the pre-treatment baseline and throughout the study and was scored using a 0–100 scale. Scores ≥50 were at or above the population average (“normal”). At Week 12, domain-specific SF-36 scores for Bodily Pain (BP), General Health, Mental Health, Role Physical Functioning (RP), Role-Emotional, Social Functioning (SF), and Vitality were assessed for patients who achieved a ≥75%, ≥50%, and <25% RR.

Results: Chronic migraine had a unique pattern of disease impact as measured by the SF-36. Baseline domain scores with the greatest impact were role physical (RP), bodily pain (BP), and social functioning (SF). Persons achieving a ≥75% RR for weeks 1–12 showed improvement in all SF-36 domain scores with mean scores being >50 for all domains and average increases ranging from 1.9–7.1. Greatest improvement was noted in the domains most impacted by migraine. Patients with a ≥50% RR improved to a lesser degree and those with <25% RR showed a low degree of change. More subjects achieved ≥75% RR with ALD-403 than placebo (33.3%, 31.4% and 20.7% for 300 mg, 100 mg and placebo respectively, one-sided, p-values 0.016 and 0.039).

Conclusion: SF-36 domain scores provided a unique pattern of impact with the RP, BP, and SF being the most impacted SF-36 domains. ≥75% RR resulted in improvements in all SF-36 domain scores with mean scores being >50 for all domains for the weeks 1–12 analysis. The domains most impacted by migraine showed the most improvement. ≥50% RR improved to a lesser degree and <25% RR resulted in an even lower degree of improvement. These data suggest that SF-36 may be a valuable outcome tool for CM and that a ≥75% RR tends to normalize all SF-36 domains, with significantly more subjects achieving a ≥75% RR with ALD403 (eptinezumab) than placebo.

Disclosure of Interest: None Declared

Abstract number: PO-01-100

Table: 1 Domain; Mean SF-36 Domain Scores at Week 12

<table>
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<tr>
<th>Domain</th>
<th>Mean SF-36 Domain Scores (n = 93)</th>
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<tbody>
<tr>
<td>Bodily Pain (BP)</td>
<td>44.07/50.67/+6.58</td>
</tr>
<tr>
<td>Social Functioning (SF)</td>
<td>46.41/52.38/+/6.01</td>
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<tr>
<td>Role Physical Score (RP)</td>
<td>45.67/52.88/+/6.96</td>
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<tr>
<td>Physical Functioning</td>
<td>51.58/54.33/+/3.24</td>
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<td>Vitality</td>
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<td>Physical Component</td>
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</tbody>
</table>

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Migraine Preventive Therapy

PO-01-101

Predicting treatment response to candesartan in migraine patients

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Objectives: Recent randomised studies reported a positive effect of candesartan, an angiotensin II receptor antagonist, in migraine prevention. The aim of our study was to identify response predictors to candesartan in a sample of migraine patients.

Methods: We retrospectively reviewed the clinical records of patients who have attended the Headache Clinic from February 2015 to December 2016, looking specifically at their response to candesartan. Univariate and multivariate logistic regression models were used to assess for predictors of outcome. Odds ratios (OR) with confidence intervals (CI) 95% were also calculated.

Results: The clinical history of 118 migraine patients was reviewed. A total of 104 patients (84 females, 81%), with a mean age of 43 (range: 17–77), were included in the final analysis. Fourteen patients were excluded cause to missing data. Thirty-two (31%) patients reported a positive response to candesartan, while 72 (69%) did not have any significant therapeutic effect. In the univariate logistic regression analysis, no one of the predictors was associated with the outcome. In the multivariate logistic regression model including a positive history of triptan-overuse headache, the number of migraine days per month, disease duration, presence of aura, presence of allodynia, presence of cranial autonomic symptoms and the total number of preventive therapies tried by patients, a positive history of triptan-overuse headache was associated with higher odds of a positive response to candesartan (OR 6.37, 95% CI 1.73–23.46, p = 0.03).

Conclusion: Patients with triptan-overuse headache might benefit from taking candesartan. On the other hand, neither the disease activity or migraine associated symptoms nor the number of preventive treatments tried by patients can help us to predict the response to candesartan in migraine patients.

Disclosure of Interest: R. Messina: None Declared, P. Goadsby Conflict with: Allergan, Amgen, and Eli-Lilly and Company, Conflict with: Allergan, Amgen, Eli-Lilly and Company, Akita Biomedical, Alder Biopharmaceuticals, Autonomic Technologies Inc, Avanir Pharma, Cipla Ltd, Colucid Pharmaceuticals, Ltd, Dr Reddy’s Laboratories, eNeura, Electrocore LLC, Novartis, Pfizer Inc, Promius Pharma, Quest Diagnostics, Scion, Teva Pharmaceuticals, Trigemina Inc., Scion; and in addition, Dr. Goadsby has a patent Magnetic stimulation for headache pending assigned to eNeura, Conflict with: MedicoLegal work, Journal Watch, Up-to-Date, Oxford University Press

Migraine Preventive Therapy

PO-01-102

Long term results for occipital nerve stimulation in refractory chronic migraine

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Objectives: Although some prophylactic medications have been proposed to treat chronic migraine (CM) there are still many refractory patients and other treatments are warranted. Occipital nerve stimulation is a potentially promising therapy for CM patients, although long term experience is scarce. The aim of this study is to evaluate the long term efficacy and tolerability of occipital nerve stimulation for the treatment of refractory CM.

Methods: Twenty eight patients (12 men, 16 women, average age 53.9 ± 12.1) meeting the IHS criteria for refractory CM were enrolled in this study and implanted with a neurostimulation device near the occipital nerves. The primary endpoint was the reduction in Analogical Visual Scale (AVS). Patient satisfaction, migraine frequency, side effects and reasons for discontinuation were also studied. Significance level was set at P < 0.05. Average follow up period was 6.7 ± 2.2 years.

Results: Headache severity according to the AVS was reduced from 8.7 ± 0.2 before occipital nerve stimulation to 3.6 ± 2.8 after treatment initiation. There was also a significant difference in reduction of number of headache days and 80% of the patients were satisfied or very satisfied with the procedure. The most common adverse event was persistent implant site pain and only one patient required to be explanted due to inefficacy. Good efficacy and tolerability were maintained after the follow-up period.

Conclusion: Occipital nerve stimulation has been explored as a possible treatment option in selective drug-resistant primary headache disorders and, according to our results, this technique may be effective, safe and well tolerated in treating refractory CM. These good results seem to remain stable after several years. An increasing experience and a more routine use of these techniques can be forecasted in the near future.

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Disclosures of Interest: None Declared

Neuromodulation for Headache

**PO-01-103**

**Novel use of Radiofrequency Ablation in a case of a severely refractory New Daily Persistent Headache**

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**Objectives:** New daily persistent headache (NDPH) is a severely refractory headache disorder with a chronic, daily persistence from date of onset without specific guidelines for treatment. Despite management of NDPH being aimed towards treatment of the predominant headache phenotype, this headache disorder continues to be resistant to the most aggressive measures implemented by headache providers. Radiofrequency ablation is an neuro-ablative procedure implemented by interventional pain physicians that has been commonly applied to the treatment of chronic disorders including the neck, back, joint as well as intercostal neuralgia. There are multiple studies and growing use of RFA in the headache community in the management of other headache disorders including cervicogenic headache, trigeminal neuralgia, hemicranias continua, and occipital neuralgia that have shown promising results. We present a case in a veteran with NDPH who was refractory to all treatment modalities over the last two decades until RFA was introduced and has since provided significant and long lasting relief over the last years.

**Methods:** Conventional RFA utilizes alternating currents to create a thermal lesion along a targeted nerve via an intricately placed needle. The targeted nerve is isolated under image guidance (with use of anatomical landmarks, ultrasound or fluoroscopy) and is followed by generating a temperature between 80–85 degrees at the tip of the uninsulated needle via an alternating current for approximately 60–90 seconds to create an adequately sized lesion. Creation of this lesion involves the disruption of the neuronal architecture without compromising the fascicular structure itself. The incurred lesion serves as a temporizing block, preventing transmission of nociceptive signals along the target nerve. We targeted the greater occipital, the lesser occipital and the supraorbital nerve as sites for neuromodulation in this case.

**Results:** We present a 47-year-old male veteran with migraine variant NDPH, whose initial headache presentation began following an incident while active duty wherein he was enveloped with an unknown chemical from an overhead missile and subsequently lost consciousness with no injuries to report of otherwise. His headaches over the next two decades were unsuccessfully treated with numerous ablative therapies (including sumatriptan, NSAIDs, and methadone), preventative therapies (including propranolol, metoprolol, topiramate, valproate, gabapentin, pregabalin, levetiracetam, lamotrigine, amitriptyline, nortriptyline, paroxetine, venlafaxine, indomethacin, and onabotulinum toxin A) as well as cervical branch blocks. This patient’s daily headache was debilitating, requiring daily and frequent high dose opiate use and becoming functionally dependent on his family. With the introduction of conventional RFA on a biannual basis 6 years from present day, he has tapered himself from these opiates, is back to work on a full time basis with regained independence. He is pain free for a most of the days of the month with occasional mild headaches and at most, three severe headache days in a month. Additionally, he has not experienced nor encountered any side effects or neurologic sequelae on exam since starting this ablative therapy.

**Conclusion:** Thermal lesions created along targeted nerves as facilitated by conventional RFA can serve as a potentially safe, effective, and alternative means for treatment of NDPH as demonstrated in the case of this veteran. RFA has been similarly applied with success to other refractory chronic headache disorders, but to the knowledge of our authors, there are no published reports using conventional RFA to treat NDPH.

Disclosure of Interest: None Declared

Neuromodulation for Headache

**PO-01-104**

**Prevention of frequent episodic migraine and chronic migraine with a supraorbital transcutaneous stimulator in Japan**

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3Department of Neurology, Japanese Red Cross Shizuoka Hospital, Shizuoka  
4Headache Care Unit, Fujitsu Clinic, Kanagawa  
5Department of Neurology, Headache Center, Tominaga Hospital, Osaka, Japan

**Objectives:** To examine the preventive effect for frequent episodic migraine and chronic migraine of a supraorbital transcutaneous stimulator (Cefaly®; Cefaly Technology, Grâce-Hollogne, Belgium) in Japan.

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Methods: Patients were prospectively collected from four headache units in Japan between April 7 and September 6, 2016. The inclusion criteria for the study were as follows: age 18–65 years old, migraine with and without aura (International Headache Classification 3rd Edition beta version Code 1.1, and 1.2.1.1), and at least two attacks per month. The patients who started or changed their prophylactic treatment and had received botulinum toxin type A or a nerve block injection within the previous three months were excluded. The migraine patients with secondary headache except for medication overuse headache were also excluded. After four weeks of a run-in phase, the patients started the active phase for 12 weeks, in which they were stimulated by Cefaly® with the following characteristics: square wave, pulse width 300 μsec, frequency 60 Hz, maximum 16 mA, and 20 minutes every 24 h. The headache status was recorded every day in an electronic headache diary (Zutsuclick®; J-MAC SYSTEM, INC., Sapporo, Japan). We analyzed the change in the number of migraine days between the run-in month and the second and third months. We also evaluated the comprehensive effectiveness as the following three degrees: improved, no change, and deteriorated. Furthermore, we measured the patients’ satisfaction using a questionnaire.

Results: A total of 100 patients (19 males, 81 females) were analyzed; 95 completed the study in accordance with the protocol. The average age at the study initiation was 43.5 years in males and 44.7 years in females. Seventy-four cases were diagnosed with migraine without aura, 40 with chronic migraine, 9 with migraine with aura, and 5 with chronic migraine with medication overuse. Regarding the effectiveness, 74 cases improved (highly improved in 20 cases, moderately improved in 31 cases, mildly improved in 23 cases), 24 saw no change, and 2 deteriorated. Regarding the satisfaction, 63 were satisfied, 24 were dissatisfied, and 9 had no opinion. Adverse events were reported in seven patients: pain or discomfort at the site of stimulation in three patients, sleepiness in two patients, fatigue in one patient, and headache in one patient. All of the adverse events were mild to moderate, and there were no severe adverse events.

Conclusion: Supraorbital transcutaneous stimulation for frequent episodic migraine and chronic migraine is thought to be an effective and relatively safe treatment. In this study, the supraorbital transcutaneous stimulator (Cefaly®) was offered by IMI Co., Ltd. (Saitama, Japan). We also received technical cooperation with the J-MAC SYSTEM for the electronic headache diary (Zutsuclick®).

Disclosure of Interest: D. Danno Conflict with: In this study, the supraorbital transcutaneous stimulator (Cefaly®) was offered by IMI Co., Ltd. (Saitama, Japan). We also received technical cooperation with the J-MAC SYSTEM for the electronic headache diary (Zutsuclick®). M. Iigaya Conflict with: In this study, the supraorbital transcutaneous stimulator (Cefaly®) was offered by IMI Co., Ltd. (Saitama, Japan). We also received technical cooperation with the J-MAC SYSTEM for the electronic headache diary (Zutsuclick®). N. Imai Conflict with: In this study, the supraorbital transcutaneous stimulator (Cefaly®) was offered by IMI Co., Ltd. (Saitama, Japan). We also received technical cooperation with the J-MAC SYSTEM for the electronic headache diary (Zutsuclick®). H. Igarashi Conflict with: In this study, the supraorbital transcutaneous stimulator (Cefaly®) was offered by IMI Co., Ltd. (Saitama, Japan). We also received technical cooperation with the J-MAC SYSTEM for the electronic headache diary (Zutsuclick®). T. Takeshima Conflict with: In this study, the supraorbital transcutaneous stimulator (Cefaly®) was offered by IMI Co., Ltd. (Saitama, Japan). We also received technical cooperation with the J-MAC SYSTEM for the electronic headache diary (Zutsuclick®).

Neuromodulation for Headache

PO-01-105
Anodal transcranial direct current stimulation over the left temporal pole restores normal visual information processing in migraine patients

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Objectives: Many neuroimaging studies have implicated the temporal pole (TP) in migraine pathophysiology; its morphology and function were reported to change per the so-called migraine cycle. The link between TP morphology changes and the electro functional abnormalities of the migraine brain is unknown. In humans, the TP serves as a multimodal neural hub that receives and integrates all sensory modalities except for somatosensory information. Here, we aim to verify whether a non-invasive enhancement of TP excitability by means of anodal transcranial direct current stimulation (tDCS) may change the interictal abnormal multimodal sensory processing in migraine.

Methods: Thirty-two interictal migraineurs underwent visual (VEPs, 600 sweeps, 3.1 Hz reversal rate, 15 min of arc check) and median nerve somatosensory (SSEPs, 200 sweeps, 4.4 Hz) evoked potentials before and immediately after 20-minute real anodal tDCS (N = 16) or sham (N = 16) delivered over the left TP (2 mA, cathode placed on the right arm). We measured VEPs N1-P1 and SSEPs N20-P25 amplitudes respectively in 6 and in 2 sequential blocks of 100 sweeps as well as habituation as...
Disclosure of Interest: None Declared

Neuromodulation for Headache

PO-01-106

Neuromodulation by electroacupuncture for migraine without aura Analysis using Diffusion Tensor Imaging

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5Department of Neurology, Ibaraki Prefectural University of Health Sciences Hospital, Ami, Japan

Objectives: Migraine is one of the most common diseases. Medication therapy is the first choice for primary headache, but some patients show resistance for medical therapy. Recently, neuromodulation such as peripheral nerve field stimulation (PNfS) is used for the treatment of migraine and neuralgia. Further more, in the group of patients with fibromyalgia PNfS for Cervical 2 area (C2 PNfS) is reported as effective for headache, trunk pain and depression. However, PNfS requires implantation surgery, so some complications such as infection and hardware erosion were reported. In addition, the mechanism of PNfS has not yet been fully understood. In this study, we investigated whether electro-acupuncture could reproduce the effects of C2 PNfS (EAP-C2-PNfS).

Methods: A board accredited headache physician diagnosed the headache using the International Classification of Headache Disorders 3rd edition (ICHD-3β). The 36 patients were diagnosed as migraine without aura (MWoA) (4 men, 32 women, mean age 46.2 ± 13.2 years-old) and they underwent 3.0T MRI (SIEMENS, Erlangen, Germany) with 32-channel head coil including Diffusion Tensor Imaging (DTI) before and after EAP-C2-PNfS. We assessed headache intensity using Numerical rating scale (NRS). We measured the impact of headache on daily disability using Short-form 36 (SF-36) and Headache Impact Test (HIT-6). We used self-rating depression scale (SDS) as the depression assessment tool. Each scale was evaluated before and after EAP-C2-PNfS.

The acupuncture needles (50 mm length, 0.18 mm diameter, SEIRIN JSP-type, Shizuoka, Japan) were subcutaneously inserted into the bilateral occipital scalp about 15 to 20 mm and biphasic electrical pulse waves were applied for 15 minutes using electrical stimulator. The EAP-C2-PNfS was performed once per a week for 3 months.

The DTI were acquired by single-shot echo planar imaging (EPI) (TR = 6800 ms, TE = 75 ms, GRAPPA factor = 2, b values is 0 and 1000 s/mm², 20 motion proving gradient) with 50 axial slices (slice thickness = 3 mm, no gap, field of view = 230 x 230 mm², matrix size = 128 x 128 mm²). The DTI scan time was 5 minutes 21 seconds.

For imaging analysis, we used tract-based spatial statistics (TBSS) in Oxford Centre for Functional MRI of the Brain (FMRIB) Software Library (FSL). Using this software, we analyzed Fractional anisotropy (FA) in whole brain.

Results: Clinical indexes of NRS, HIT-6, SF-36 and SDS significantly improved after 3 months of EAP-C2-PNfS. On the other hand, FA decreased at some brain regions such as right thalamus, right minor forceps, right internal capsule and bilateral corpus callosum. All subjects showed no adverse event with EAP-C2-PNfS.

Conclusion: Recently some reports suggest that functional dysfunction and central sensitization are present in pathology of chronic headache such as migraine. In DTI studies for MWoA, the patients at interictal phase showed increased FA in bilateral thalamus compared with those of healthy control. On the other hand, there are studies that report no significant difference of FA values among 3 groups: chronic, episodic migraine and healthy control. Right hemisphere is involved in cognitive aspect of pain. Our study showed that FA decrease in right hemisphere, so EAP-C2-PNfS may be effective by inhibiting neural activity in right hemisphere.

In this study, clinical indexes of headache and depression were significantly improved and right hemisphere FA decreased after EAP-C2-PNfS for 3 months. EAP-C2-PNfS is low invasive and safe procedure. This study
indicated that EAP-C2-PNIS is effective by neuromodulation for MWoA.

Disclosure of Interest: None Declared

Neuromodulation for Headache

PO-01-107
Effects of Occipital Nerve Stimulation on Cerebral Blood Flow in Patients with Medically Intractable Chronic Cluster Headache
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Objectives: Pilot studies have suggested that occipital nerve stimulation could be effective in medically intractable chronic cluster headache. It is currently not known how occipital nerve stimulation affects cerebral blood flow (CBF) and whether clinical outcome is related to changes in CBF. Here, we assessed the effects of occipital nerve stimulation on both attack frequency and CBF.

Methods: CBF was measured using dynamic [15O]H2O PET scans before (‘baseline’) and after six months treatment with occipital nerve stimulation in 17 medically intractable chronic cluster headache patients. A low-dose CT scan was performed immediately before each [15O]H2O scan to correct the latter for attenuation. Emission data were acquired for 10 minutes following intravenous injection of 800 MBq [15O]H2O. In addition, arterial blood was sampled continuously during this scan. A co-registered cerebral structural T1 weighted MRI scan was used for segmentation of volume of interest. CBF was obtained by fitting region of interest time-activity curves to the standard single tissue compartment model for [15O]H2O using the arterial blood curve as input function. The primary outcome was the effect of the absolute change in attack frequency on the CBF in our regions of interest (i) associated with pain processing (ACC, insula, thalamus, cerebellum, pons), as well as (ii) the area near the occipital nerve stimulator: occipital lobe, and (iii) the hypothalamus associated with cluster headache attacks.

Results: At baseline, age correlated significantly with CBF (p = 0.02). Cluster headache attacks were significantly reduced from 64.4 at baseline to 32.4 after 6 months occipital nerve stimulation (p = 0.01). An increase in CBF in the contralateral ACC (p = 0.001) and ipsilateral hypothalamus (p = 0.035) were significantly associated with a reduction in absolute attack frequency corrected for age, gender and baseline attack frequency. Change in CBF in other regions of interest did not correlate with a change in cluster headache attacks.

Conclusion: This is the first report of changes in CBF following occipital nerve stimulation in medically intractable chronic cluster headache. Reduction in attack frequency was associated with an increase in CBF in both ipsilateral hypothalamus and contralateral ACC.

Disclosure of Interest: None Declared

Neuromodulation for Headache

PO-01-108
Long term experience in peripheral nerve stimulation in drug-resistant cranial neuralgias
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Objectives: Cranial neuralgias are distinct, treatable syndromes which comprise one of the possible causes of facial pain. Although some prophylactic medications and techniques have been proposed as treatments, there are still many refractory patients and other therapeutic options are warranted. Peripheral nerve stimulation (PNS) has been proposed as a promising therapy for these patients although long term experience is scarce.

The aim of this study is to evaluate the long term efficacy and tolerability of PNS for the treatment of refractory cranial neuralgias

Methods: Sixteen patients (5 men, 11 women, average age 51.0 ± 11.3) suffering from different drug-resistant cranial neuralgia were enrolled and implanted with a neurostimulation device. Six suffered from occipital neuralgia, 6 had postherpetic neuralgia and 4 had trigeminal neuralgia. The primary endpoint was the reduction in Analogical Visual Scale (AVS). Patient satisfaction, side effects and reasons for discontinuation were also studied. Significance level was set at P < 0.05.

Average follow-up period was 6.1 ± 1.3 years.

Results: Pain severity according to the AVS was reduced from 8.7 ± 1.1 before PNS to 4.9 ± 2.7 after treatment initiation. 55% of treated patients were satisfied or very satisfied with the procedure. The most common diverse event was persistent implant site pain and three patients required to be explanted due to inefficacy. There were not differences between different subgroups.

Efficacy and tolerability remained stable during the follow-up period.

Conclusion: PNS has been explored as a possible treatment option in selective drug-resistant cranial neuralgias and, according to our results, this technique may be
Subjective Hyperosmia in Burning Mouth Syndrome: The Burn and the Smell

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Objectives: While hypogeusia (Grushka, 2002) and hyposmia (Yakov, 2010) have been noted in those with burning mouth syndrome (BMS), neither subjective nor true hyperosmia heretofore have been described. Such a case is presented.

Methods: A 45 year old woman, six weeks after beginning treatment with duloxetine, quetiapine and alprazolam for an episode of Major Depression and Generalized Anxiety Disorder, noted a gradual onset of oral irritation while eating spicy foods. This progressed over the following year to a constant burning sensation in the anterior tongue and palate, independent of eating. Initially mild, this became more severe (10/10 at night), and she was diagnosed with BMS. One and a half years after burning onset, she perceived hyperosmia, whereby smells were more intense than normal. For instance, the aroma of perfume, cleaning supplies, spices, dog feces, tomato sauce, pizza, orange juice and other citrus scents were 200% greater than the normal smell; cinnamon, onions, and shampoo were 120% greater than normal.


Conclusion: Burning pain often causes depression, which may induce the patient to focus more on the chemosensory system (Lorig, 1988). With concentrated attention, there is activation of afferent sensory systems, inducing sensory stimuli to be perceived as more intense (Hummel, 2006). Furthermore, odors may worsen BMS (Hirsch, 2004), and thus the patient may be focused on odors to avoid precipitating BMS. Moreover, patients with BMS are often supertasters and supersmellers (Bartoshuk, 1998), and a supersmelling patient may actually perceive smell as greater than others. Query as to subjective hyperosmia in those with BMS is warranted.


Other Primary Headache Disorders

PO-01-110

Sumatriptan Responsive Olfactory Hallucinations: Treatment of Phantosmia of Amigrainous Migraine

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Results: Abnormalities in Physical Examination:

Abnormalities: General: a similar effect.

returning the next day. Recurrent trial on sumatriptan had which remained reduced for 5 hours until she fell asleep, after another 5 mg reduced the intensity to a level 2/10 25 mg reduced the intensity to 5/10 a half hour later and zinc, acupuncture, and aromatherapy. Trial of sumatriptan unresponsive to lamotrigene, carbamazepine, gabapentin, Phantosmias are usually level 8/10 in intensity. She was and there is no dirurnal variation to the headaches.

were not manifest. She is not impaired by the headaches light-headedness and nausea even when the headaches progressing in frequency to every day. It is made worse with stress and 70% of the time it is precipitated with sneezing. It is made better with holding her breath or occluding her nostrils. She admits to getting ice cream headaches, bloating with her menses and frequently fainted as a child. The headaches are holocephalgic, associated with light-headedness and nausea. The phantosmia would usually accompany the light-headedness and nausea even when the headaches were not manifest. She is not impaired by the headaches and there is no dirurnal variation to the headaches. Phantosmias are usually level 8/10 in intensity. She was unresponsive to lamotrigene, carbamazepine, gabapentin, zinc, acupuncture, and aromatherapy. Trial of sumatriptan 25 mg reduced the intensity to 5/10 a half hour later and after another 5 mg reduced the intensity to a level 2/10 which remained reduced for 5 hours until she fell asleep, returning the next day. Recurrent trial on sumatriptan had a similar effect.


Conclusion: Phantosmia have been reported to respond to a variety of different medications including anticonvulsants (Majumdar, 2003), anti-depressants, anti-psychotics (Henkin, 2013), beta blockers and calcium-channel blockers (Coleman, 2011). This is the first recorded case of phantosmia responsive to sumatriptan. While the patient’s response to sumatriptan strongly suggests it is of a migraineous nature, other possibilities should be considered. The phantosmia may be a manifestation of serotonergic imbalance which sumatriptan modulates. Since, sumatriptan has been demonstrated to affect the chemosensory system (Doty, 2004) it may be acting on the olfactory system independent of its effects on headaches. This case suggests that trial with anti-migraine drugs or with other serotonergic agonists may be useful with treatment of phantosmia. Such an effect warrants further study.

Disclosure of Interest: None Declared

Other Primary Headache Disorders

PO-01-111

Evaluation of electroencephalogram using eLORETA during photic stimulation in patients with migraine

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2The KEY Institute for Brain-Mind Research, Zurich, Switzerland

Objectives: Migraine patients indicate various type of abnormal information processing. Photophobia may be one of abnormal information procession. In electroencephalograms(EEG), photic driving is known as a reaction to visual stimulation. Both photophobia and the photic driving response are similar to appear during light stimulation. We considered that evaluation of migraine patients photic driving response may lead to elucidation of the mechanism of their sensitive condition. Our study aimed to investigate EEG photic driving responses with a source-localizing method.

Methods: We recruited 50 migraine patients (migraine with aura (MWA) 21;migraine without aura (MWOA) 29). We recorded spontaneous eyes-closedresting EEG from 20 electrodes on the scalp during the interictal phase. After recording, each photic stimulation was separately selected. We also analyzedEEG by fast Fourier transform and observed the spectrum frequency peaks and topographies in response to photic stimulation. We recruited 50 migraine patients (migraine with aura...
New Daily Persistent Headache (NDPH): possible triggers for remission and relapsing

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2Saitama International Headache Center, Saitama, Japan

Objectives: New daily persistent headache (NDPH) has two subforms: a self-limiting subform that typically resolves within several months and a refractory form that is resistant to pharmacological treatment. Previous studies showed that the prognosis of NDPH is poor and is resistant to treatment. We studied clinical features of NDPH to know the factors which may influence the prognosis of the disease.

Methods: A retrospective study was conducted at our headache center during the period of April 2014 to August 2015. All the patients with NDPH fulfilled the ICHD-3b criteria. Secondary headaches were excluded by clinical and MRI studies. All the patients received pharmacologic treatment of various combination. The usefulness of integrated headache care including psychological counseling, acupuncture, daily life planning, physical therapy and yoga was also evaluated.

Results: Clinical features were studied in 40 patients diagnosed as NDPH (23 women and 17 men) with the age of onset 24 ± 17 (mean ± SD) years. Patients visited our clinic 1.9 ± 4.0 years after the onset. Pain of NDPH was like tension-type headache (22.5%), migraine (17.5%), mixture of tension-type and migraine (57.5%) and thunderclap or stabbing headache (1 patient each). Headache was unilateral in 12.5%, bilateral in 55.0% and holocranial in 32.5%. None of the patient presented with nummular headache type. Seventy-eight percent of the patients reported pain intensity as moderate to severe. Accompanying symptoms were dizziness in 45.0%, nausea in 42.5%, photophobia in 30.0% and phonophobia in 20.0%.

Triggering events of NDPH were reported by 16 patients (40.0%) which included stressful life event, anxiety, flu, HPV vaccination, bronchial asthma, tonsillitis, menstrual pain, exercise, diet, and transient global amnesia. Seven patients with NDPH (17.5%) had a history of migraine, and episodic migraine returned in the course of remission. Complete remission was seen in 7 patients (22.6%) after 227 ± 191 days, remission and relapsing was seen in 5 patients (16.1%). Twenty one patients (63.6%) continued daily headache without any remission. There was no significant difference in the mean observation period between remission group and persistent group (306 ± 273 vs 314 ± 254 days). The period from the onset to the start of treatment was 0.6 ± 0.7 years in remission group, which was shorter than persistent group of 1.7 ± 2.2 years.

Pharmacological treatment alone (67% vs combination of integrated treatment (33%) did not show significant difference as to the remission rate of the disease.

Possible factors inducing remission of NDPH observed in 7 patients were changes in life style such as living with grandmother, regular vacation, morning walk. Effective non-pharmacological treatment included psychiatric therapy, abdominal respiration of yoga, fasting (weight loss), psychological counseling and daily life guidance.

Conclusion: We categorized NDPH patients in two group: non-persistent group (remission, remission/relapsing) and persistent group (continuous). Remission occurred more in the group of early clinic visit. Possible triggers were reported by the patients but we could not identify any specific triggers common to the onset of all the NDPH. Non-pharmacologic treatment or lifestyle ingenuity may also be considered as useful therapeutic option.

Disclosure of Interest: None Declared
Other Primary Headache Disorders

PO-01-113

Our current experience in infiltration in a series of patients with trigeminal neuralgia
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\textsuperscript{2}Neurology, Clínica Universidad de Navarra, Pamplona
\textsuperscript{3}Neurology, Universidad Católica de Valencia, Valencia, Spain

Objectives: Pharmacological treatment is first choice for the prophylactic management of trigeminal neuralgia (TN), but in some cases is ineffective or has unacceptable side effects. Botulinum Toxin A has been reported as effective in patients with TN. We represent our experience in a cohort of patients with TN. We represent our experience in a cohort of patients with TN.

Methods: Twelve patients (7 men, 5 women; age: 61–84 years-old) suffering from drug-refractory TN were treated. We injected 25–50 UI reconstituted Botulinum Toxin A solution in the trigger zone (V2-V3). The injection was repeated after 3 months depending on the clinical response.

Results: In 8 patients a decrease of more than 75% of the pain was obtained with a reduction also of prophylactic medication. Two patient's response was of 50% and the other two were no responders. Adverse events were no more than esthetical changes in face appearance in 7 patients. The duration of the efficacy was from 3 to 6 months.

Conclusion: Infiltration with Botulinum Toxin A is an alternative therapeutic treatment for patients with TN refractory to drugs. Adverse events are frequent but reversibles.

Disclosure of Interest: None Declared

Other Primary Headache Disorders

PO-01-114

Chronic paroxysmal hemicrania in paediatric age: report of four cases
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\textsuperscript{1}Neuroscience, Bambino Gesù Children Hospital
\textsuperscript{2}Neuroscience
\textsuperscript{3}Bambino Gesù Children Hospital, Rome, Italy

Objectives: Chronic paroxysmal hemicrania (CPH) is a rare and well-characterised headache, classified amongst the trigeminal autonomic cephalgias (TACs). CPH has been only rarely and incompletely described in the developmental age. The objective of the present report was to describe the features of chronic paroxysmal migraine in four pediatric patients.

Methods: We retrospectively review the clinical features of patients with CPH seen at our Headache Pediatric Centre at Bambino Gesù Children Hospital of Rome in the last 10 years. According to ICHD 3beta criteria for CPH, we considered attacks duration and frequency, autonomic signs and response to indomethacin.

Results: We detected 4 patients with CPH. Clinical features are reported in Table 1. Our children presented with a long history of severe and unilateral pain, which occurred in the fronto-orbital region without side shift. Attacks were accompanied by at least one autonomic symptom, ipsilateral to pain. During the attacks, besides conjunctival injection, eyelid oedema and rhinorrhea and all children showed a dramatic response to indomethacin.

Conclusion: Here, we describe four patients with short-lasting, recurrent headache combined with cranial autonomic features. The clinical features of our children’s headache and the positive response to indomethacin led us to propose the diagnosis of CPH. Clinical symptoms and pain characteristics of our children are similar to those found in typical adult CPH. However in line with the previous cases of CPH reported during developmental age, our patients showed some atypical features, not fully meeting the ICHD-III beta criteria. First, although the ICHD criteria require an attack frequency higher than 5 attacks per day, in our patients, the attack frequency was lower. Second, attack duration was variable in all our children, but in three of four children it was sometimes longer than 30 min, which represents the maximal duration.

Abstract number: PO-01-114

Table: I MBCT-M Adaptation

<table>
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<tr>
<th>Features</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
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<td>14/F</td>
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<td>Attack duration (min)</td>
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<td>5–40</td>
<td>20–40</td>
<td>20–50</td>
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<tr>
<td>Attack frequency/day</td>
<td>1–3</td>
<td>3–4</td>
<td>2–3</td>
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</tr>
<tr>
<td>Autonomic signs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Lacrimation</td>
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</tr>
<tr>
<td>2. Conjunctival injection</td>
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<td>yes</td>
<td>yes</td>
</tr>
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<td>3. Eyelid oedema</td>
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</tr>
<tr>
<td>4. Nasal Congestion/rhinorrhea</td>
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<td>yes</td>
<td>yes</td>
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</tr>
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<td>5. Miosis/ptosis</td>
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<td>Trigger</td>
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<td>Indomethacin response</td>
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</table>

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for a CPH attack. However, several reports showed CPH patients with attack duration longer than 30 min in both adults and children. Frequency and duration of the attacks, nevertheless, are commonly different between paediatric and adult population also in more common primary headaches, such as migraine and tension-type headache. If attack duration and frequency can make the diagnosis more difficult, especially in paediatric age, the absolute response to indomethacin represents the diagnostic key for CPH in both adults and children (indotest).

In conclusion, the characteristics of our children’s headache, particularly the positive response to indomethacin, led us to consider the diagnosis of CPH. However, the frequency and duration of our patient attacks did not fulfill the ICHD-III beta criteria. These elements suggest that a revision of the current CPH diagnostic criteria, possibly with the inclusion of special notes for developmental age, would be necessary.

**Disclosure of Interest:** None Declared

**Other Primary Headache Disorders**

**PO-01-115**

**Vitamin D deficiency is associated with the severity of migraine: a case-control study**

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**Objectives:** It is well recognized that vitamin D deficiency may occur in patients with headache. However, if the serum vitamin D levels correlate with severity of migraine remains uncertain. The aim of this study was to investigate if the severity of vitamin D deficiency correlates with the frequency of headaches in migraine patients.

**Methods:** In this prospective study we enrolled 140 consecutive headache suffers (18 men, 122 women; mean age: 43.1 years) and 41 healthy controls (18 men, 23 women; mean age 43.1 ± 14.2 years). Each patient underwent a neurological evaluation, and migraine was diagnosed according to IHS diagnostic criteria. The frequency of headaches was measured by using a monthly headache diary recorded for three months from the headache sufferers. All participant underwent a venous blood sampling for 25-hydroxyvitamin D.

**Results:** According to serum vitamin D levels we grouped patients into 3 groups: Group 1 included 28 patients with 25-(OH) vitamin D level between 20 and 30 ng/ml; Group 2 included 71 patients with 25-(OH) vitamin D levels between 10 and 20 ng/ml; Group 3 included 41 patients with 25(OH) vitamin D levels lower than 10 ng/ml. Serum 25-(OH) vitamin D levels of migraine patients revealed that the most severe vitamin D deficiency was associated with higher frequency of headaches. Indeed, Group 3 had a mean serum 25-(OH) vitamin D levels of 7.3 ± 1.7 ng/ml and a mean number of monthly headache days of 26.7 ± 7.5; Group 2 had mean serum 25-(OH) vitamin D levels of 14.7 ± 2.6 ng/ml and mean frequency of monthly headache days of 20.1 ± 10; Group 1 had mean serum 25-(OH) vitamin D level of 23.4 ± 2.9 ng/ml and a mean frequency of monthly headache days of 17 ± 9.5. Whereas, all subject in control group had serum vitamin D levels above 20 ng/ml.

**Conclusion:** Our data indicate that severe vitamin D deficiency is associated with higher frequency of headaches in migraine patients, suggesting that serum vitamin D levels correlate with severity of migraine. Since low vitamin D levels are implicated in descending modulation of endogenous pain control, we speculated that severe vitamin D deficiency may ease the headache attacks in migraine patients.

**Disclosure of Interest:** None Declared

**Other Primary Headache Disorders**

**PO-01-116**

**Linear headache: clinical and algometric characteristics of 3 new cases**

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**Objectives:** Linear headache has been recently described as a headache of variable duration and intensity, located in a well circumscribed antero-posterior lineal trajectory. Its characteristics and accompanying symptoms may resemble migrainous or epicranial features. We describe three cases of linear headache including an analysis of pressure pain sensitivity to suggest a potential pathogenesis of this new entity.

**Methods:** We considered all patients attending a headache office at a tertiary hospital from January 2016 to March 2017. We identified three cases with a clinical picture comprised under previous descriptions of Linear Headache. In all of them we gathered demographic and
clinical characteristics. A complete neurological exam and magnetic resonance study ruled out underlying disease. We evaluated pressure pain thresholds (PPT) over 21 points distributed over the scalp, based on the standard positions of 10/20 system for electroencephalogram recordings: 8 points on the right side (Fp2, F4, F8, C4, T4, P4, T6 and O2), 8 points on the left (Fp1, F3, F7, C3, T3, P3, T5 and O1) and 5 points along the mid-sagittal line (Fpz, Fz, Cz, Pz, and Oz). Topographical pressure pain sensitivity maps were constructed.

**Results:**

**CASE 1:** A 65-year-old woman with arterial hypertension. She came to our office due to a one year history of a continuous mild pain, rated 2 out of 10 on a Visual Analogue Scale (VAS) described as oppressive, and located in a 2 centimeters-width band, extending from right supraciliary to ipsilateral occipital scalp. Pain increased with pressure and was not accompanied by any other symptom. Relief was obtained with occasional analgesia and our patient did not require preventive therapy.

**CASE 2:** A 33-year-old female complained of almost daily episodes, triggered by stressful events, of pain located in a linear trajectory of 2 centimeters in width over left parasagittal region. Pain was either oppressive or stabbing and was rated as 7/10 on VAS. Episodes lasted hours and related to allodynia. No response was achieved with topiramate, gabapentin and lamotrigine as preventive therapies.

**CASE 3:** 16-year-old male consulted due to the presentation 20 days a month during the previous year of oppressive pain, rated 7 out of 10 on VAS, located over a 1 centimeter-width band from forehead to occipital right parasagittal scalp, accompanied with photophobia and intolerance to physical exercise; partial response to analgesia. Topographical pressure pain sensitivity maps showed a decrease in PPT over the painful area in patients 2 and 3. In none of the 3 cases, the common pattern of frontal and temporal hyperalgesia previously described in migraine was evident.

**Conclusion:** In these patients with linear headache, and although clinical features of the pain sometimes suggest migraine characteristics, topographical pressure sensitivity maps would correspond epicranial headaches.

**Disclosure of Interest:** None Declared

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**Other Primary Headache Disorders**

**PO-01-117**

**Cephalalgia as an enantiopathy to salty hypogeusia: Restoration of salty taste concomitant with headache**

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2Aureus University School of Medicine, Oranjestad, Aruba
3Smell & Taste Treatment and Research Foundation, Chicago, United States

**Objectives:** Heightened sensation in auditory and visual spheres, during the aura or headache phases of migraine is well described in the literature (Hupp, 1989). While headaches have been associated with hyposmia (Hirsch, 1992) osmophobia (Hirsch, 2005) and undefined taste abnormalities (Kelman, 2005), restoration of taste during the headache has not heretofore been described. Such a case is presented.

**Methods:** A 36 year-old right handed male, two weeks prior to presentation, struck his head without loss of consciousness, resulting in a 40% reduction in smell and taste, with no ability to taste salt and sour, and a constant salty phantageusia. Four days after this event he began to experience headache which presents, altering sides, in both temples but always is unilateral, with a severity of 8/10, at times dull and at times sharp in nature. His headaches are associated with neck stiffness and improves with neck stretching. They occur every 3 days and last two minutes in duration. There is no warning or aura to the headache. He has a history of headaches, which began in the 1st grade, ice cream headaches, and car sickness as a child. He does snore. During the headache phase he states that his taste remains impaired except for salty taste that recovers to totally normal. After the headache resolves, the ability to taste salt diminishes to the impaired baseline level.


**Conclusion:** The mechanisms for the restitution of salty taste associated with the headache is unclear. Possibly the same physiologic dysfunction which is inducing the headache is concomitantly inducing the taste sensation.
abnormality. (Hutchins, 2016). Thalamocortical discharges could be inducing the cephalalgia as well as the salty taste (Marmura, 2014; Small, 2006). While taste inhibits pain (Gibbs, 2013), in this case pain may actually reduce taste threshold, allowing greater taste to salt. However, the short duration of the headache is inconsistent since disturbances of taste correlate with longer duration of cephalalgia (Kelman, 2005). It may not be the taste which is affected but rather the smell. With headache, parasympathetic activation induces nasal mucosal engorgement (Marmura, 2014). This may act to disinhibit odor induced inhibition of taste, thus intensifying the true salty taste. What is also unknown is why salty taste is specifically involved in contrast to other tastes. Possibly this represents activation of the trigeminal nerve inducing both cephalalgia and also savory discharge, since palatal trigeminal nerve fibers are responsive to sapid stimuli (Kelman, 2005). In those who suffer from headache, taste sensation should be queried and medication used in the management of cephalalgia might also influence gustatory ability. Investigation of this is warranted.

Disclosure of Interest: None Declared

Other Primary Headache Disorders

PO-01-118
Seasonal headache associated with sexual activity. A case report
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2Neurology, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

Objectives: To describe a patient who presents a primary headache associated with sexual activity for the last 23 years occurring only between November and January, every year since it started, determining a seasonal pattern. This seems to be the first description of such a case.

Methods: A 40 y-o white male patient describes an orgasmic (through masturbation or sexual intercourses) headache for the last 23 years. The pain is explosive, always starts few seconds before the orgasm (grade 5 in a 0–10 intensity scale), and reaches grade 8 within one minute following orgasm. The pain is always frontal, bilateral, usually lasting 2 hours when treated with combined analgesics, or 8 hours if untreated. He insisted his sexual-related headache occurs only between the end of November and the end of January, with a maximum bout duration of 6 to 8 weeks. Sexual headaches are absent for the rest of the year, except when related to 5 mg Tadalafil occasional use. During the bout all orgasms are followed by headache. Normal brain MRI and MRA scans were obtained twice during the symptomatic period. No autonomic phenomena of any kind was ever noted. Surprisingly, he presented last year HSA in July, prompting him to see a neurologist. He suffers from co-morbid, low frequency episodic migraine without aura. His medical history includes hypertension since his early 30’s, insulin resistance, and dyslipidemia, treated with Valsartan HCT 160/25, 850 mg Metformin bid, and 5 mg Rosuvastatin qd.

Results: The International Classification of Headache Disorders (ICHD 3rd edition, beta version) diagnostic criteria considers two possible forms of primary HSA: definitive, with at least two episodes of HSA; and probable, for patients with only one episode. Exclusion of a secondary cause is firmly advised at the first manifestation. Episodic, chronic or paroxysmal forms are not recognized in the ICHD.

Frese et al, noted that HSA may occur in bouts lasting 3.3 ± 5.2 months. Most of their patients presented only one bout during a mean follow-up of 6 years. Few patients presented a chronic form, with episodes persisting for more than 12 months. They divided this latter group in infrequent attacks (<20% of the sexual activity), frequent attacks (20 – 50% of the sexual activity) and regular attacks (present in nearly all sexual activity). Interestingly, none of their patients reported a seasonal pattern like our. Overlapping of headache characteristics as well as co-occurrence of two or more primary headaches is often observed in headache practice. Migraine with seasonal variation, side-locked migraine with autonomic symptoms, and association of trigeminal-autonomic symptoms with trigeminal neuralgia; and cluster-tic and CPH-tic syndromes are well recognized possible forms of “mixed” primary headaches. Orgasm is a needed condition to consider the occurrence of HSA. Both orgasm and CH show hypothalamic activation in functional MRI studies, allowing us to consider that a common pathophysiological mechanism. The described patient could be classified as having a chronic primary HSA with seasonal variation.

Conclusion: The case presented here is the first case of seasonal headache associated with sexual activity. The previous descriptions observed the fact that headache associated with sexual activity may present in bouts, but no seasonal aspect has been described until now. Long term follow up of these patients may help us understand the pathophysiological mechanism involved in such headache type.

Disclosure of Interest: None Declared
**Other Primary Headache Disorders**

**PO-01-119**

**Kleine Levin Syndrome: An Episodic Syndrome that may be associated with Migraine?**

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¹King’s College London
²Sleep Disorders Centre, Guy’s and St Thomas’ NHS Foundation Trust
³Headache Group, Department of Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King’s College London
⁴Headache Group, Department of Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, London, United Kingdom

**Objectives:** To phenotype headache and associated symptoms in patients with Kleine-Levin Syndrome (KLS), a rare sleep disorder characterised by fully reversible, recurrent episodes of hypersomnia, behavioural, perceptual and cognitive disturbances.

**Methods:** Consecutive patients with KLS presenting to a tertiary sleep neurology service over a 24-month period were asked about a range of symptoms associated with primary headache disorders using a semi-structured interview approach.

**Results:** Of 17 patients identified, 11 were interviewed. Of these, eight patients (73%) received a concurrent diagnosis of migraine, with the majority complaining of a symptom complex consistent with a migraine attack during their KLS episodes, as well as separate migraine attacks in between KLS episodes.

**Conclusion:** The high frequency of migraine in this small and rare illness cohort alludes to either a strong co-association, or shared pathophysiological mechanisms, between KLS and migraine; both being disorders of episodic neurological dysfunction. Indeed, KLS could potentially be considered an “episodic syndrome that may be associated with migraine”, a group of disorders representing a sub-category of migraine defined by the International Classification of Headache Disorders (3rd Edition). Even without definitive proof, using this hypothesis as a novel frame of reference could lead to a better mechanistic understanding of the disorder, as well as allow testing of simpler, and more effective treatment options, for it.

**Disclosure of Interest:** None Declared

**Other Primary Headache Disorders**

**PO-01-120**

**Features of chronic primary headaches (CPH) in children and adolescents referred to two third level headache centers**

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¹Neuroscience, Bambino Gesù Children Hospital, Rome
²Infantile Neuropsychiatry, Insubria University, Varese, Italy

**Objectives:** Chronic migraine (CM), Chronic tension-type headache (CTTH) and new daily persistent headache (NDPH) are the main forms of CPH reported in the ICHD-III beta version. Medication-overuse headache (MOH) is classified among secondary headache but it generally affects patients with a pre-existing primary headache. CPH have been well described in adults and their diagnostic criteria were designed based on the clinical characteristics in the adult population. However, CPH are not a rare condition in children and adolescence with negative impact on their quality of life. Our aim was to investigate the clinical features of CPH in a cohort of pediatric patients.

**Methods:** We retrospectively reviewed the charts of patients attending the Headache Centre of Bambino Gesù Children and Insubria University Hospital. The ICHD-III criteria were used for diagnosis. Statistical analysis was conducted by SPPS version 22.0 and χ² test was used to study possible correlations between: - CPH and population features (age and sex); - CPH and headache qualitative features; - CPH and risk of MOH; - CPH and response to prophylactic therapies.

**Results:** We included 377 patients with CPH (66.4% female, 33.6% male, age between 0 and 18 years). The most frequent CPH type was CM (73.5%), followed by CTTH (13.5%) and NDPH (13%). MOH was detected in 10.9% of total patients. CPH are less frequent under 6 years of age (0.8%; p<0.05); significant greater frequency in females than in males was found in the age group between 0–6 years (23/31 F, 8/31 M) and between 15–18 years (41/51 F, 10/51 M) (p<0.05). No correlations between age/sex and different CPH types were detected. We found a more frequent incidence of vegetative symptoms (photo/phonophobia and vertigo) in female sex (p<0.05). Nausea and vertigo are the two most frequent vegetative symptoms under 10 years of age (p<0.05) while photo/phonophobia are more frequently in patients older than 15 years (p<0.05). Possible development of MOH has been found correlated with CM types (p<0.05) and age above 15 years (p<0.05).
Conclusion: Our results showed that CPH presented a correlation with patients’ age and sex. No significant differences were found between CPH types and population/pain features. Development of MOH was related to CM onset and adolescent age. Amitriptyline and topiramate had the best effectiveness. However, it is to be underlined that follow up data could not be issued from a moderate percentage of patients. It will be useful in the future to reduce the number of missing patients by improving patients’ compliance and promoting the concept of migraine as a disease that can cause relevant disability.

Disclosure of Interest: None Declared

Other Primary Headache Disorders

PO-01-121

Cell phone associated headache: Is it new variant of chronic daily headache?

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2Neurology, KIMS, Hyderabad, India

Objectives: There are more than three billion cellphone uses across the globe across all socio economics standards of population. Health related issues related to mobile or cellphone are topic of active debate and under active evaluation. There is hardly any data on headache associated with cellphone use in pubmed. Here we present atypical cases who reported chronic daily headache related only with cellphone use.

Methods: this is case report of 4 patients from tertiary centre from India. We followed patients from opd basis from 2013 to 2016 prospectively for six months or more. There MRI and other lab parameters were normal and no evidence of secondary headache ethology.

Results: In 2013 to 2016 patients out patients basis follow up we have noted avoidance of cellphone during migraine episode is new avoidance behaviour(60%) Here we report four patients who had stereotypical pattern of headache related to use of cellphone only. They reported use of cellphone for at least six hours per day for more than 3 years on regular basis. The reported headache pattern was more than fifteen days headache per month for more than six months, mostly dullaching in nature but disturbing the work and activities of daily living. There was no photo or phonophobia or nausea associated with headache. Dullaching headache satisfies IHS chronic daily criteria. Two reported starting associated with stress and two denied any form of stress. There was no significant relief with routine treatment and counselling. Two patients changed job which involves less or no use of mobile phone.

Conclusion: Use of cellphone is part of everyday life for most of adults worldwide. Excessive use of cellphone with possible underlying stress may trigger a form of chronic daily headache in few patients, this form are tough to treat as well. This entity needs further evaluation, follow up and more assessment. In patients of chronic headache use of cellphone and its association should be actively searched for.

Disclosure of Interest: None Declared
Other Primary Headache Disorders

PO-01-122

Episodic cluster headache responsive to orgasm.
Case presentation and considerations

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²Neurology, Hospital Israelita Albert Einstein, São Paulo, Brazil

Objectives: To describe a male cluster headache patient who achieves relief from his cluster attacks through orgasms.

Methods: LMP, male, 53 years old, with attacks initiated in 1994, when bouts of Cluster Headache lasting 1–2 months occurred every 6–18 months. The duration was around 10–15 minutes, always on the right fronto-temporal-retrocular area. There may be a combination of ipsilateral conjunctival injection, tearing, nasal obstruction, and mild reduction of the inter palpebral fissure during attacks. Symptoms have always occurred to the right side, but in February 2014 he experienced attacks on the left. He noticed that the left inter palpebral fissure became permanently shorter after these late attacks. Two weeks before his first visit, October 2014, the attacks returned at the right side, up to three times a day, stopping two days prior to the visit. The cluster attacks are almost immediately and effectively aborted by orgasm, either during sexual intercourse or masturbation. Frequently he asks her wife for a sexual intercourse if possible, or masturbates to get rid of the pain. He mentioned entering once in a public restroom in a shopping mall to masturbate in order to abort an imminent attack. Orgasm has been effective in 100% of the pain episodes. He suffers from gout and takes allopurinol regularly. No other present or past diseases were reported. The neurological examination was normal except for an asymmetry in the left palpebral slit. Patient perception is that orgasm acts faster than sumatriptan nasal spray or subcutaneous.

Results: Sexual related headache is known since mid seventies. Primary headache associated with sexual activity was first described by Kriz in 1970, followed by the classic publication of Lance in 1976. More recently few reports have been published showing that sexual activity can relief or even resolve a headache attack, either migraine or cluster headache.

Male CH patients seem to found more pain relief than women. Differences between men and women in reaching an orgasm, as well as the sexual habits may explain the observed differences. Possible explanations for the sexual activity headache relief include distraction from pain, endorphins release, and postorgasmic relaxation. Both CH and orgasm show hypothalamic activation in studies of Function MRI studies, increasing the possibility of the influence of one condition on the other in both directions. Probably, orgasm may be the first noninvasive treatment for CH directed to act in hypothalamus.

Conclusion: Sexual activity can interact with headache in many ways, trigerring, changing the behavior of a previously diagnosed headache, and even be able to treat it, aborting a acute headache attack. We present a case of a male cluster headache patient who responds unequivocally to orgasm, as a treatment for his attacks. Both CH and orgasm show hypothalamic activation, leading us to consider that orgasm may act like a hypothalamic target treatment for some patients, being even faster than sumatriptan in abort a cluster headache attack.

Disclosure of Interest: None Declared

Other Secondary Headache Disorders

PO-01-123

Stroke-Like Migraine Attacks after Radiation Therapy (SMART): A Case Report

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²Neurosurgery, Nashik hospital, Nashik, India

Objectives: To report uncommon cause for secondary headache.

Methods: - Case report- 40 year old gentleman came with acute onset of severe throbbing headache, vomiting and left sided weakness of 8–10 hours duration. No prior history of headache or seizure. In 1998, he was operated for Right parietal glioma and then radiation was given over 1 month. He was asymptomatic for 17 years. He was conscious, alert with left sided hemiparesis and pyramidal signs. Mild sensory impairment and mild anosognosia was noted. Power was 1/5 in the left arm and 3-/5 in left leg. He developed cluster of secondary generalised seizures on day 3 of admission. L and M T I diagnoses thought were Right MCA infarct, RCVS (reversible cerebrovascular constriction syndrome), cortical venous sinus thrombosis, Right capsuloganglonic bleed, tumor recurrence or bleed in the tumor. Investigations- Routine lab tests within normal limits. CT Brain with contrast-showed only residual right parietal gliosis. His MRI Brain with Diffusion and ADC failed to reveal any fresh infarct. MR Venogram and MR Angiogram-Brain was normal. CSF-was normal and EEG showed only focal slowing over right parietal region. Image:

© International Headache Society 2017
Results: Final Diagnosis- SMART (Stroke-Like Migraine Attacks after Radiation Therapy).
Pt recovered fully with symptomatic management and anti-epileptic therapy. He followed up three months with complete recovery from his left hemiparesis and was headache- and seizure free.

Conclusion: SMART is a syndrome considered to be a delayed and sometimes reversible complication of whole-brain irradiation. Recurrent attacks of migrainous headaches, seizures (with or without prior history of migraine and seizure), complex neurological deficit (hemiparesis, hemianopia, dysarthria) and characteristic imaging findings are noted. The underlying pathophysiology is unknown. It is differentiated from Post-Ictal pseudo regression by less headache, milder deficit and quicker recovery favouring latter. Recognition of SMART syndrome is important to safeguard against misdiagnosis and prevention of aggressive treatment like cerebral angiography or Brain biopsy.

Disclosure of Interest: None Declared

Other Secondary Headache Disorders

PO-01-124

Headache improvement after intracranial endovascular procedures in Chinese patients with unruptured intracranial aneurysm: A Prospective Observational Study

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Objectives: To investigated whether there is long-term improvement in headache of patients with unruptured intracranial aneurysms (UIAs) treated with intracranial endovascular procedures.

Methods: Using a prospective design, consecutive patients with unruptured intracranial aneurysms (UIAs) with neuroendovascular treatment from January 2014 to December 2014 were asked to participated in. Headache outcomes were established prior to aneurysm treatment and for 6 months following treatment. Factors associated with different headache outcomes were investigated.

Results: Ultimately, fifty-eight patients completed the 6-month follow-up. In total, 29 patients had preoperative headache. Six months after the intracranial endovascular procedure, thirteen patients (44.8%) stated that their headaches were relieved after endovascular treatment; headache in one patient improved slightly, and six reported disappearance of headache and marked improvement. Overall, the mean headache scores of 29 patients improved on the self-reported Numeric Rating Scale (NRS) after endovascular treatment (6.00 vs. 2.30; p < 0.001). Patients with pretreatment tension-type headache, more severe headaches, stent-assisted coiling and stent implantation of the aneurysm were the important disadvantage for patients in improvement of post-procedure headache.

Conclusion: Treatment of unruptured intracranial aneurysms resulted in relief of headaches in about half of patients who had headaches pre-operatively.

Disclosure of Interest: None Declared

Table:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number</th>
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<tr>
<td>Severe morbid obesity (BMI 60) with no papilledema noted</td>
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<tr>
<td>Vagal neuropathy</td>
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<td>Intracranial meningioma with transtorial herniation¹</td>
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<td>Severe proximal basilar artery stenosis</td>
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<td>Daily use of Excedrin-headache resolved after discontinuation of Excedrin (MOH)</td>
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</table>
Other Secondary Headache Disorders

PO-01-125

Orthostatic Headache- Etiologies different than CSF Hypovolemia

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2Neurology, Mayo Clinic, Rochester, United States

Objectives: To report on possibly clinically relevant features other than CSF hypovolemia that may contribute to orthostatic headache.

Methods: We performed a retrospective chart review of patients age 18 to 80 years old evaluated at Mayo Clinic’s Department of Neurology from 2004–2014 identifying patients with the term “orthostatic headache” as a diagnosis. Those with surgical etiologies, identifiable CSF leaks or intracranial imaging suggesting CSF hypovolemia were excluded. Patients’ charts then were reviewed for other possible causes and diagnoses to which the orthostatic headache was attributed (by the treating physician) after thorough evaluation.

Results: Sixty patients met inclusion criteria. Of those, 37 were suspected to have a spontaneous CSF leak despite neuroimaging (MRI brain, MRI entire spine, CT myelogram, and nuclear cisternography) failing to identify a causal leak. No other etiologies were found to cause the orthostatic nature of their headaches. The orthostatic headaches in the remaining 21 patients were of unclear etiology, but many had potentially significant comorbidities to which the treating physician attributed their headaches. These are listed in Table 1. Thirteen of 21 had some form of autonomic dysfunction diagnosed clinically or with formal autonomic diagnostic procedures such as autonomic reflex screen and/or thermoregulatory sweat test.

Conclusion: In patients presenting with orthostatic headache where a thorough evaluation for CSF hypovolemia has been negative, there may be other potentially relevant comorbidities contributing to the headaches. It appears that autonomic dysfunction may account for a sizeable number of patients with orthostatic headache who do not have CSF hypovolemia. This is consistent with previous reports on orthostatic headache in postural orthostatic tachycardia syndrome and the so called “coat hanger headache” with orthostatic hypotension2. A few of our patients appeared to have a paradoxical orthostatic headache in the setting of presumed increased intracranial pressure. Despite thorough evaluation, there remain a considerable number of patients for whom no etiology for orthostatic headache can be identified, creating a diagnostic and therapeutic challenge.

References


Disclosure of Interest: R. Smith Conflict with: Avanir, I. Garza Conflict with: Contributor to UpToDate Inc, C. Robertson Conflict with: UpToDate, Amgen

Other Secondary Headache Disorders

PO-01-126

Characterising the effect of lumbar puncture on headache in IIH

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Objectives: This study aimed to evaluate the temporal change in headache severity in the week following lumbar puncture (LP) in patients with active Idiopathic Intracranial Hypertension (IIH). Furthermore we characterised the likelihood of headache improving or deteriorating following LP, depending on baseline headache severity. Finally, we evaluated the factors which influenced headache severity post LP.

Methods: Patients with IIH (diagnosed according to the modified Dandy criteria) were prospectively recruited from University Hospitals Birmingham NHS foundation Trust, a UK tertiary referral hospital. All patients recruited had active IIH (papilloedema with a Frisén grade >1, LP pressure >25cmCSF). Exclusion criteria included significant comorbidity and previous CSF diversion procedure. Headache severity was prospectively recorded using a verbal rating scale (VRS) 0 (no pain) to 10 (most severe pain) immediately prior to LP and following the LP (at 1, 4 and 6 hours and then daily to 7 days). Headache severity was further categorised into mild (VRS 1–3), moderate (VRS 4–6), severe (VRS 7–10). Demographic data and variables hypothesised to impact on the post LP headache severity were recorded.

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**Results:** 37 IIH patients were recruited, 20 had LPs performed on 2 occasions with mean age 31 ± 6.5, BMI 40.5 ± 10.4 Kgm−2, LP opening pressure 33.5 ± 6.3 cmCSF, CSF drainage 10.8 ± 1.6mls. A deterioration in headache severity at some point in the week post LP was noted in 65% with 28% experiencing an exacerbation of pain by ≥4 points on the VRS. Overall, headaches improved as early as 1 hour in 60% (33% reduction in VRS (p < 0.001)) and this was maintained at 7 days in 51% (38% reduction in VRS (p = 0.005)). There was no significant variability in the headache VRS between 1 hour through to 7 days post LP. In those with severe headaches pre LP, 82% improve at 1 hour (p = 0.043) and 73% improved at 7 days (p = 0.018) whilst the likelihood of deterioration over the week was 36%. In patients with moderate headaches pre LP, 90% improve at 1 hour (p < 0.001) and 62% improved at 7 days (p = 0.005), with a likelihood of deterioration of 67%. In those with mild headaches pre LP, 46% improved at 1 hour (p = 0.924) and 62% improved at 7 days (p = 0.811), with a likelihood of deterioration of 92%. Patients with no headache at the time of LP, 17% develop headache at 1 hour (p = 0.157) and at 7 days 25% will have developed headache (p = 0.18), whilst the overall likelihood of developing headache at some point during the week was 58%

The only factor which influenced the post LP headache severity was pre LP headache severity (p < 0.001). There was no relationship between the response of the headache severity post LP and BMI, height, skin to dura depth, LP opening or closing pressure, CSF volume withdrawn, number of LP attempts, CSF red blood cell count, acute analgesics, acetazolamide use and Frisen grade.

**Conclusion:** The majority of IIH patients will experience deterioration in headache at some point during the week post LP. Headache severity pre-LP significantly influenced the likelihood of improving or deteriorating after LP. Additionally, we noted that the improvement at 1 hour post LP was maintained at 7 days. This characterisation of headache outcomes post LP in IIH patients has relevance when counselling patients about the procedure.

**Disclosure of Interest:** None Declared

**Other Secondary Headache Disorders**

**PO-01-127**

**Invasive spinal interventions for the treatment of head pain outside of occipital nerve distribution**

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References:

Disclosure of Interest: None Declared

Other Secondary Headache Disorders

PO-01-128
Sildenafil-Related Cerebral Venous Sinus Thrombosis and Papilledema: A Case Report of a Rare Entity
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Objectives: We present a rare case of cerebral venous sinus thrombosis associated with long-term and high dose use of sildenafil.

Methods: case report

Figure 1. Post-gadolinium enhanced T1WI of Brain magnetic resonance venographic image demonstrating occlusion filling defect within right transverse and sigmoid sinus and juguler vein.

Results: A 29-year-old man was referred to our neuroophthalmology clinic for bilateral visual deterioration and severe headache. He had stage 2 papilledema and other clinical and neurological examinations were normal. He had used the drug for nearly two years, two to three times a day. All laboratory parameters including blood count cell, coagulation panels and genetic tests including methylene-tetrahydrofolate reductase and factor V Leiden mutation were unremarkable. Brain magnetic resonance imaging result confirmed transverse cerebral venous sinus thrombosis (CVST) (figure 1). The opening pressure of cerebrospinal fluid (CSF) was 43 cm H2O with normal biochemistry and no cells.

Conclusion: Clinicians must be aware of the possibility of CVST when the patient use sildenafil.

Disclosure of Interest: None Declared

Other Secondary Headache Disorders

PO-01-129
Topiramate is as effective as Acetazolamide at lowering intracranial pressure in healthy rodents
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Objectives: Management of Idiopathic Intracranial Hypertension (IIH) aims to reduce intracranial pressure (ICP). Acetazolamide is the most commonly used drug, with class 1 evidence demonstrating modest improvement in patients with mild visual loss. Other drugs used include Topiramate, Furosemide, Amiloride and Octreotide, despite little mechanistic or clinical evidence to support their use.

The aim of this study was to ascertain which of these drugs has the greatest effect on lowering ICP in-vivo.

Methods: Using a validated epidural ICP recording method we measured changes in ICP in conscious female rodents after subcutaneous administration of these drugs at clinically equivalent and supra-clinical doses over 2 hours (peak plasma concentrations).

Results: At clinical doses, Topiramate lowered ICP by 32% (p = 0.0009) compared to a 25% reduction for Acetazolamide (p = 0.0081). Post-hoc analysis showed no significant difference between the two (p = 0.85).

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Furosemide, Amiloride and Octreotide had no significant effect.

**Conclusion:** Our in-vivo studies have demonstrated that, at clinically equivalent doses, Topiramate significantly lowers ICP and is as effective as acetazolamide. Topiramate may have additional advantages in IIH, including its migraine prevention properties and weight loss effects. These findings support the need for future randomised controlled trials evaluating the therapeutic efficacy of topiramate in IIH.

**Disclosure of Interest:** None Declared

**Other Secondary Headache Disorders**

**PO-01-130**

The prevalence rate, risk factors, and surgical treatment of cervicogenic headache in patients with cervical spine disorders requiring surgery

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2Department of Spine Surgery, Niigata Spine Surgery Center
3Department of Neurology, Brain Research Institute, Niigata University, Niigata, Japan

**Objectives:** Cervicogenic headache (CEH) is caused by cervical spine disorders that was first identified by Sjaastad (1983). Surprisingly, 86–88% of patients with cervical myelopathy or radiculopathy requiring anterior cervical surgery presented headache in 2 prospective studies, although these studies did not diagnose headache according to the International Classification of Headache Disorders criteria. The International Classification of Headache Disorders-Third Edition beta (ICHD-3beta) CEH criteria represents the first instance of verification of cervical spondylosis as causing disorder of CEH. However, it remains unknown about the prevalence rate, risk factors of CEH in patients with cervical spine disorders requiring surgery. The aim of the present study was to clarify the prevalence rate, clinical features and risk factors of CEH as diagnosed according to ICHD-3beta in patients with cervical spine disorders requiring surgery.

**Methods:** In this single hospital-based prospective cross-sectional study, we enrolled 70 consecutive patients with cervical spine disorders such as cervical spondylotic myelopathy (CSM), ossification of the posterior longitudinal ligament (OPLL), cervical spondylotic radiculopathy (CSR), and cervical spondylotic myeloradiculopathy (CSMR) who had been scheduled to undergo anterior cervical fusion or dorsal cervical laminoplasty between June 2014 and December 2015. All patients were asked structured interview and headache was diagnosed according to ICHD-3beta pre-operatively. Limited cervical range of motion, identification of the spinal lesion levels and intramedullary high signal intensity on T2-weighted MRI, the Japanese Orthopaedic Association Cervical Myelopathy Evaluation Questionnaire, Neck Disability Index (NDI), and a 0–100 mm visual analog scale (VAS) of headache and neck pain were used to evaluate clinical features, and scores were compared between preoperatively and 3, 6, and 12 months post-surgery. We also compared clinical difference between patients with CEH and those without CEH.

**Results:** We enrolled 70 patients (M:F = 46:24, 64.5 ± 11.5 years old) with CSM (53 patients), OPLL (7 patients), CSM (5 patients), and CSMR (5 patients). The prevalence rate of CEH in our population was 15/70 (21.4%; 95%CI: 11.8% to 31.0%). 12 patients were diagnosed with CH, 2 with CH and tension-type headache, and 1 with CH and psychogenic disorder. The main clinical features were dull and tightening/pressing headache sensations in the occipital region. All our patient with CEH had cervical lesion below C4. Headache severity was mild (VAS, 32 ± 11 mm). The CEH group had a higher frequencies of neck pain (87% vs.51%; P < 0.05), cervical range of motion limitation (67% vs. 38%; P < 0.05), and higher NDI score (14 vs.3; P < 0.001). Among the different cervical spine disorders, the prevalence of CEH was highest in CSMR patients (60%), being ≤20% for all other disorders. Surgical treatments including cervical laminoplasty produced initial improvements in CEH that slightly diminished by 12 months post-surgery. The headache VAS at 3, 6month and 12month after surgery was lower than that before surgery (P < 0.001, F = 9.728, 9 ± 15.11 ± 18.12 ± 15). The neck pain VAS at 3, 6month and 12month after surgery also significantly reduced than before surgery (P < 0.001, F = 6.69).

**Conclusion:** We demonstrated that the prevalence rate of CEH (21%) was much lower than the previous report. Potential risk factors for CEH included neck pain, limited cervical ROM, high NDI score and a diagnosis of cervical spondylotic myeloradiculopathy.

**Disclosure of Interest:** None Declared

**Other Secondary Headache Disorders**

**PO-01-131**

Acute ischemic stroke with prominent headache symptom: A case series study

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2Neurology, Eulji university hospital, Seoul, Korea, Republic Of
Objectives: Headache in stroke is usually caused by cerebral hemorrhages such as subarachnoid hemorrhage (SAH), subdural hemorrhage (SDH) and lobar hemorrhages. Acute ischemic stroke can also show headache with various neurological signs and symptoms and usually managed in emergency room. But some patient with acute ischemic stroke walks in outpatient clinic with isolated headache. We retrospectively analyzed clinical and radiological characteristics in such patients.

Methods: We conducted a retrospective review of 18 patients (male = 5, female = 13) who showed isolated headache diagnosed as acute ischemic stroke in outpatient clinic. We investigated their clinical features, neurological findings and radiologic findings.

Results: All patients showed abrupt onset headache that was disappeared within 7 days. The mean age of patients was 65 year-olds. Characteristics of headache was mostly dull-aching pain (n = 12) followed by throbbing pain (n = 5). Thunderclap headache was presenting mode in one patient. One patient showed very mild limb weakness and 3 patients showed hemianopia. But none of the patients noticed such symptoms. The location of infarction were temporal (n = 12), occipital (n = 10), cerebellar (n = 5) and pons (n = 1) infarction in posterior circulation of brain.

Conclusion: In case of newly developed sudden onset headache without any other prominent neurological symptoms in outpatient clinic, we have to consider acute ischemic stroke, especially in elderly patients.

Disclosure of Interest: None Declared

Other Secondary Headache Disorders

PO-01-132

Headache as the only symptom of atypical tuberculous meningitis

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Objectives: TB meningitis - a secondary disease, specific inflammatory process primarily localized on meninges in the base of the brain, which leads to the typical picture basilar tuberculous meningitis. There are some atypical forms of tuberculosis of the brain, which are due to inadequate application of anti-TB drugs.

Methods: Patient M., 52 years, during 6 months of 2016 was delivered four times through the ambulance in different neurological department of Bishkek. And each time with monotonous complaints: chronic headaches in the parietal-occipital areas Expander nature radiating to the eyeballs, accompanied by nausea, repeated vomiting.

According to his son, occasionally marked by episodes of “thought and pour”, during which he did not immediately respond to a verbal appeal. Last deterioration observed 1 December 2016, when the headaches became severe, he could not talk, by the ambulance he was admitted to the angioneurology department with the DS: Supratentorial aneurysm of the left internal carotid artery. On MRA: the restriction and intermittent progress of both the middle cerebral artery in M2 segments, thinning A1 segment both anterior cerebral arteries, aplasia of the right vertebral artery, the depletion of the vascular pattern of the terminal branches of both pools of blood supply to the brain. Blood sugar, common blood and urine tests, kidney tests, ECG were within normal limits. Then he was transferred to the Department of Neurosurgery to exclude the aneurysm supratentorial department of the left internal carotid artery. In the neurological status: apathetic, slightly retarded, face pained, pale skin. Questions answered in monosyllables. Convergence weakness on the left side. Trigeminal point slightly painful. Palpable occipital pain points, the spinous processes of the cervical localization. Meningeal symptoms negative. Angiography of cerebral vessels: aneurisms were excluded. Markers for viral hepatitis, blood for HIV, Wasserman - Neg. Blood sugar, prothrombin index, total protein serum within the normal range. Ultrasound of the internal organs: cholecystitis, a cyst of the left kidney. Chest x-ray: lungs roots extended with the presence of small calcifications on the left. Optometrist: VOD = 0.8; VOS = 0.8. Optic disc more bloodshot, efface the border narrowed artery, veins slightly expanded. Antibodies to Mycobacterium tuberculosis - Neg. There was recommended diagnostic lumbar puncture to rule out meningitis tuberculous origin. The CSF assay detected changes are listed in Table 1.

Table: 1

<table>
<thead>
<tr>
<th>Colour</th>
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<td>Transparency</td>
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<td>Cytosis</td>
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<td>The fibrin fiber</td>
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Abstract number: PO-01-132

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**Results:** He was transferred to the National TB Center. The patient was scheduled for TB therapy first category DOTS (isoniazid, pyrazinamide, ethambutol, rifampicin, kanamycin) and symptomatic treatment. During the time spent in the department noted regression of headaches, nausea, vomiting.

**Conclusion:** Thus, this clinical example shows that the diagnosis and treatment of TB meningitis problem can not be considered solved, even with greatly increased the arsenal of diagnostic and therapeutic agents. TM Early diagnosis is very difficult. In this described case, symptoms were stable nature, which were assessed by experts as a vascular process. It is necessary to pay attention to soft course over 6 months, with an extension of each phase of the disease. This, apparently, can be explained by the appointment of broad-spectrum antibiotics while another hospitalization in the form of symptomatic treatment. In conclusion, we can say about the evolution of the modern course of infection, which is caused by the active use of drugs as a symptomatic therapy, which brings change for the seemingly classical infectious diseases.

**Disclosure of Interest:** None Declared

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**Other Secondary Headache Disorders**

**PO-01-133**

**Characteristics of headache in the patients with anti-neutrophil cytoplasmic antibody associated disorders**

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**Objectives:** Anti-neutrophil cytoplasmic antibody (ANCA) is one of autoantibodies detected in some autoimmune disorders. The characteristics of headache due to ANCA associated disorders remains to be elucidated. The aim of this study was to elucidate the characteristics of headache in patients with ANCA associated disorders.

**Methods:** We retrospectively reviewed the medical records of 10 Japanese patients with ANCA associated disorders (7 men, and 3 women), who were admitted to our hospital between January 2014 and December 2016. We investigated clinical, radiological, and serological profiles including myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA in these patients.

**Results:** MPO-ANCA alone-positive patients was found in 8, PR3-ANCA alone-positive patient in 1, and both of them-positive patient in 1, respectively. Three patients complained headache as the chief complaint. Those patients were all positive for MPO-ANCA and had lesions limited to the intracranial space without systemic organ disorders. The location of headache in each patient was forehead, temporal, and occipital, respectively. The comorbidities were diverse (otitis media in 2, cranial polyneuropathy in 1, chronic sinusitis in 1, and mastoiditis in 1). MRI demonstrated that all patients with headache had no brain parenchymal involvement and two of three patients were radiologically diagnosed as hypertrophic pachymeningitis. Great efficacy was observed in immunosuppressive therapy including prednisolone in two patients.

**Conclusion:** Previous reports had been demonstrated MPO-ANCA positivity was predominant in Asian countries, whereas PR3-ANCA positivity was predominant in northern Europe. In this study, we elucidated that the prevalence of otitis media in patients suffering from headache due to MPO-ANCA associated disorders was high. Otitis media might be an important clue in diagnosis of headache with MPO-ANCA associated disorders and we should take into consideration for MPO-ANCA associated disorders in differential diagnosis of headache in Japanese patients with refractory otitis media.

**Disclosure of Interest:** None Declared

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**Other Secondary Headache Disorders**

**PO-01-134**

**10-year follow-up of CSF leakage by serial neuroimages in a patient with protracted spontaneous intracranial hypotension**

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**Objectives:** Protracted spontaneous intracranial hypotension (SIH) is uncommon. Long-term follow-up of these patients is rare in the literature. The pathophysiology of protracted SIH and the relationship between clinical symptoms and neuroimaging in these patients are not clearly understood.

**Methods:** A 52-year-old female had a protracted course of SIH and received 3 epidural blood patches within 2 years (at 1 month, 2.5 months, and 10 months). Her symptoms improved gradually over a period of 4.5 years. During the 10-year follow-up, we serially evaluated her neuroimaging of brain magnetic resonance imaging (MRI) and heavily T2-weighted magnetic resonance myelography (HT2W MRM). The correlation between clinical symptomatology and neuroimaging was analyzed.

**Disclosure of Interest:** None Declared

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Objectives: To identify clinical and psychological factors associated to MOH

Methods: The study was conducted at the Headache Science Center of “Mondino” Institute, Pavia, Italy. We enrolled consecutive patients with long-term episodic migraine (EM, with a history of illness >10 years who never had Medication Overuse MO) and patients with chronic migraine and MO (MOH). We compared socio-demographical, clinical and psychological variables between EM and MOH patients. Clinical variables included lifestyle habits, migraine characteristics/history, endocrinogynecological history, familiar pathological history, and general medical history. Psychological assessment included psychopathological history, Toronto Alexithymia Scale (TAS-20), Hospital Anxiety and Depression Scale (HADS), Childhood Trauma questionnaire and stressful life-events questionnaire. Univariate and multivariate logistic regressions were applied in order to determine predictors of MOH. The criterion for variable inclusion in the multivariate model was based on statistical significance at the level of p < 0.10 as obtained by univariate analysis.

Results: Three hundred and eighteen patients were enrolled: 156 with EM and 162 with MOH. The mean age was 42.1 ± 10.3, 80.8% of subjects were female. The duration of migraine (before MOH onset in the case of MOH patients) was not significantly different between the two groups (24.0 yrs EM vs 24.6 yrs MOH; p = 0.57). After the multivariate analysis the factors associated to MOH were: age of onset of migraine [OR 0.94 (0.89–0.98) p = 0.016], use of at least one migraine preventive medication [OR 2.36 (1.18–4.71), p = 0.014], marital status [married vs unmarried OR 3.65 (1.63–8.19) p = 0.002; separated/divorced/widowed versus unmarried OR 4.19 (1.13–15.47) p = 0.031], physical activity [0.42 (0.19–0.91) p = 0.029], history of depression [2.91 (1.25–6.73) p = 0.012], insomnia [insomnia associated to use of hypnhetics versus absence of insomnia OR 5.59 (1.65–18.93) p = 0.006], traumatic head injuries [OR 3.54 (1.57–7.99), p = 0.002] snoring [OR 2.24 (1.05–4.79), p = 0.036], and higher score at Childhood Trauma questionnaire [OR 1.48 (1.09–2.02), p = 0.012].

Conclusion: The factors associated to the development of MOH are elusive. Few studies have attempted to answer this question, although with some limitations (i.e. diagnosis made with questionnaires, a small number of variables considered, impossibility to compare duration of illness between groups). In this study run in a headache center, we evaluated and compared a high number of clinical and psychological variables between two large and well characterized groups of patients suffering from EM or MOH. In this frame, it is worth noting that the similar duration of illness in the two groups strongly speaks against a possible overlap between them. The present study is interesting as it considered together several aspects that can be involved in MOH development. Multivariate analysis identified 9 factors belonging to 4 different areas, indicating that MOH derives from a mixture of factors. This is useful to know as MOH can be optimally treated by considering perspectives and strategies (medical, social/lifestyle, psychological).

Acknowledgements
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Disclosure of Interest: None Declared
Other Secondary Headache Disorders

PO-01-136

Evaluating the use of spectral domain optical coherence tomography to measure retinal nerve fibre layer thickness in idiopathic intracranial hypertension

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Objectives: Identification and monitoring papilloedema is an essential aspect to managing patients with idiopathic intracranial hypertension (IIH). Direct inspection to quantify papilloedema is subjective and prone to inaccuracy and inter-rater variability. Spectral domain optical coherence tomography (SD OCT) can quantify peripapillary retinal nerve fibre layer (RNFL) thickness, a measure of papilloedema. This has been a major advance in the field as it enables quantification of optic disc oedema and can track changes over time. Consequently, OCT imaging of the RNFL is being increasingly used in both the clinical and research setting to monitor IIH patients. We have noted that the automated OCT RNFL measurements are not consistently accurate in IIH. Here we aim to conduct an in-depth analysis of the extent and location of the automated RNFL segmentation error in a cohort of IIH patients and provide a practical paradigm for clinicians to re-analysed with the Heidelberg Eye Explorer software, version 1.9.1. (Heidelberg Engineering, Heidelberg, Germany). The percentage change was determined.

Methods: Baseline SD OCT scans of patients with IIH (active papilloedema) and controls with no retinal or optic nerve pathology were examined. In each patient, the OCT RNFL of the most severely affected eye was assessed for errors with the automated segmentation values. The automated segmentation errors were then manually corrected as needed. The distribution, around the optic disc (superior, temporal, inferior, nasal) of RNFL errors were qualitatively assessed. The difference between the original automated area of the RNFL and the manually adjusted RNFL area were quantified using ImageJ and also reanalysed with the Heidelberg Eye Explorer software, version 1.9.1. (Heidelberg Engineering, Heidelberg, Germany). The percentage change was determined.

Results: 46 IIH and 14 control subjects were recruited. Significantly greater segmentation error (p = 0.009) was present in RNFL total area, assessed using ImageJ, in IIH patients (error 5% ± 0–58%) compared to controls (error 1% ± 0–6%). This was particularly evident in patients with moderate to severe papilloedema (n = 23, 10% ± 0–58%, p < 0.001). Automated re-analysis of the adjusted average RNFL indicated that the superior retina was predominantly affected (error 40% in IIH v 3% in control) with least error noted in the temporal region (error 5% in IIH v 2% in controls). Qualitative analysis also highlighted that the error was predominantly located in the superior retina of 50% of IIH patients. Finally, in those with very severe papilloedema the RNFL thickness was so inaccurate that it could not be quantified.

Conclusion: Clinicians should be cautious when interpreting SD OCT RNFL in IIH patients with papilloedema as automated segmentation values can be significantly inaccurate, especially in the superior retinal quadrant. Importantly, errors in the automated RNFL values are greatest in those with moderate to severe papilloedema. We suggest that SD OCT RNFL scans are systematically reviewed in IIH patients with moderate to severe papilloedema. Scans should be evaluated particularly in the superior retinal quadrants and manually adjusted and then re-segmented to allow corrected values to be generated and utilised for monitoring papilloedema in IIH.

Disclosure of Interest: None Declared

Other Secondary Headache Disorders

PO-01-137

Effect of SSRI treatment on the prognosis of patients with medication overuse headache

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Objectives: In this study, patients with MOH were treated and followed up to explore the role of SSRIs in the treatment of MOH patients and the risk factors for relapse in patients with MOH.

Methods: In this cohort study, we were followed up for MOH patients diagnosed at the West China Hospital at an average follow-up duration of 1.5 years to analyze patient outcomes and relapse. We used logistic regression to assess the relationship between patient medication and withdrawal treatment success rate. We used COX regression analysis to assess the relationship between withdrawal treatments and relapse rate in patients with MOH.

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Results: A total of 72 MOH patients were enrolled in this study, of which 14 (19.4%) were discontinued. In the successful treatment of patients, there are 13 (20.7%) relapse patients. SSRIs treatment can increase the effect of withdrawal therapy (odds ratio [OR] 0.016, 95% confidence interval [CI] 0.003, 0.091, p < 0.001). No significant association was found between SSRIs treatment and the risk of relapse.

Conclusion: SSRIs can increase the therapeutic effect in MOH withdrawal therapy.

Disclosure of Interest: None Declared

Other Secondary Headache Disorders

PO-01-138
Headache and neck pain in vertebral artery dissection
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Objectives: Headache and neck pain are frequent symptoms in spontaneous vertebral artery dissection (VAD). VAD is being increasingly diagnosed because of magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA). The purpose of this study was to analyze the clinical features of VAD.

Methods: We reviewed medical records of 34 consecutive patients who showed VAD and were diagnosed between 2014 and 2016. Headache topography, severity and quality, presence of migraine or vascular risk factors such as hypertension, diabetes mellitus, dyslipidemia and smoking and outcome were examined.

Results: The mean age was 52 years. Twenty-seven of 34 patients presented with headache. Of them, 6 had brainstem infarcts, 3 had subarachnoid hemorrhages and 18 had neither infarction nor bleeding (Headache group). Onset of headache was progressive in 9, acute in 11 and thunderclap-type in 7 patients. Headache was throbbing in 21 and constrictive in 6. Neck pain was present in 10 patients. Neck pain was constrictive in all patients. Pain was unilateral in 23 and bilateral in 4 who showed bilateral VAD. All patients were pain free at 2 months. Headaches were distributed posteriorly in all patients. Migraine was present in 3 patients. There were no significant differences in age, dynamics and quality of headache, and rates of vascular risk factors between Headache group and brain ischemia patients. Antithrombotic therapy was administered, but no reattacks were noted in the follow-up period.

Conclusion: Pain may be the only symptom in VAD, but pain dynamics, quality and duration were heterogenous. Present study shows that imaging study should be necessary in patients with newly-developed unexplained headache or neck pain.

Disclosure of Interest: None Declared

PO-01-139
Moyamoya syndrome in a patient with hemiplegic migraine type 1: A case report
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Objectives: We present an association between moyamoya syndrome and sporadic hemiplegic migraine type 1. Moyamoya syndrome is a rare cerebrovascular condition characterized by the progressive stenosis of proximal intracranial vessels. Stroke is the most feared complication of this disease. Many patients complain of headaches although an association between moyamoya and migraine syndromes has not been described. The patient had multiple episodes of headache associated with transient neurological deficits. She was diagnosed with probable moyamoya syndrome based on intracranial vessel imaging. However not all symptoms could be attributed to the stenosis observed and therefore hemiplegic migraine was considered. A pathogenic heterozygous mutation in the CACNA1A gene was indeed identified confirming this diagnosis.

Methods: Case report.

Image:
Results: A 43 year old Caucasian woman without relevant prior medical history experienced sudden transient loss of consciousness followed by headache without any other neurological deficit during several hours. More than one year later similar symptoms occurred although this episode was complicated with a transient left sided hemiparesis which lasted for one day. She presented to an outside hospital in which magnetic resonance (MR) imaging revealed a recent ischemic lesion in the right frontal lobe. Six months later she developed transient neurological symptoms with dizziness, a right sided hemiparesis and visual disturbances of the right eye during multiple hours. In the outside hospital a cardiac etiology for the loss of consciousness was excluded by implanting a continuous cardiac monitoring device (REVEAL) which did not show any cardiac arrhythmias.

Thereafter she visited our outpatient clinic for medical advice on the episode of transient neurological deficits and chronic symptoms of headache. She described chronic daily headache for many years, with episodic exacerbations characterized by severe, pulsating and uni/holocranial headache associated with photophobia, sonophobia, nausea and vomiting. These severe headaches were not preceded by auras. Severe headache we present simultaneously with the transient neurological symptoms or started even before these symptoms occurred. Familial history was negative for migraine or other neurological syndromes.

On clinical examination, there was a mild right sided sensorimotor hemiparesis. Comparing the neuro-imaging performed following the second event versus a MR angiography few months prior a progressive narrowing of the right M1 segment of the middle cerebral artery was identified. The recurrent episodes of headache with associated transient, but prolonged neurological deficits suggested a diagnosis of hemiplegic migraine. This was confirmed by genetic analysis of the CACNA1A gene which identified a heterozygous pathogenic mutation: rs16024 c.3043G>A (p.Glu1015Lys).

Conclusion: To our knowledge and after reviewing available literature, this is the first case report of moyamoya syndrome in a patient with (sporadic) hemiplegic migraine type 1. We also did not find a current link between CACNA1A and moyamoya disease as a causative or involved gene. Headache is a very common symptom in patients with moyamoya disease with frequent migraine-like phenotype. Therefore, we suggest that CACNA1A might play a role in the pathophysiology or symptomatology of moyamoya disease. Because we cannot confirm its relevance in moyamoya disease with this sole case study, further research is needed to elaborate this hypothesis.

Disclosure of Interest: None Declared

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Results: Patient has been suffering from 17 purely stereotypical high-intensity abrupt onset and short (10–15 min) headache attack during the period of 9 years. In 2008 thunderclap headache (6 attacks) was developed after non-traumatic intracranial haemorrhage of unknown etiology. In 2015 and 2017 thunderclap headache was triggered by emotional stress, but during this period general discomfort and mild-moderate headache was not presented any more. Blood pressure was elevated (>180/100 mmHg) only during 10 attacks out of 17. If admitted that all the researches were provided on timely and adequate basis - last 11 headache attacks by ICHD-3 beta may be classified as “Primary thunderclap headache” (code 4.4).

Conclusion: Thunderclap headache resulted from intracranial lesion (e.g. haemorrhage of unknown etiology) may later become recurrent primary one. According to the analysis of our case complete stereotypeness of severe headache in the late period with the absence of other type (between or after attacks) headaches, patient's good general condition, normal instrumental and lab researches make us to think that maybe at early stage in case of intracranial hemorrhage “clap of thunder pattern” was saved somewhere in “pain memory” which may play the role of “generator” of “nonorganic” headache triggered by psychological stress. It is necessary to continue recurrent stereotypical thunderclap headache analysis in the future.

Disclosure of Interest: None Declared

Other Secondary Headache Disorders

PO-01-141

Headache attributed to craniocervical dystonia

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Objectives: We studied the prevalence, characteristics and impact of headache attributed to craniocervical dystonia in cervical dystonia patients.

Methods: 24 consecutive patients had been evaluated regarding the dystonia and headaches clinical characteristics and followed for about 4 months after botulinum neurotoxin type A injections. Patients had been evaluated in three distinct moments by a neurologist with experience in treating movement disorders and headaches: 1- first baseline visit, when they had taken their scheduled botulinum toxin A injections; 2- second revaluation visit, approximately four-weeks later; 3- third visit, expected sixteen-weeks later than the first visit. Semistructured interviews, headache diaries, Hospital Anxiety and Depression Scale (HADS), Headache Impact Test-6 (HIT-6) and Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) were used. Reported headaches were classified at baseline visit in accordance with the diagnostic criteria established by the third edition beta of the International Classification of Headache Disorders. According to the identified headaches characteristics, the patients were assigned to one of the cohort groups: headache attributed to craniocervical dystonia group, “other headaches” group and “without headaches” group. All patients had given their informed consent. The Universidade Federal de Pernambuco’s Research Ethics Committee had provided ethics approval (ethics report number 777.590/2014).

Results: 19 patients (79%) had cervical dystonia associated pain, 18 (75%) had headaches. Seven patients (29%) had headache attributed to craniocervical dystonia, all of them with migraine-like headaches, mean HIT-6 score: 60.1 ± 9.9. These patients had more disability related to dystonia compared to those without headaches (TWSTRS; Kruskal-Wallis test; p = 0.02). Headache impact did not vary significantly through time in the “other headaches” group. Those with headache attributed to craniocervical dystonia had an significant improvement in HIT-6 scores between first and second visits, followed by a significant worsening of HIT-6 scores between second and third visits (MANOVA; p < 0.05). Considering the analysis of HADS scores through the visits, no statistical significant differences were found among the groups (MANOVA; p > 0.05).

Conclusion: Headache attributed to craniocervical dystonia is commonly prevalent among cervical dystonia patients, have a high impact and have different behavior from other headaches presented by these patients.

Disclosure of Interest: None Declared

Other Secondary Headache Disorders

PO-01-142

A Pain From The Neck: Hemicrania Continua-Like Headache After Carotid Dissection

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Objectives: Hemicrania continua is a rare primary headache subtype characterized by unilateral, constant pain, autonomic features, and responsiveness to indomethacin. The condition is frequently subject to diagnostic error, leading to significant delay in appropriate diagnosis and treatment. The objective of this report is to present a
case of hemicrania continua-like headache occurring secondary to carotid dissection with immediate response to sphenopalatine ganglion (SPG) blockade. 

Methods: A 44-year-old right-handed man was referred to the University of Washington Headache Clinic for a second opinion on “uncontrolled headaches,” previously diagnosed as migraine prior to his referral. A thorough headache history and neurologic exam were performed. The patient had developed a spontaneous left carotid dissection two years ago, and the headache had been constantly present since. He did not have any headache history prior to the dissection. His pain was determined to be unilateral, moderate-to-strong in intensity with spikes of more severe discomfort, and associated with left-sided tearing and ptosis. His extensive previous medication trials were reviewed and included many acute and prophylactic agents, though never indomethacin. General and neurologic exam were unremarkable with exception of left-sided miosis and ptosis. His previous vessel imaging and MRI in 2014 were reviewed, and revealed left carotid dissection. Follow-up MRI in 2016 showed resolution of the dissection.

Results: The patient was diagnosed with hemicrania continua-like headache secondary to carotid dissection. He underwent same-day bilateral sphenopalatine ganglion blockade, with immediate, full response. He was unable to tolerate indomethacin uptitration, but continued weekly SPG blocks for three weeks, followed by biweekly SPG blocks over the following months. He continued to have excellent results, with full pain relief following each block.

Conclusion: Hemicrania continua-like headache may occur after carotid dissection, and should be a diagnostic consideration. In this case, secondary hemicrania continua responded to sphenopalatine ganglion blockade, potentially via suppression of unopposed parasympathetic activity. SPG blockade may be a useful modality for secondary hemicrania continua treatment in the future, particularly for patients who cannot tolerate or who do not have complete response to indomethacin.

Disclosure of Interest: None Declared

Other Secondary Headache Disorders

PO-01-143

Intracranial hypertension after massive blood transfusion

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Objectives: Idiopathic intracranial hypertension is an uncommon syndrome presenting with chronic headache, papilledema, diplopia, tinnitus and other neurological symptoms. However, the pathophysiology of the syndrome is unknown, although many hypotheses have been proposed, including hormonal change, cerebrospinal fluid (CSF) dynamics, and cerebral venous blood pressure change. We experienced a patient with idiopathic intracranial hypertension after rapid massive blood transfusion, who had chronic anemia due to multiple uterine myomas.

Methods: CASE: A 38-year-old woman presented to the emergency department with uncontrolled vaginal bleeding for 2 days. She had history of uterine myoma operation in 2007, otherwise there was no relevant medical or family history. The body mass index was 20.78. Initial vital signs were stable. She had mild dizziness and anemic conjunctiva, however her mental status was alert and the neurologic exam showed no focal deficits. Anemia with uterine myoma was considered as a possible cause. The hemoglobin level was 2.4 g/dl, mean cell volume (MCV) 51.5 fL, mean cell hemoglobin (MCH) 14.3 pg, mean cell hemoglobin concentration (MCHC) 27.7 g/dL, Fe < 10 ug/dL, total iron binding capacity (TIBC) 468 ug/dL, ferritin 2.4 ng/mL and laboratory findings were compatible with iron deficiency anemia. She had 7 pints of red blood cell transfusion for 2 days and follow up hemoglobin level was 10.8 g/dl. Three days after last transfusion, she started to suffer severe pulsatile headache from occipital area radiating to frontal area with visual analog scale score of 10. She also had nausea and excessive daytime somnolence. The CSF study through lumbar puncture was done, the pressure was 25.0 cmH2O and the other profiles were within normal range. The magnetic resonance imaging with angiography and venography showed suspicious leptomeningeal enhancement without any vessel abnormalities. She had multiple retinal hemorrhages on both eyes but no papilledema on the ophthalmic exam.

Results: In this case, the papilledema was absent and the CSF pressure was not high enough to diagnose idiopathic intracranial hypertension, however, suddenly developed severe headache and multiple retinal hemorrhages on both eyes suggested idiopathic intracranial hypertension. She was treated with 20% intravenous dextrose mannitol and oral acetazolamide. The headache was improved gradually for next 7 days and no other complications occurred. The multiple uterine myomas were confirmed on sonography and myomectomy was done 1 month later. Her hemoglobin level was stable and the headache has resolved completely.

Conclusion: The chronic iron deficiency anemia is well known as risk factor of idiopathic intracranial hypertension with young, obese women. In this case, the severe chronic anemia was present before headache and the onset of headache was the time after massive rapid blood transfusion was done. We made a hypothesis that the sudden
blood transfusion in chronic anemia patient might damage cerebral vascular endothelium, releasing free radicals, resulting in vasogenic cerebral edema. Finally, the massive rapid blood transfusion might be the cause of idiopathic intracranial hypertension. Therefore, it is important to investigate carefully when the chronic anemia patient have sudden headache after blood transfusion.

Disclosure of Interest: None Declared

Other Secondary Headache Disorders

PO-01-144

Minimum important difference of the Headache Impact Test Questionnaire (HIT-6) in subjects with temporomandibular disorders and concomitant headache

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2Oral Kinesiology Department, Academic Center for Dentistry Amsterdam, Amsterdam, Netherlands
3Faculty of Rehabilitation Medicine, University of Alberta, Edmonton, Canada

Objectives: The prevalence of pain-related Temporomandibular Disorders (TMD-pain) in adults is estimated to range from 5–10%, while there is a high prevalence of primary headaches. The two disorders often co-occur; up to 70% of TMD patients also present with headache. The Headache Impact Test questionnaire (HIT-6) covers domains of pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress. It has been used in clinical trials to verify the effect of treatments regarding headache impact. However, the Minimum Important Difference (MID) of the HIT-6 has not been reported for subjects with TMD and concomitant headache (TMDH). Therefore, this study aims to estimate the MID of the HIT-6 to measure changes of headache impact after an intervention in subjects with TMDH.

Methods: Fifty-eight women (mean age 26.2 ± 5.2) diagnosed with a myofascial TMD according to the Research Diagnostic Criteria for TMD and concomitant headache complaints were included. All of them had orofacial pain for more than 6 months, with a score of at least 4 points in the Chronic Pain Inventory (which ranges from 0–10), and more than 50 points on HIT-6, which ranges from 36–78. They were excluded in case of pregnancy, fibromyalgia, rheumatic or neurologic conditions, history of neck or jaw fracture, tooth loss or previous orofacial treatment in the last 6 months. They were randomized in 2 equal groups. The intervention group (IG) received physiotherapy treatment composed of upper cervical manual therapy techniques and a training protocol for the deep neck flexor muscles with biofeedback for 5 weeks. The control group (CG) did not receive any therapy or counseling for 5 weeks. A blind rater applied the HIT-6 at baseline and at follow-up and applied the Global Rating Scale (GRS) on follow-up. The GRS measures changes in a clinical condition based on the patient perspective. It varies from −7 to 7 (‘a very great deal worse’ to ‘a very great deal better’). Based on the GRS, subjects were classified as non-responders (−7–0), moderate responders (1–3) and strong responders (4–7) to the treatment. For all participants, the difference between the baseline and follow-up HIT-6 score was calculated. The Anchor-method approach was used to estimate the MID of the HIT-6 using the GRS as the anchor. A ROC curve was built on SPSS to calculate sensitivity and specificity of HIT-6 comparing moderate/strong responders to non-responders and to estimate the MID for which the values of sensitivity and specificity are maximized.

Results: At baseline, the mean scores of the HIT-6 were 62.5 ± 6.1 for the CG and 61.4 ± 6 for the IG. Data from the classification of subjects according to the GRS are described in Table 1. All strong responders were on the IG as were 3 (out of the 17) moderate responders and 3 (out of the 29) non-responders. The area under the ROC curve (AUC) was 0.749 and the MID of the HIT-6 to discriminate between responders and non-responders was 3.5 (with sensitivity of .72 and specificity of .76).

Conclusion: According to the AUC, sensitivity and specificity values, HIT-6 has a reasonable responsiveness to variations on headache impact in the population with TMDH and the MID should be considered to verify the effect of future interventions.

Disclosure of Interest: None Declared

Table: 1 Mean change in HIT-6 scores between baseline and 5-week follow up for subjects classified according to the GRS.

<table>
<thead>
<tr>
<th>GRS</th>
<th>Sample size</th>
<th>HIT-6 Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-responders</td>
<td>29</td>
<td>2.34 (0.43–5.11)</td>
</tr>
<tr>
<td>Moderate responders</td>
<td>17</td>
<td>7.74 (3.3–12.2)</td>
</tr>
<tr>
<td>Strong responders</td>
<td>12</td>
<td>11.75 (7.5–16)</td>
</tr>
</tbody>
</table>
Other Secondary Headache Disorders

PO-01-145

Handl syndrome in pediatric age
Irene Salfa 1, Laura Papetti 2, Barbara Battan 2, Federico Vigevano 2 and Massimiliano Valeriani 2

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Objectives: The syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis (HaNDL) is a rare syndrome of unclear pathogenesis characterized by one or more episodes of severe headache, transient neurologic deficits and lymphocytic pleocytosis in the cerebrospinal fluid, seldom reported in paediatric age. In most cases it is a benign and self limited disorder, although it may mimic various serious, including life-threatening, diseases, such as stroke and meningoencephalitis, which is why vigorous tests should be sought before this diagnosis of exclusion can be reached.

Methods: We report three cases of HaNDL occurred in 2 boys (14 years and 10 years old) and in a 17 years old girl.

Results: Each patient presented with headache, altered conscious state and papilledema associated with different neurological symptoms such as dysarthria, hemiplegia, perronious vomiting, ideomotor slowing and psychomotor agitation. None of them had fever and there was no evidence of meningal irritation. They received Ceftriaxone, Aciclovir, and Dexamethasone for possible encephalitis and/or autoimmune disorders. Clinical manifestations were compatible with a variety of disorders including structural brain lesions, meningitis, seizures, autoimmune, vasculitic and paraneoplastic disorders. We performed neuroimaging examinations (CT scan and MRI of the brain), EEG and serum/CSF studies for infectious, autoimmune and vasculitic diseases. All of these aetiologies were ruled out. In one case, a complete tox screen was added and it resulted negative. The laboratory finding common to all three cases was a clear CSF lymphocytic pleocytosis and an elevated opening pressure during lumbar puncture. The intracranial hypertension treated in all three cases with acetazolamide per os with complete remission. In one case, it was necessary the admission in the intensive care unit because of the worsening of psychomotor agitation of the patient, requiring sedation and endotracheal intubation. All three patients recovered without any neurological sequelae during the follow up.

Conclusion: The possibility of HaNDL should be considered in patients presenting with unusual patterns of headache and transient neurological symptoms. It is most commonly diagnosed in the third or fourth decades of life and is rare in the paediatric population. However, awareness of HaNDL existence also in children and adolescents can avoid unnecessary and potentially harmful investigations and therapies.

Disclosure of Interest: None Declared

Other Secondary Headache Disorders

PO-01-146

Hypertensive Posterior Reversible Leukoencephalopathy with Spinal Cord Involvement Presenting as Migraine like Headaches in a Young Child
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Objectives: Posterior reversible encephalopathy syndrome with spinal cord involvement (PRES-SCI) is a rare entity with only about 15 cases being reported in the literatures so far. The Aim is to present a case of 7-year-old girl who presented with complaints of migraine like headache and was later found to be hypertensive with features of PRES-SCI.

Methods: A 7-year-old girl presented with recurrent episodic, bilateral fronto-temporal throbbing headache since 3 months. Headaches occurred every 3–4 days, lasting for 2–3 hours with nausea, vomiting, vertiginous sensations and phonophobia and used to subside after a bout of vomiting or sleep. There was no history of aura. There was no significant past history. Her initial evaluation by a GP revealed no abnormality including fundus examination. However, no record of her BP measurement was available. She was referred to our centre as her headaches became continuous for the past 7 days. On examination, patient was conscious but jittery. She was well oriented but her sustained attention was impaired. Her pulse was 106/min and BP 240/130 mm of Hg. Peripheral pulses were normal, without any radio-femoral delay. Eye examination showed bilateral grade-4 hypertensive retinopathy with bilateral exudative retinal detachment. Neurological examination revealed bilateral hyper-reflexia, dysdiadochokinesia and impaired tandem gait. Planters were flexors. There was no neck rigidity. A diagnosis of malignant hypertension with hypertensive encephalopathy was entertained which was treated immediately with tablet Amlodipine followed by addition of tablet Telmisartan and Clonidine hydrochloride.
Her routine biochemistry including KFT was normal. She had albuminuria without any pyuria or casts. Both her spot urinary protein and 24-hour urinary protein were raised. ANA, rheumatoid factor were negative. MRI brain showed patchy areas of signal alteration (hyper-intense in T2/FLAIR and iso-intense to hypo-intense signals in T1 images) involving cortical, sub-cortical white matter of bilateral frontal, temporal, parietal and occipital lobes, bilateral basal ganglia, cerebellum,pons, medulla and upper cervical spinal cord. There were focal intramedullary patchy areas of similar signal alteration with swelling of cervical, dorsal, lumbar cord and conus without any significant post-contrast enhancement. Her ECG and ECHO revealed concentric LVH thereby suggesting chronic hypertension. USG showed bilateral loss of renal cortical medullary differentiation suggestive of medical renal disease. CT angiography of thoracic and abdominal aorta and renal vessels was normal. Her urinary VMA was normal. Subsequent DPTA renal scan was also normal without any evidence of reflux uropathy. CSF examination showed clear fluid, normal pressure with 3 cells (all mononuclear)/field, glucose was 91 mg/dl, protein was 137 mg/dl. CSF stains and culture for bacteria, AFB, and fungus were negative. Pan-neurotropic virus panel for different viral nucleic acids (by PCR) was negative. Thus based on above investigations a diagnosis of medical renal disease. CT revealed concentric LVH thereby suggesting chronic hypertension, hypertensive encephalopathy and exudative retinal detachment was made.

Results: Over next 6 weeks, her BP normalized on treatment and repeat MRI brain and spine became absolutely normal thereby confirming the diagnosis of PRES-SCI. Her headaches improved dramatically. Her retinal detachment also improved on conservative management by 8 weeks. Her urinary VMA was normal. CSF examination showed clear fluid, normal pressure with 3 cells (all mononuclear)/field, glucose was 91 mg/dl, protein was 137 mg/dl. CSF stains and culture for bacteria, AFB, and fungus were negative. Pan-neurotropic virus panel for different viral nucleic acids (by PCR) was negative. Thus based on above investigations a diagnosis of medical renal disease. CT angiography of thoracic and abdominal aorta and renal vessels was normal. Her urinary VMA was normal. Subsequent DPTA renal scan was also normal without any evidence of reflux uropathy. CSF examination showed clear fluid, normal pressure with 3 cells (all mononuclear)/field, glucose was 91 mg/dl, protein was 137 mg/dl. CSF stains and culture for bacteria, AFB, and fungus were negative. Pan-neurotropic virus panel for different viral nucleic acids (by PCR) was negative. Thus based on above investigations a diagnosis of medical renal disease. CT revealed concentric LVH thereby suggesting chronic hypertension, hypertensive encephalopathy and exudative retinal detachment was made.

Conclusion: BP measurement should be an integral part of headache evaluation even in young children. PRES-SCI although rare can present with migraine like headaches.

Disclosure of Interest: None Declared

Other Secondary Headache Disorders

PO-01-147

Clinical evaluation of dissection of the cerebral arteries with headache

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Objectives: Arterial dissections are recognized as an important cause of stroke in young person. Some patients with cerebral artery dissection shows no signs and symptoms except for headache. It remains unclear how we treat these patients with cerebral artery dissection without ischemic signs.

The purpose of our study is to evaluate clinical characteristics of dissection of the cerebral arteries with headache. In serial 27 patients (21 men, 6 women, 50.0 years) who admitted Kyorin University Stroke Center between October 2013 and July 2016 because of cerebral artery dissection were evaluated.

Methods: Information about clinical characteristics, history about headache, imaging study and clinical course were obtained from medical records retrospectively. Twenty-seven patients with dissection of the cerebral artery, comprising 21 men and 6 women with a mean age of 50.0 years were studied. We assessed the difference between Group H (patients without ischemic sign) and Group I (patients with ischemic sign).

Results: Lesions of dissection were anterior circulation in 5 (ICA:2, ACA:2, MCA:1) cases and posterior circulation in 22 (BA:2, BA + VA:1, VA:19) cases. Ten of 27 patients show no signs and symptoms except for headache. Fourteen of 27 patients had subjective symptoms, vertigo was most frequent. Nine of 27 patients had objective neurological findings, dysarthria was most frequent. Nine of 27 patients had objective neurological findings, dysarthria was most frequent. The ratio of negative neurological findings of group H was significantly higher than group I (p < 0.001).

About risk factors of cerebrovascular disease (history of hypertension, diabetes mellitus, hyperlipidemia, hyperuricemia, chronic kidney disease, and smoking), clinical character of headache, region and shape of dissection, and blood pressure at first visit, there were no differences between group H and group I.

Two patients (one in group H and one in group I) developed asymptomatic ischemic stroke during hospitalization.

Conclusion: Fifty-six percent of cerebral artery dissection patients with headache had no ischemic lesion at onset. Except for objective neurological findings, there were no difference between group H and group I. In this study, we were not able to clarify the factors to be related to development of ischemic lesion. Careful neurological examination and appropriate neurological imaging study were recommended for patients with dissection of cerebral arteries with headache.

Disclosure of Interest: None Declared
Cerebral blood flow changes after withdrawal from medication overuse in patients with chronic migraine

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Objectives: Cerebral blood flow (CBF) changes in chronic migraine patients with medication overuse (CM-MO) before and after withdrawal and their relationship to the clinical outcomes are yet unknown. In this study, we aimed to evaluate CBF changes before and after stopping overused drugs in CM-MO by transcranial Doppler (TCD).

Methods: Patients with CM-MO (code 1.3 and 8.2 of the international classification of headache disorders-3beta) included and were followed-up for 1 month. After withdrawal of the overused medication, patients were treated with prophylactic treatments. Headache diaries, the headache impact test (HIT-6), the migraine disability assessment (MIDAS), and the Beck Depression Inventory (BDI) were administered before withdrawal and at 1 month after. The mean CBF velocities of the bilateral middle and anterior cerebral arteries (MCA and ACA) and basilar artery (BA) were measured by TCD.

Results: A total of 21 patients participated in the study, with the average age being 58.5, average headache frequency/month was 22.1, and average monthly medication intake was 20.7 pills. Headache Frequency (approximately 8–10 days reduction), use of Medication (approximately 3 intakes reduction), MIDAS, HIT-6 and BDI showed significant improvement after withdrawal with prophylactic treatments. The mean CBF velocities of the BA and MCA were found to be significantly increased before withdrawal when compared with those at 1 month after (p < 0.05). No significant differences in CBF velocities of the ACA were observed (p > 0.05).

Conclusion: Our results show that medication overuse increased CBF velocities via vasoconstriction, especially of the BA and MCA in patients with CM-MO. Withdrawal of the overuse medication could lead to vasodilation.

Disclosure of Interest: None Declared

Diagnosis of a primary brain tumor after a woman developed a holocranial headache post-partum

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Objectives: Women experience significant physiologic and anatomic changes associated with pregnancy. These adaptations involve most organs, and are largely driven by hormonal fluctuations. After delivery there is a sudden adjustment in physiology that can take up to eight weeks to normalize, while the woman returns to her pre-pregnancy state. While robust research about brain tumors during pregnancy is limited, it has been suggested that these changes during pregnancy can both promote and delay tumor growth depending on the type of tumor1. The pathophysiology has yet to be fully understood, though theories exist regarding the role of growth hormones and angiogenesis1. We present the case of a young woman who developed post-partum headaches that were found to be secondary to a large primary brain tumor.

Methods: Case report

Image:

Results: A healthy 23 year-old woman presented two weeks post-partum with worsening headache. She became pregnant via in-vitro fertilization and had an uneventful pregnancy, though did complain of occasional mild headaches that were self-limiting. She had a normal vaginal delivery at 40 weeks with intact placenta. Post-partum course was complicated by severe preeclampsia.
that resolved with medical management. She was also given three units of packed red blood cells for excessive bleeding.

The patient developed a holocranial pressure-like headache the night of delivery. She reported associated bilateral tinnitus, lightheadedness and blurry vision with minimal relief from over-the-counter medications. She had no history of migraines but had mild headaches in the past. Neurologic exam exhibited bilateral papilledema, but was otherwise unremarkable. CT head showed a right temporal cystic mass with associated vasogenic edema and midline shift. She was treated with steroids, and underwent neurosurgical intervention with a temporal craniotomy and tumor resection. Post-operatively she had no neurologic deficits. She remained stable and was discharged home four days after craniotomy.

Conclusion: Pregnancy causes various physiologic changes, which then reverse following delivery. While sex hormones have been suggested to influence the progression of some brain tumors, the role of pregnancy is unclear. One study of fourteen pregnant women used MRI before and after delivery to evaluate for change in brain and ventricle volume. They found that both healthy and preeclamptic women had a statistically significant decrease in brain size and increase in ventricle size during pregnancy. They then displayed that these changes had reversed within six weeks of delivery. While preeclampsia has not been implicated in affecting tumor growth, the pathophysiology involves generalized endothelial dysfunction. This may result in a sudden increase in blood pressure and vascular permeability, contributing to accelerated vasogenic edema. This case suggests that pregnancy provides some form of neuro-protection, and that delivery or preeclampsia resulted in a sudden physiologic change in our patient causing rapidly increasing edema.

Disclosure of Interest: None Declared

Other Secondary Headache Disorders

PO-01-151

A case-study of cavernous sinus thrombosis manifested with headache in young woman in Kyrgyzstan

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Objectives: To display an unique course of headache in Tolosa-Hunt syndrome (THS), which include episode(s) of unilateral orbital pain for an average of 8 weeks if untreated, with associated paresis of one or more of the third, fourth, and sixth cranial nerves.

Methods: We present a case of Tolosa-Hunt syndrome with bacterial thrombosis of cavernous sinus manifested with intense headache in 39 y.o. female. Patient was interviewed about headache intensity according to visual analog scale (VAS), general neurological observation was made and diagnose was confirmed with MRI with MR venography.

Results: The patient experienced intensive stabbing headache in the left orbita, 9 scores according to VAS. Headache was paralyzing and disabling with acute onset, followed in 2 days with left ptosis and midriasis. MRI and MR-venography demonstrated a stasis of venous blood in the left cavernous sinus with perifocal edema and infarction in left temporal lobe. The combination of several chronic inflammatory diseases (hepatitis, pancreatitis, duodenitis, ureteritis, adnexitis, gastritis, choleystitis, mastoiditis, periodontitis) lead to septicemia, latent disseminated intravascular coagulation syndrome, and later to severe complication - bacterial cavernous sinus thrombosis. Prescription of wide spectrum antibacterial drugs and corticosteroid antiplatelets lead to full relief of headache and focal oculomotor symptoms.

Conclusion: Tolosa-Hunt syndrome must not be overlooked taking into account high rate of complications such as strokes. Anticonvulsants showed inefficacy compared to steroids leading to immediate relief of pain till 2 scores according to VAS

Disclosure of Interest: None Declared

Post-Traumatic Headache

PO-01-152

Lifestyle and Behavioral Occupational Therapy Treatment for Post-Concussive Syndrome Headache: Case Reports

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Objectives: According to the Centers for Disease Control, an estimated 2.5 million people in the United States sustain a traumatic brain injury (TBI) annually, and about 75% are classified as concussions or other forms of mild TBI. An estimated 15–30% of people who have a concussion may develop post-concussion syndrome (PCS), which is characterized by the persistence of symptoms including headaches, dizziness, fatigue, irritability, insomnia, concentration or memory difficulty, and increased risk for depression. Treatment of PCS focuses on gradual activity reintegration, functional rehabilitation, and learning how to cope, manage and prevent symptom
onset. Evidence demonstrates that patient education, compensatory cognitive strategies, graded physical activity, and mental health interventions can improve symptoms of PCS and related headaches. Occupational therapists (OTs) are typically involved in acute concussion treatment for physical and cognitive rehabilitation, but OTs can also provide lifestyle and behavioral treatment for management and rehabilitation of PCS with headache (PCSH). To demonstrate the methodology and efficacy of lifestyle behavioral OT for managing PCSH, clinical outcomes for a group of patients with PCSH who attended individual outpatient OT treatment is presented.

**Methods:** Lifestyle Redesign (LR) is a module-based behavioral OT technique that facilitates the development of health-promoting habits and routines, and has been shown to improve health management and slow disease progression. LR OT treatment for PCSH focuses on helping patients understand the disease process, gradually reintegrate into functional daily activities, and manage persistent symptoms through active participation in self-management habits. Treatment topics can include eating routines, activity pacing, energy management, body mechanics, sleep hygiene and positioning, physical activity, stress and depression management, and community/work reintegration.

Clinical outcome data for a small sample of patients with PCSH receiving LR OT outpatient clinic-based treatment as part of their typical plan of neurological care were collected to determine efficacy of treatment. Inclusion criteria was diagnosis of PCSH, and attendance of 3 or more sessions of OT. Outcome measures were completed at initial evaluation and discharge, and included the SF-36 Quality of Life Scale, Canadian Occupational Performance Measure (COPM), Headache Impact Test-6 (HIT-6), Headache Management Self-Efficacy Scale (HMSE), Migraine Specific Quality of Life Questionnaire (MSQL), and Migraine Disability Assessment Questionnaire (MIDAS).

**Results:** Seven patients’ clinical outcomes were collected (two male, five female). The average age of the patients was 36 years, and the average number of OT sessions had between evaluation and discharge was 7.14. On average, patients demonstrated improvements in almost all outcome measures, with the most substantial gains noted in certain SF-36 subscales (role limitations due to physical or emotional problems, energy and fatigue, social function), COPM Performance and Satisfaction scores, HMSE score, and MIDAS number of headache days.

**Conclusion:** These clinical case studies contribute to the evidence that lifestyle and behavioral OT treatment can be used to successfully help patients with PCSH improve their self-management abilities, symptoms, quality of life, and function. More research with a larger sample size of patients is needed to further investigate the significance to which lifestyle and behavioral OT can improve PCSH.

**Disclosure of Interest:** None Declared

**Post-Traumatic Headache**

**PO-01-153**

**Hidden Disability: Mild Traumatic Brain Injury**

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**Objectives:** Purpose: Through systematic review of the literature, describe interprofessional interventions for post-traumatic syndrome following mild traumatic brain injury.

**Methods:** The World Health Organization reports that 70–80% of traumatic brain injury (TBI) is mild with a yearly incidence of 600 per 100,000. Minor sport, combat or accidental head trauma may go unnoticed. Often, emotional pressure is applied to return to activity by coaches, peers, or one’s self. In addition to pain, patients may experience somatic, psychological and cognitive symptoms. Dizziness, tinnitus, light or sound sensitivity, blurred vision, decreased smell, decreased libido and fatigue may trouble patients. Common psychological complaints of depression, anxiety, irritability, apathy and insomnia are seen. Cognitive changes include impaired attention, concentration and memory. This constellation of symptoms coupled with headache pain after a seemingly inconsequential injury affects areas of thinking, mood and emotional control. Appearing physically “normal”, anxiety, depression and irritability lead to occupational difficulties and interpersonal stress. This hidden disability reduces meaningful participation in work, family or social events and predisposes those injured to second impact syndrome increasing the possibility for lasting cognitive, somatic or emotional changes associated with mild TBI.

**Results:** This literature review explores genetic and environmental risk factors in development of mild traumatic brain injury. Using pathophysiologic changes following mild TBI as a framework, cognitive, somatic and emotional alterations are discussed. Successful symptom identification and interprofessional collaboration are fundamental best practices in improving quality of life in the mild traumatic brain injured patient. Effective treatment requires a comprehensive approach with pharmacotherapy, physical therapy, biofeedback and counseling for patients and significant others.
**Conclusion:** It's essential that clinicians recognize and understand physical, cognitive and emotional manifestations that may occur with mild traumatic brain injury. These manifestations are a result of trauma induced pathophysiology. Interprofessional team approach with collaborative documentation and clinical decision making promotes a multifaceted recovery in patients with this hidden disability.

**Disclosure of Interest:** None Declared

**Post-Traumatic Headache**

**PO-01-154**

**Post-Traumatic Stress Disorder and Depression in relation to the Different Phenotypes of Post-Traumatic Headache and comparison with matched controls**

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**Objectives:** Post-Traumatic Headache (PTH) is classified as a headache of any type following a TBI. This study evaluates the occurrence of Post-Traumatic Stress Disorder (PTSD) and Depression in relation to the various phenotypes of PTH following a deployment-related TBI (DTBI) for Veterans of the Iraq (OIF) and Afghanistan (OEF) wars with comparison to matched controls.

**Methods:** All subjects were Veterans who had been deployed to OEF/OIF and subsequently joined Operation New Dawn (OND), a VA program to assist in re-entering civilian life after discharge. OND Veterans were screened for possible DTBI and screen positive subjects were referred to our TBI clinic to confirm presence of a DTBI. A recruitment pool was established by taking the first 500 confirmed DTBI subjects (TBIS) and matching them to OND participants without DTBI (CS) by age, sex, race and time of deployment. Subjects were recruited from this pool and were interviewed by telephone. All subjects received the same questionnaires (QS) including: (a) TBI QS, (b) Headache QS, (c) Beck Depression Inventory 2 (BDI), and (d) Brief PTSD QS consisting of 7 “yes/no” questions. For depression, BDI score categories were: (a) Minimal/none – 0–11, (b) Mild – 12–19, (c) Moderate – 20–28, (d) Severe – ≥29. For PTSD, categories included: (a) none (0–3 yes answers), (b) possible (4–5 yes), and definite (6–7 yes). Headache phenotypes included: Migraine with (MA) and without (MO) aura, Tension/Probable Migraine (T/PM) and No Headache (NoHA). Statistics included Fisher’s Exact and Odds Ratio tests.

**Results:** There were 84 TBIS (81 male) and 85 CS (82 male). These subjects suffered their TBI 2–11 years before interview. Results are presented in the Table showing the distribution of PTSD and Depression categories for each headache phenotype. For the TBIS, 77 (92%) had migraine of which 70% had MA and 30% had MO. For MA and MO there was no significant difference in the distribution of PTSD or Depression categories with 59% having definite PTSD and 46% severe Depression. For their controls, only 16% had definite PTSD and 8% had severe Depression. For T/PM, There were 6 TBIS and 30 CS. For TBIS, 4 (67%) had definite PTSD, but only 1 (17%) had severe Depression. There were 30 CS with T/PM phenotype of which 3 (10%) had definite PTSD and 2 (7%) had severe Depression. Differences between overall distribution of PTSD categories and Depression- categories between TBIS and CS were highly significant (p < .001).

**Conclusion:** There is a strong propensity for PTSD to occur in conjunction with PTH whether this is MA, MOM or T/PM in phenotype. For Depression, the propensity is limited to MA and MO. There are too few subjects in the T/PM group to allow a judgement. The results suggest a co-morbidity or even a causal link between these entities. Further research is needed in this regard.

**Disclosure of Interest:** None Declared
Psychological and Behavioural Factors and Management

PO-01-155
Inpatient Headache Therapy at the Berolina Clinic, Germany
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Objectives: Headache disorders are third cause of disability worldwide (Stovner et al. 2015). The annual cost of treating migraine in Germany has been estimated at €478 million, the indirect costs at €6.237 million (Neubauer 2002). Evidence-based guidelines recommend a multimodal approach that combines drug therapy, educational programs in disease and stress management, biofeedback, relaxation techniques, and aerobic exercise. The German healthcare system has an extensive network of rehabilitation facilities where persons with present or impending work disabilities can receive inpatient or outpatient treatment for up to six weeks. The Berolina Clinic is one of these facilities. It specializes in psychosomatic disorders and chronic pain including migraine and headache and cognitive-behavioral therapy for orthopedics and utilizes a treatment program that follows evidence-based guidelines.

Methods: The clinic's three-week inpatient treatment program for headache includes: medical supervision by a physician specialized in the treatment of headache, CBT in groups and in individual sessions, headache lectures, relaxation techniques, biofeedback, medical setting, detoxification of headache medicine, various forms of exercise with variable levels of intensity, art therapy, TENS therapy, and employment counseling.

Headache patients are treated either in the department of psychosomatics or of cognitive behavioral therapy for orthopedics depending on comorbidity. Over the past eight years, 4800 headache patients have been treated in the Berolina Clinic.

Results: The Berolina Clinic participates in an extensive quality assurance program mandated by the German statutory pension insurance scheme that includes reviews of patient satisfaction, therapy concepts, and treatment results. The results are communicated to the participating clinics after ca. 12 months. In the national scoring system, the quality score for subjective treatment success for 2015 was 70.9 -out of 100- for the department of psychosomatic medicine, compared to 67.3 for 146 other German psychosomatic clinics. The department of cognitive behavioral Therapy for orthopedics attained a score of 78.2, as compared to 72.2 for 254 other German orthopedics clinics.

Conclusion: Possible causes of this relatively high patient-reported satisfaction are the strict adherence to treatment guidelines, our multidisciplinary approach, a highly qualified team, and supervised care by experienced rehabilitation physicians specialized in psychosomatic medicine, neurology, orthopedics as well as physical and rehabilitative medicine and psychiatry.

Disclosure of Interest: None Declared

Psychological and Behavioural Factors and Management

PO-01-156
Self-reported triggers vs prospectively statistically determined factors associated with attacks in individuals with episodic and chronic migraine
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Objectives: Migraine attacks may be triggered by combinations of internal and external factors which differ markedly between individuals (1). Most migraineurs suspect a range of triggers (2), usually based on (unreliable) retrospective recall which is subject to misinterpretation and recall bias. Previously we reported that less than 20% of suspected self-reported triggers could be shown to be statistically associated with attacks when using individuals’ prospective data collected using a digital platform (Curelator HeadacheTM) (2). Here we compare in groups of individuals with episodic or chronic migraine their self-reported triggers and attack risk factors identified statistically.

Methods: Individuals with migraine registered to use Curelator Headache via website or the App Store (iOS only) and completed a questionnaire about personal suspected triggers and their importance (1 = low; 10 = maximal). They then used Curelator Headache daily for 90 days, entering details about headaches and tracking factors that may affect migraine attack occurrence. After 90 days all factors were analyzed for each individual (3) and those significantly associated with attacks were compared with self-reported triggers.

Results: Of 528 individuals, 429 (81%) were classed as episodic and 99 (19%) chronic migraine. Mean age (SD) was 43.5 (13.8) years and the majority (90%) were female: there were no major demographic differences
between groups. Overall, individuals each suspected between 3 and 47 different triggers; mean (SD) = 23.6 (12.7). The most frequently suspected at all by both groups were: neck pain, stress, eyestrain, bright light, menstruation, fatigue, odors, dehydration, missed meals, travel, sleep duration, and sleep quality. The triggers most frequently strongly suspected (7 – 10 on the rating scale) were similar but alcohol and tiredness were proportionately more often strongly suspected.

Of self-reported triggers, on average (SD) only 3.4 (2.8) (14%) were shown to be statistically associated with attack occurrence. A further 12.5 (7.7) (53%) were shown to have no statistical association to attacks and for 5.5 (4.6) (23%) there was not enough data to determine an association. The proportion of self-reported triggers also identified statistically was similar in the two groups (14.1% vs 15.4%). In both groups ≥ self-reported triggers also identified statistically by 20% individuals were neck pain, anxiety, sadness, stress, bright light, menstruation, irritability and skin sensitivity; in addition were eyestrain, tiredness and loud noise in the episodic group and odors and angri ness in the chronic group. In both groups, for the majority of factors, a relationship was seen between strength of suspicion as a trigger and statistical confirmation of an association with attack occurrence.

Conclusion: Individuals vary greatly in the factors statistically associated with their attacks but, as groups, there are no clear differences between those with episodic or chronic migraine in terms of self-reported triggers or the proportion of those confirmed statistically. This may be because 1) all individuals are guessing their risk factors with very low accuracy (essentially random guessing or based on the same lists of triggers circulated by media and internet) or 2) risk factors for episodic or chronic migraine are indeed similar, suggesting shared aspects of pathophysiology.

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Psychological and Behavioural Factors and Management

PO-01-157
Mindfulness for Chronic Migraine with Medication Overuse: Clinical Results and Biological markers at 12 Month Follow-up after withdrawal

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Objectives: Chronic migraine (CM) arises from a complex mixture of interconnected biological, psychological and social factors. CM is a disabling condition, worsened when associated with medication overuse. Mindfulness is emerging as a helpful treatment for pain, but it has yet to be explored fully for CM accompanied by Medication Overuse (MO). We report initial clinical findings from an on-going trial exploring the feasibility and utility of mindfulness as a primary treatment for this condition. We also investigated whether mindfulness (and medication treatment as well) produced meaningful changes in key hemato logical parameters, IL-6 and specific biological markers of tyrosine metabolism which have been revealed altered in chronic migraine patients.

Methods: Forty-four patients, diagnosed as CM with MO (IHS-III-beta 2013 criteria), were enrolled. All patients completed a standardized medication withdrawal in a day-hospital setting and were then assigned to 1 of 2 conditions: Prophylactic Medication Alone (MED) or Mindfulness Training Alone (MT). MT was administered during 6 weekly sessions: 30 minutes of guided mindfulness, with patients instructed to engage in at-home practice 7 minutes/day. Daily pain diaries and measures of disability (MIDAS), quality of life (HIT-6), state-trait anxiety (STAI X1-X2), depression (BDI-II), collected at BL and at 12 months follow up, served as the clinical outcomes. Blood samples were collected at all measurement periods to explore potential biological mediators of outcome.

Results: Twenty patients in MT-group and nineteen in MED-group reached the 12-month follow-up assessment. Significant decreases were reported in clinical parameters and disability from BL to 12 months: 1) Headache Days/ Month-MED: 19.6 ± 7.4 vs 9.8 ± 7.3 (50% reduction); MT: 18.5 ± 7.5 vs 12.4 ± 8.5 (33% reduction). 2) Medications Intake/ Month-MED: 17.5 ± 6.4 vs 8.1 ± 5.08 (54% reduction); MT: 17.9 ± 6.3 vs 10.3 ± 5.3 (43% reduction). 3) MIDAS Score-MED: 81.1 ± 37.5 vs 51.5 ± 50.2 (36%
Comorbidity of migraine and mood episodes in a population-based study in north-eastern Iran

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Objectives: Migraine has been found to be comorbid with bipolar disorder and major depressive disorder in clinical and population-based samples. However, significant variability in findings between studies has been found and this proposes that mood episodes examination may be useful in determining which of these mood episodes are specifically associated with migraine and clarify the burden of this problem in population.

Methods: Using a cross-sectional, population-based sample, a group of Iranians at city of Mashhad (North-eastern Iran) have been studied. In this observational study, data on all 450 adult participants, were analyzed. Sociodemographic and clinical correlates of migraine were examined in each combination of mood episodes as well as controls. The relationships between self-reported migraine, perceived mental health, and mood/anxiety disorders were modeled using univariate and multivariate logistic regression. The migraine-depression association was also explored in a subset of participants using the Farsi version of Composite International Diagnostic Interview-Short Form (CIDI-SF) depression scale.

Results: Compared with controls, the adjusted odds ratio of having migraine was 1.8 (95% confidence interval [CI] 1.3–2.9) for manic episodes alone, 1.9 (95% CI 1.6–2.1) for depressive episodes alone, and 3.0 (95% CI 2.3–3.9) for subjects with both manic and depressive episodes. By using CIDI-SF depression scale, the migraine-mood disorders association was significant. The odds of migraine were higher among those with anxiety disorders. The was inverse association between high perceived mental health and the odds of migraine.

Conclusion: Migraine comorbidity seems to outline a subset of individuals with earlier onset of affective illness and more psychiatric complications, suggesting that migraine assessment in mood disorder patients may be useful as an indicator of clinical severity and possible poor response to treatment. Surveillance for mood disorders and comorbid migraine is necessary in clinical settings.

Disclosure of Interest: None Declared

Psychological and Behavioural Factors and Management

PO-01-159

Modeling chronic migraine-like headache in mice using a conditioned place aversion paradigm

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Objectives: Current animal models of chronic migraine-like headache involve activating nociceptors of the trigeminal afferents present on the meninges by repeatedly administering a mixture of inflammatory mediators into the cisterna magna or via direct topical application on the dura. These models utilize repeated artificial recreation of the pathophysiological changes that induce migraine-like headaches to establish chronicity. The pain of migraine is commonly determined by assessing the development of facial allodynia due to sensitization of
trigeminal nociceptors and central neurons in trigemino-cervical complex. Conditioned place aversion (CPA) is a commonly used paradigm that uses classical conditioning to pair environment with a motivationally aversive stimulus (pain or foot-shock). This pairing leads to induction of the negative affective state whenever the animal is exposed to the environment. CPA has been used to study neural circuits involved in negative affective components of pain. In this study, we have proposed a novel method involving the use of complete Freund's adjuvant (CFA) as an inflammatory mediator in conjunction with the CPA paradigm to induce an animal model of chronic migraine-like headache.

**Methods**: Experiments were performed in C57BL/6 mice at ages of 3–4 months of either sex. Under a brief anesthesia by isoflurane, 5 µl of CFA was injected into the dura. Cutaneous allodynia was determined by using von Frey filaments applied to the craniofacial region. The CPA paradigm was used to establish a pain-paired compartment where the animal was conditioned for facial pain state. The effect of the conditioning on the prolongation of CFA-induced acute migraine-like pain was tested and evaluated.

**Results**: We observed that cutaneous allodynia persisted for 72 hours after single CFA application. After 72 hours, thresholds for mechanical stimuli in the craniofacial regions reverted back to baseline. Interestingly, after conditioning the animals using the CPA paradigm, we found that the mice that had been conditioned continued to demonstrate facial allodynia induced by CFA administration for as long as they were exposed to the pain-paired environment. We were able to maintain the facial allodynic pain state induced by CFA administration for up to 10 days.

**Conclusion**: These results indicate that although pathophysiological effects of single CFA application persisted for acute stages, the negative affective component associated with migraine pain facilitated by CPA paradigm persisted for much longer. Thus, our pilot study demonstrates a potential use of CPA paradigm in the development of a chronic migraine model, which mimics a feature of chronic migraine-like headache.

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**Psychological and Behavioural Factors and Management**

**PO-01-160**

**Headache worsened by MRI**

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**Objectives**: Imaging is not always required when a primary headache diagnosis such as migraine can be set. Imaging in primary headache disorders is performed to exclude a secondary headache with similar phenotype. Physicians must be aware that incidental and clinically insignificant findings might worsen the patient’s condition.

**Methods**: We report a 41-year-old lady with a migraine started at the age of 22, which chronified after 35 years of age and worsened significantly after a huge arachnoid cyst was revealed by MRI.
Results: Our patient used to have menstrually related migraine attacks in her twenties. Pain was pulsating in character, with intensity of VAS = 7. Headache started from the left or right side of the forehead and irradiated occipitally. The pain could spread also towards the ear, or upper teeth. The patient experienced photophobia during the attacks and she was unable to perform any tasks. Sometimes the headache was accompanied by nausea and vomiting. Frequency was around 5 attacks monthly. She aborted the severe ones by oral sumatriptan. In patient’s late 30s, the number of headache attacks per month raised to 10. She had a concomitant chronic sinusitis and mother with migraine. Brain MRI showed a huge inborn arachnoid cyst in the left temporal region with mild dislocation of the ventricular system. After the patient was informed, headache complaints worsened, despite the fact that the incidental finding was not progressive, not clinically significant. The neurological and cognitive status were both normal. EEG had no abnormalities. Headache was not triggered by exertion, neither by cough. Frequency of the severe attacks raised to 16 per month. She began to use paracofdal (paracetamol 200 mg, metamisol natrium 300 mg, codeine phosphate 20 mg, caffeine 30 mg) and cofergamine (ergotamine tartrate 1 mg, caffeine 100 mg) frequently: two to three tablets of each daily. Depression and insomnia were diagnosed together with a milder persistent daily headache in the vertex and occipital area. Conclusion: The case report serves as a clear example of how an imaging study performed in the absence of additional worrying symptoms and signs can worsen the condition and the quality of life of a patient with a primary headache. The brain cyst should be monitored in time, but we believe the discomfort and stress that the MRI finding caused to our patient cannot be justified.

Disclosure of Interest: None Declared

Psychological and Behavioural Factors and Management

PO-01-161
The Headache Triggers Sensitivity and Avoidance Questionnaire (HTSAQ-G) – Psychometric Evaluation of a German Adaptation

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Objectives: This study aims to develop and validate a German version of Kubik and Martin’s Headache Triggers Sensitivity and Avoidance Questionnaire (HTSAQ, [1]). The HTSAQ was established with regard to the Trigger Avoidance Model of Headaches, which suggests that the avoidance of headache triggers may lead to developing a primary headache disorder. Similar to anxiety disorders, avoidance behavior may generate sensitization and thus an increase in trigger potency. This model has led to a novel approach in the behavioral treatment of primary headache disorders, i.e., the Learning to Cope with Triggers (LCT). While traditional counseling aims at the avoidance of all triggers, the LCT proposes a more differentiated handling of potential triggers. To examine the effectiveness of LCT, the HTSAQ was developed including 24 of the most commonly reported triggers (e.g., stress, odors, lack of sleep) and two open-ended questions for two individual triggers that can be added.

Methods: Like in the original version, respondents are asked to rate for each trigger on a 5-point Likert-scale (a) whether it is a trigger for the respondent’s headaches, (b) how sensitive the respondent is to the trigger compared with other people, (c) how sensitive the respondent is to the trigger compared with the time of least sensitivity, and (d) how hard the respondent tries to avoid the trigger. A sample of N = 99 consecutive patients (75% female; age: M = 44.4, range 15–83; diagnosed with either migraine, tension-type headache, cluster headache or a combination of two or more headache disorders) completed a battery of measures (including the HTSAQ-G and the Depression, Anxiety and Stress Scales, Headache Impact Test-6, Headache Disability Inventory and Chronic Pain Acceptance Questionnaire) at admission for a residential treatment in a headache clinic. With an interval of approx. 4 weeks (at discharge), N = 93 patients completed the battery of tests for a second time.

Results: The HTSAQ-G showed excellent reliability evaluated through internal consistency (alpha = .88) and test-retest reliability (r = .85) over a period of approx. 4 weeks. As first evidence of construct validity, headache patients reporting higher triggers sensitivity and more avoidance behavior showed higher levels of depression (r = .31 to .38), anxiety (r = .33 to .45), stress (r = .29 to .44), and impairment due to pain (r = .31 to .45), and concurrently lower levels of acceptance of pain (r = −.24 to −.41). As the Trigger Avoidance Model of Headache would predict, correlations between the HTSAQ-G Sensitivity scales and the Avoidance scale were strong (r = .69 to .76).

Conclusion: The results of this study support the use of the German adaptation of the HTSAQ as a reliable and valid measure of sensitivity to headache triggers and avoidance of headache triggers. The HTSAQ-G will be of use investigating the effectiveness of novel behavioral treatment approaches to migraine. Future studies should examine the factor structure of the HTSAQ-G using...
exploratory and confirmatory factor analysis in order to identify possible different types of triggers.

References

Disclosure of Interest: None Declared

Psychological and Behavioural Factors and Management

PO-01-162

An Integrative Cognitive Behavioral Therapy Program for Adults with Migraine: A Pilot Study

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Objectives: Behavioral therapy (BT) is efficacy in the treatment of migraine [1]. There are different approaches to behavioral treatments for migraine, including relaxation therapy, biofeedback, cognitive-behavioral therapy (CBT) to enhance stress-management, the concept of “learning to cope with triggers” (LCT, [2]), and counselling. It is still unknown, which approach fits to which patient or if a combination of all approaches is superior. The aim of our study was to evaluate the feasibility, acceptability, and preliminary effects of a specific CBT-program for adults with migraine. The program integrates several important approaches (except biofeedback) and comprises 7 sessions: (1) psychoeducation, (2) life-style counselling, (3) coping fear of migraine-attacks, (4) coping the current migraine-attack, (5) LCT, (6) stress-management and (7) relapse prevention. Every session includes a brief relaxation exercise.

Methods: A pilot nonrandomized trial was conducted with N = 10 adults with migraine (age: M = 40.7; SD = 16.7; 80% female; 50% Migraine without aura, 20% Migraine with aura, 30% Chronic migraine). After each of the 7 outpatient group therapy sessions, evaluation questionnaires (5 point scale from 1 = “disagree” to 5 = “agree”) were filled out as a primary outcome measure. Secondary outcome measures were the German Version of the Headache Disability Inventory (IBK), the German Version of the Headache Management Self-Efficacy Scale in a short form (HMSE-G-SF) and the Depression-Anxiety-Stress Scales (DASS). A daily headache e-diary using smartphone and web-based application technology was conducted during the treatment.

Results: The group intervention was feasible and highly accepted. Only N = 1 dropped out (after one session, a further participation was not possible due to repeated migraine attacks ahead of the subsequent sessions). The following results refer to the completer sample (N = 9). The compliance was good (total participation rate of the sessions was M = 86%, SD = 14%). The evaluation of the 7 sessions by the patients showed a high acceptability for every session: contents were comprehensible (M = 4.75; SD = 0.24), session was supporting the coping (M = 4.22; SD = 0.42), and session was satisfying (M = 4.74; SD = 0.35). Pre-Post-Effect-sizes were large (IBK: d = 0.84; HMSE-G-SF: d = −0.86), or small (DASS-Depression: d = −0.09; DASS-Anxiety: d = 0.10; DASS-Stress: d = 0.29).

Conclusion: Our idea to combine several approaches of BT into a specific therapy program for adults with migraine seems to be feasible and promising. The acceptability for the novel approaches (session 3, 4, and 5) including LCT was as good as for the traditional approaches (session 1, 2, and 6). Effect sizes showed a reduced disability and an enhanced self-efficacy. Effect sizes referring to the emotional impairment showed no clear trend, which may be due to the small sample. A randomized controlled trial with headache frequency as a primary outcome to determine the efficacy of our program is now warranted.

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Psychological and Behavioural Factors and Management

PO-01-163

Alterations in attention, fatigue and alertness associated with the premonitory and prodrome stages of triggered migraine attacks

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The premonitory phase was defined as the presence of symptomatology that the subject would associate with headache. The postdrome phase was defined as the premonitory and postdrome stages of nitroglycerin-triggered migraine attacks, using validated psychological tests.

Methods: Subjects aged 18–50 years with spontaneous migraine with or without aura were pre-screened over the telephone and if deemed eligible for the study, invited to a screening appointment. Following informed consent, detailed migraine history taking, observations, an electrocardiogram, a pregnancy test where applicable and a physical examination, each subject was exposed to a 0.5 mcg/kg/min nitroglycerin (NTG) infusion over 20 minutes, to attempt to trigger premonitory symptoms and headache. Following the development of headache, where applicable, headache was treated with either 1 g intravenous aspirin (the premonitory patients) or 6 mg subcutaneous Sumatriptan (the postdrome patients). Baseline (symptom free) scores for all tests for each subject (n = 21) were collected prior to any drug administration. The same tests were conducted in the premonitory (n = 9) or postdrome (n = 12) phases of triggered attacks, following display of symptoms after NTG infusion and when appropriate, after effective headache treatment.

Subjects were chosen for which arm of the study they were put into, based on their usual attacks and which treatment they usually responded to with spontaneous attacks. The premonitory phase was defined as the presence of three or more non-headache symptoms which started before the onset of headache, which the subject would usually associate with successfully predicting the onset of headache. The postdrome phase was defined as the presence of three or more symptoms following headache resolution, which the subject would associate with headache freedom but not feeling completely back to normal. Statistical analyses were performed using Pearson correlation and paired t-tests. $\text{P} < 0.05$ was considered significant.

Results: There were statistically significant increases in scores on the DFIS in the premonitory stage compared to baseline ($t_{X} = -3.76, 95\% \text{CI} -17.465 - -4.090, \text{p} = 0.006$) and in the postdrome stage compared to baseline ($t_{X} = -3.668, 95\% \text{CI} -3.635 - -3.688, \text{p} = 0.004$). There were statistically significant increases in scores on the KSS in the premonitory stage compared to baseline ($t_{X} = -3.255, 95\% \text{CI} -3.796 - -0.648, \text{p} = 0.012$) and in the postdrome stage compared to baseline ($t_{X} = -6.402, 95\% \text{CI} -5.515 - -2.667, \text{p} < 0.001$). No statistically significant differences in SART scores in the premonitory phase or postdrome phase were observed compared to baseline. There was no significant correlation between the baseline DFIS, KSS and SART scores and headache days at baseline.

Conclusion: Despite a small sample size, we have demonstrated notable changes in alertness and fatigue in the premonitory and postdrome stages of a migraine attack. This is an area that warrants increased clinical and research attention.

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Psychological and Behavioural Factors and Management

PO-01-164

A Multidisciplinary Team Approach for Chronic Migraine Treatment: A Clinical Case Study

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Objectives: Chronic migraine (CM) affects up to 5% of the global population and negatively impacts a person’s quality of life and ability to engage in daily activities. While primary care physicians and neurologists frequently treat CM with pharmacological interventions, lifestyle, behavioral and physical rehabilitation provided by occupational therapists (OT) and physical therapists (PT) can be effective for treating and managing CM. At the USC Keck Medical Center a multidisciplinary team including neurologists, OTs, PTs and pain psychologists has been established to treat patients with head, neck and facial pain disorders, including CM.

The aim of this study is to understand how a multidisciplinary treatment approach can be used for CM, explain the rule of neurology, OT and PT, and present a case study.
to demonstrate the effectiveness of a multidisciplinary approach.

**Methods:** A neurologist initially evaluates the patient and will refer the patient to OT, PT and pain psychology as needed to provide multidisciplinary care. Lifestyle Redesign (LR) is a behavioral OT technique that facilitates the development of health-promoting habits and routines, and has been shown to improve health management and slow disease progression. LR OT treatment for CM focuses on assessing how a person’s daily activities are impacted by their migraines and providing patient education and training of lifestyle factors that can improve their self-management of migraines. PTs help to assist patients’ recognition and management of musculoskeletal, postural, stress, and fatigued-related triggers. PTs will prescribe exercises to improve postural strength and aerobic endurance and perform manual therapy to improve cervical and thoracic spine mobility and reduce musculoskeletal triggers to decrease frequency and intensity of migraine pain.

**Results:** A 36 year-old female patient who works as a chef with a diagnosis of CM without aura was used for this case study. She had worsening of headaches for 8 months and was experiencing left-sided neck tightness and jaw pain. Neurology evaluated the client, implemented pharmacological changes, and referred the patient to OT and PT. LR OT and PT treatment was provided at outpatient clinics where the patient was seen for 8 sessions, by each discipline, over the course of 3 months. OT treatment topics included sleep hygiene and positioning, activity pacing, stress management, trigger identification, ergonomics and time management. PT prescribed exercises to improve strength of deep neck flexors, scapular stabilizers, and core muscles and spine flexibility to improve postural mechanics and tolerance to complete daily and work-related tasks. PT treatment also included manual therapy to reduce neck and jaw symptoms. Clinical outcomes are included in Table 1.

**Conclusion:** This case study demonstrates the effectiveness of using a multidisciplinary approach for treating chronic migraine and improving a patient’s symptoms, quality of life and function.

**Disclosure of Interest:** None Declared
ambiguous information is provided and the outcome of choices is not defined by clear probabilities (decision under ambiguity). 2) explicit information is provided and the outcome is defined by probabilities (decision under risk). We recruited 47 patients, n. 22 suffered from MOH evolved from migraine (chronic migraine + MOH) (77.3% female, Age: 46.7 ± 11.1, Years of education: 12.4 ± 3.7), while 25 suffered from MIG (68.0% female; Age: 41.9 ± 13.9, Years of education: 14.3 ± 3.8). The diagnosis in the 2 groups was operationally defined according to ICHD-IIIβ. Within the MOH group, 12 patients suffered of chronic headache since at least 10 years (long-lasting MOH, 83.3% female; Age: 51.8 ± 8.2, Years of education: 12.6 ± 3.5, Chronification duration: 20.3 ± 9.6), whereas 10 since less than this duration (short-lasting MOH, 70.0% female; Age: 44.5 ± 11.8, Years of education: 12.7 ± 3.9, Chronification duration: 7.1 ± 2.6). All individuals were recruited at the Headache Center of Neurological National Institute “Mondino”, Pavia. All patients completed the two different tasks being comparable in terms of intrinsic characteristics of the game: one decision-making task under risk, the Game of Dice Task (GDT), and one decision task under ambiguity, the Iowa Gambling Task (IGT). Demographic and clinical information was collected as well.

**Results:** As regards the decision task under ambiguity, interesting differences resulted between the MOH group and the MIG group as the MOH made significantly more disadvantageous and risky choices than the MIG group: IGT net score for MOH group = 11.6, MIG 7.4, p = 0.013. No difference was instead detected as regards the task under risk: GDT net score: MOH 4.9; MIG 7.4, p = 0.66. Interestingly, when evaluating the impact of MOH duration on the decision-making performance, we found that patients with the longer duration of disease made significantly more disadvantageous and risky choices at the task under risk: GDT net score: long-lasting = −0.5 ± 12.3; short-lasting = −4.3 ± 19.1; short-lasting = −8.7 ± 27.7; F(1,19) = 0.18, p = 0.67.

**Conclusion:** Patients with chronic pain conditions such as chronic migraine have to face important and complex decisions with respects to their health care. For this reason, the ability to make advantageous decisions may have a relevant impact on different steps of management, such as intake of medications and adherence to treatment. Our data are very interesting as they show two different patterns of decision making according to the kind of patients considered. MOH group as a whole showed a reduced performance in decision-making under ambiguity. When the duration of disease is long (>10 years) also the performance in decision-making under risk becomes affected in this group of patients. Though preliminary, these findings highlight an important component in the complex approach to MOH.

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**Disclosure of Interest:** None Declared

**Psychological and Behavioural Factors and Management**

**PO-01-166**

The Women’s Health and Migraine Trial (WHAM): A Randomized Controlled Trial of Behavioral Weight Loss as a Treatment for Migraine in Women with Overweight/Obesity

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**Objectives:** Research suggests that obesity is both a risk and an exacerbating factor for migraine, particularly in reproductive-aged women. Additionally, uncontrolled studies suggest that weight loss has potential to reduce migraine frequency and severity in the context of obesity. The present study is the first to test the efficacy of a standardized behavioral weight loss (BWL) intervention for decreasing headache frequency and severity in women with comorbid migraine and overweight/obesity within a randomized controlled trial.

**Methods:** A total of 108 women aged 18–50 years who had neurologist-confirmed migraine with or without aura, >4–20 headache days/month and body mass index (BMI) between 25 and 49.9 kg/m² were randomly assigned to 16 weekly in-person group sessions of either: 1) BWL (n = 52), that aimed to produce weight loss via instruction in behavioral strategies targeting physical activity and diet (but did not address migraine); or 2) Migraine education control (ME; n = 56), involving didactic information on migraine headaches and evidence-based pharmacological/non-pharmacological management approaches (but did not address weight loss). Both groups used a smartphone diary to record headache activity for 4 weeks at both baseline, prior to randomization, and the end of treatment (16 weeks). The primary outcome measure was change in number of migraine headache days. Analyses focused on
changes in body weight, migraine headache days, and other variables of interest controlled for baseline values and employed the intention-to-treat principle with no change imputed for missing data.

**Results:** Retention rate at the primary end point was 77.8% and similar between groups. BWL and ME did not differ in age (39.2 ± 7.2 years), BMI (35.2 ± 6.7 kg/m²), monthly migraine days (8.3 ± 4.5), and % using preventive (20.2%) medications at baseline (ps > .30). BWL achieved significantly greater mean (±SD) weight loss than ME at 16 weeks (−3.2 ± 4.4 vs. +0.6 ± 2.3 kg, p < .001). Number of monthly migraine days decreased significantly between baseline and end-of-treatment in both BWL (8.1 ± 3.9 to 6.0 ± 4.3 days/month; p < .001) and ME (8.6 ± 4.8 to 5.3 ± 4.8 days/month; p < .001), but did not differ from each other (p = .11). A similar pattern of findings with significant (p < .05) decreases between baseline and end-of-treatment occurring in both the BWL and ME groups, but no significant between-group differences (BWL vs. ME), was shown for average headache intensity (5.8 ± 1.4 to 5.1 ± 2.2 vs. 5.8 ± 1.6 vs. 5.0 ± 2.4 on 0–10 scale, p = .61), attack duration (20.4 ± 17.6 to 19.6 ± 20.6 hours/attack vs. 19.8 ± 14.4 to 15.4 hours/attack, p = .13), and disability measured via the Headache Impact Test—6 (65.7 ± 4.3 to 61.5 ± 6.4 vs. 63.9 ± 4.2 to 60.8 ± 5.3, p = .62).

**Conclusion:** Intensive, 16-week long BWL and ME control interventions produced significant but similar reductions in migraine frequency and severity among women who with both migraine and overweight/obesity. Further research in this population is needed to determine whether: 1) mechanisms of migraine improvement differ between BWL and ME; 2) either intervention is superior in maintaining migraine improvements over time; and 3) combining BWL and ME yield greater migraine improvements than either treatment alone.


**Psychological and Behavioural Factors and Management**

**PO-01-167**

The effect of emotional and cognitive aspect of pain perception on headache related disability in migraine patients

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**Objectives:** Disability due to migraine can be influenced by emotional and cognitive aspect of pain perception. This study aims to evaluate the difference on pain perception between migraine patients and normal population. Secondly, this study aims to examine the effect of distorted pain perception on headache related disability in migraine patients.

**Methods:** A normal control of 106 health care professionals and their relatives without pain completed questionnaires on pain perception, the Korean version of the Pain Anxiety Symptoms scale (PASS), the Pain Catastrophizing Scale (PCS), and the Pain Sensitivity Questionnaire (PSQ). 145 migraine patients aged 19 to 70 years who visited outpatient neurology clinics in two hospitals were also requested to complete questionnaires on pain perception. Both normal control and migraine patients also fulfilled questionnaires on general psychological distress, the Hospital Anxiety and Depression Scale (HADS). Next, migraine patients completed questionnaires on disability due to migraine, in this case the Korean version of the Headache Impact Test-6 (HIT-6) and the Migraine Disability Assessment (MIDAS). The Pearson correlations analysis among each variable and stepwise backward multiple regression analysis were used by R-statistics.

**Results:** Migraine patients showed significantly higher scores on PASS, PCS, PSQ and HADS, compared to normal control. In migraine patients, PASS, PCS, PSQ showed correlation with each other; especially strong correlation between PASS and PCS (Pearson’s r = 0.746, P < 0.000). However, PASS, PCS, PSQ showed no significantly strong correlation with pain characteristics. Migraine patients also demonstrated correlation between questionnaires on pain perception (PASS, PCS, PSQ) and questionnaires on general psychological stress (HADS). After adjusting for pain characteristics and all questionnaires, stepwise backward multiple regression analyses demonstrated that PASS, HADS-A, headache frequency were an independent predictor associated with HIT-6 (p = 0.001, p = 0.020, p = 0.006). Associated with MIDAS, headache frequency and PASS were an independent predictor (p = 0.000, p = 0.027).

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Conclusion: These study suggested that migraine patients have distorted emotional and cognitive aspect of pain perception, independently of pain characteristics itself. PASS showed the most important contribution to HIT-6 among variables, implying effect of distorted pain perception on headache related disability in migraine patients.

Disclosure of Interest: None Declared

Psychological and Behavioural Factors and Management

PO-01-168

Circadian phase typing in episodic and chronic migraine: dim light melatonin onset and pattern of melatonin secretion

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Objectives: A strong association between primary headaches and sleep disorders is well described in literature, although the dynamics underlying this interaction are not known. Sleep disturbances are indicated among trigger factors for migraine and seem to favor its progression toward chronification. It is also possible that a central neural dysfunction in migraine leads to an imbalance in sleep-wake regulation or that the two disorders share common pathophysiological mechanisms (i.e. chronobiological dysfunction). The Dim Light Melatonin Onset (DLMO) is a reliable marker of the endogenous circadian phase and it is defined as the time of the nychtemeron when the salivary melatonin reaches and maintains the 3 pg/mL concentration. The aim of our study was to investigate subjective and biological components of the chronotype in patients with episodic and chronic migraine.

Methods: We enrolled 8 patients with episodic migraine (EM), 19 patients with chronic migraine and medication overuse headache (MOH), and 22 healthy controls (HC). We evaluated the following parameters: All subjects were evaluated with: 1) DLMO, melatonin concentration of the first post-DLMO salivary sample (ELISA method), melatonin surge in the 30-minute interval after DLMO; under-the-curve area of the post-DLMO semicurve; 2) sleep overuse headache (MOH), and 22 healthy controls (HC). We enrolled 8 patients with episodic migraine

Results: The mean sleep onset and offset times on work days and free days, the MIDwd, the MIDfd, and the MIDc occurred significantly earlier in MOH as compared to HC. In particular MIDc was 3:16 ± 0:40 in MOH, 4:03 ± 0:48 in EM and 4:29 ± 0:54 in HC. We did not find significant differences between MOH and EM regarding other sleep parameters. The mean MEQ score was significantly higher in the MOH group (59.44 ± 8.04) than in the HC group (54.88 ± 8.77, p = 0.001), with the percentage of morning type being was 61.1% in MOH, 37.5% in EM and 18.2% in HC (p = 0.04). The mean PSQI score was higher in the MOH group as compared to controls (p = 0.018). DLMO occurred at 20:43 ± 00:58 in MOH, 20:41 ± 00:48 in EM and 21:18 ± 01:11 in HC, without any significant difference between groups. Similarly distributed among groups was the percentage of morning, intermediate and evening types according to DLMO. The pattern of after-DLMO melatonin secretion was comparable in all groups.

In both MOH and EM the MIDc significantly correlated with days of headache/month (p = 0.01), days of drug intake/month (p = 0.008), age (p = 0.034), MEQ (p = 0.001) and DLMO (p = 0.001). The MIDAS and the PSQI significantly correlated in both MOH and EM groups.

Conclusion: MOH patients are more morning-oriented than HC as measured by MEQ and by MIDc. However MOH patients did not show an early circadian phase as measured by DLMO. Several factors may account for the observed discrepancy, including the impact of the disease chronicity on the patients’ lifestyle. Moreover this discrepancy could represent a predictor of migraine chronification.

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PO-01-169

Do Headache Patients require more care in between visits than other Neurology outpatients?
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Objectives: To establish whether headache patients require a high level of care in addition to clinic visits, based on the quantity of remote encounters (phone calls and secure email communication to the clinics), in comparison to other neurologic subspecialty clinics.

Methods: In an academic referral clinic, a total of 3164 established patients were included in this retrospective analysis, 275 from the Headache clinic, the remainder from the Epilepsy clinic, Movement disorder clinic, the MS/neuroimmunology clinic, the neuromuscular clinic and the General Neurology clinic. Patients presenting for a follow up visit between January 2014 and April 2016 were observed for a 12 month period during which the number of telephone and secure email (Mychart) encounters was recorded; in addition, the number of entries related to each of these encounters was registered. This analysis did not require IRB approval as per institutional guidelines.

Results: Based on preliminary analysis of available data, Headache Clinic patients required a high intensity of remote encounters (composite of both telephone- and email messages), this is only surpassed by the MS/neuroimmunology Clinic. Usage of secure email messaging (mychart) encounters was much higher in the Headache Clinic compared to the other clinics. There was no convincing negative correlation of email messaging usage to age.

Conclusion: Patients in a headache clinic in an academic tertiary care setting require a high intensity of remote outpatient care, more so than patients in other neurology subspecialty clinics and general neurology clinic, with the exception of the Neuroimmunology/MS clinic that has an even higher intensity of remote encounters (and related medical record entries). This was to a large extent secondary to the use of secure email linked to the electronic medical record by headache patients. Reconfirmation of these findings by other clinics/centers and investigation of possible predictive patient factors (e.g. psychiatric comorbidity, as has been suggested by others) is warranted.

Disclosure of Interest: None Declared

PO-01-170

The role of subjective meaning and cognitive beliefs about sensations in the provocation of sensations in head and neck
Elena Rasskazova1, Yulia Migunova1,∗ and Aleksandr Tkhostov1
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Objectives: Psychological factors play in important role in both triggering and perpetuation of somatic symptoms (Leventhal et al., 2003, Rief et al., 1998) including pain and headache (Nash et al., 2006, Smitherman et al., 2015, Ak et al., 2004). Psychological model of body function regulation (Rasskazova et al., 2014) suggests that negative subjective meaning of symptoms is associated with higher general level of sensations in the situations requiring bodily functions monitoring especially in those with dysfunctional cognitive beliefs. Positive meaning could lead to higher risk of specific head-related sensations under these tasks.

The aim of this study is to reveal the role of subjective meaning and cognitive beliefs about sensations in the provocation of head-related sensations in healthy participants.

Methods: 36 healthy students (21 male, 15 female) without history of headaches participating in the biofeedback training were randomly assigned to one of three instructions. Under the neutral instruction they were told that during this task people typically have bodily sensations, mainly in head and neck. Negative instruction added that such symptoms are typical for neurotic people with psychological problems while positive instruction portrayed people with sensations as attentive and talented. All participants filled Screening for somatoform symptoms (Rief, Hiller, 2003) and Cognitions About Body and Health Questionnaire (Rief et al., 1998).

Results: 24 participants (66.7%) reported some bodily sensations during training, 15 participants (41.7%) reported sensations in the head and neck (pain, pressure, tingling, tickling, dizziness). Under negative instruction most participants reported head-unrelated or no sensations (N = 5, 33.3% and N = 8, 53.3%, consequently). Under both neutral and positive instructions they more frequently (ϕ² = 9.5, p < .05, V = .36) reported head-related sensations (under neutral instruction: 50.0%, OR = 6.5; under positive instruction: 36.4%, OR = 3.7).

Comparing to both negative (OR = 2.3) and neutral (OR = 4.5) conditions participants under positive instruction more frequently reported any sensations.
The likelihood of any sensations was higher in those believing that their body is weak and vulnerable to environmental factors (F = 4.3, p < .05) and marginally related to the rate of unexplained somatic symptoms (F = 3.3, p < .08). Catastrophization was related to higher risk of sensations under negative and positive but not neutral instructions (F = 4.2, p < .05) while low level of health habits was related to no sensations under positive instruction comparing to the negative and the neutral ones (F = 3.2, p < .06). Patterns of results were the same for both head-related and head-unrelated sensations.

**Conclusion:** In line with a cognitive approach the frequency of head-related sensations in the task requiring attention and monitoring of the bodily functions is high under neutral condition and is related to belief about bodily weakness and general level of unexplained somatic symptoms.

According to the psychological model of body function regulation data suggests that negative meaning of head-related sensations leads to their lower frequency but higher level of head-unrelated sensations due to efforts to prevent head-related sensations. Positive meaning of head-related sensations could provoke head-related sensations especially in those concentrating of their health and health behavior. Catastrophization seems to be a risk factor of bodily sensations only under specific subjective meaning of these symptoms.

**Research was supported by the Russian Foundation of Fundamental Research, project 17-06-00849.**

**Disclosure of Interest:** E. Rasskazova Conflict with: Research was supported by the Russian Foundation of Fundamental Research, project 17-06-00849, Y. Muginova Conflict with: Research was supported by the Russian Foundation of Fundamental Research, project 17-06-00849, A. Tkhostov Conflict with: Research was supported by the Russian Foundation of Fundamental Research, project 17-06-00849

**Psychological and Behavioural Factors and Management**

**PO-01-171**

**Illness representation as a moderator of the relationship between headache severity and quality of life in patients with migraines and tension-type headaches**

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**Objectives:** According to common-sense model (Leventhal et al., 2003) illness representation regulates patients’ coping with somatic illnesses from both cognitive and emotional levels affecting their quality of life. Research demonstrated the role of anxiety sensitivity (Ocanez et al., 2016), catastrophization (Holroyd et al., 2007), perception of pain (Mongini et al., 2009, Vowles et al., 2016) in headache severity and perpetuation while cognitive behavioral therapy (CBT) suggest strategies of effective pain management (McCracken, Turk, 2002).

The aim of this study was to reveal a role of illness representation on quality of life in patients with chronic headaches.

**Methods:** 75 patients (62 females, mean age 42.0 ± 14.3 years old) with chronic migraines and tension-type headaches filled Migraine Disability Assessment Test (Stewart, 2001), revised version of Illness Perception Questionnaire (Moss-Morris et al., 2002) and a brief version of Quality of Life and Enjoyment Questionnaire (Ritsner et al., 2005).

**Results:** Headache severity negatively correlated with satisfaction with health and emotions (r = −.26, p < .01) but not with leisure time activity and communication.

After statistical control for headache severity (R² = 13.0%), satisfaction with health was higher (ΔR² = 23.1%) in those who believed in their personal control (β = .31, p < .05) and had less emotional reactions to the illness (β = −.33, p < .05). There was marginally significant interaction between headache severity and emotional representations (β = .18, p < .08, ΔR² = 3.0%): emotional reactions to illness better predicted dissatisfaction with health in those with less severe headache.

Satisfaction with emotions adjusted for headache severity (R² = 12.9%) was additionally related (ΔR² = 20.6%) to lower emotional representations (β = −.34, p < .05).

The effect of headache severity was moderated by beliefs about illness length and personal control (ΔR² = 10.3%, p < .01, β = −.38 – −.24): higher headache severity was related to dissatisfaction only in those who believed that their illness is long-term. The relationship was paradoxically stronger for patients believing in their control under headaches.

Belief in negative consequences of illness was related to dissatisfaction with leisure time activity (ΔR² = 20.6%, p < .05, β = −.31). Satisfaction with communication was unrelated to both headache severity and beliefs about illness but there was an interaction effect between belief about illness length and headache severity (ΔR² = 7.6%, p < .05, β = −.29): only in those with more severe headaches belief that illness is long-term correlated with dissatisfaction with communication.

Major patterns of relationships remained after controlling for headache type (migraines versus tension-type headaches).

**Conclusion:** From the CBT perspective, data supports that work with patients’ beliefs about illness length,
consequences, personal control and especially emotional representations could be helpful for quality of life regardless of headache severity. Patients are more satisfied with health and emotions if they have less emotional reactions to the illness and more satisfied with health if they believe that they can control their headache. Also patients with lower beliefs in the negative consequences of their headache are more satisfied with leisure time activity. Moreover, beliefs that headache is long-term and controllable seem to strengthen negative effect of headache severity on satisfaction with emotions while emotional representations could strengthen negative effect of headache severity on satisfaction with health.

Research was supported by the Russian Foundation of Fundamental Research, project 17-06-00849.

Disclosure of Interest: Y. Migunova Conflict with: Research was supported by the Russian Foundation of Fundamental Research, project 17-06-00849, E. Rasskazova Conflict with: Research was supported by the Russian Foundation of Fundamental Research, project 17-06-00849, A. Andrushenko: None Declared, A. Spivakovskaja: None Declared

Psychological and Behavioural Factors and Management

PO-01-172

Identification of herbal plants for the treatment of headaches

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Objectives: Herbs have been used in traditional medicine for several thousand years. The knowledge of medicinal plants has accumulated in the course of time in different medicinal systems such as Ayurveda, Unani and Siddha. The objective of this study was to interact with local traditional healers and document the medicinal plants effective in treating headaches.

Methods: Details regarding traditional herbal medicine were acquired from indigenous with local traditional healers and document their knowledge on medicinal plants. Prepared questionnaires were used for this purpose.

Results: Our study showed that there are 11 herbs traditionally to treat headaches. Because of the importance of these medicinal plants it is necessary to determine the distribution and availability of these herbs. Also there is need to further study the effect of these medicines.

Conclusion: The study indicated that there are plenty of medicinal plants to treat headache. Extensive study should be designed to identify the mode of action and other important aspects of these herbs.

Disclosure of Interest: None Declared

Tension-Type Headache

PO-01-173

Neurophysiological mechanisms in tension-type headache chronification

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Objectives: Aim of the study - to determine the EEG patterns of adolescents with tension-type headache (TTH) and differences in EEG patterns in various forms of TTH.

Methods: 105 adolescents with TTH were examined. Four groups: 1st (46 pers.) - patients with infrequent episodic tension-type headache (IETTH), 2nd (40 pers.) - patients with frequent episodic tension-type headache (FETTH), 3d (19 pers.) - patients with chronic tension-type headache (CTTH), 4th (20 pers.) - healthy adolescents (control group) were formed. EEG study included visual, spectral, and nonlinear multidimensional analysis (deterministic chaos, calculated Kolmgorov-Sinai entropy) EEG.

Results: Patients with TTH had increased activity of both arousal-1 system (A-1 - mesencephalic reticular formation of the brainstem), and arousal-2 (A-2 - hippocampal cortex and septum pellucidum) system. Patients with IETTH had increased activity of A-1, and patients with FETTH and CTTH - A-2. The compensatory synchronizing influence on the cerebral cortex had been associated with an increase in the functional activity of thalamocortical system (C-2) in the patients with IETTH and FETTH, and reticulocortical system (C-1) in the patients with CTTH. Imbalance between activating systems (switching A-1 to A-2) and synchronizing systems (reducing the activity of C-2 and the relative increase of the activity of the C-1) has been associated with clinical signs of transformation of FETTH to CTTH. The value Kolmogorov-Sinai entropy decreased simultaneously with increasing frequency of TTH.

Conclusion: Complex changes of cortical-subcortical relationships, such as activation of the limbic structures; lack of the activity of the synchronization thalamocortical system; the relative increase of the activity of the reticulocortical system; the formation of stable pathological dominant ("central sensitization") in key limbic structures are associated with transformation of EEG pattern of “paroxysmal” headache to pattern of “chronic” headache in adolescents with tension-type headache.

Disclosure of Interest: None Declared

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**Tension-Type Headache**

**PO-01-174**

“How do Italian osteopaths treat and manage tension-type headache? A qualitative study”

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**Objectives:** This qualitative study explored the attitudes, beliefs and values of osteopaths practising in Italy regarding the evaluation, treatment and management of patients with tension-type headache (TTH).

**Methods:** Ten osteopaths were recruited by theoretical sampling from the teaching faculty of an osteopathic college in Italy. In-depth, individual semi-structured interviews were conducted; the interviews were audiorecorded and verbatim transcribed. Data were coded and analysed using Thematic Analysis with elements of Grounded Theory to identify common trends reported by osteopaths with experience in treating and managing people with TTH. The consolidated criteria for reporting qualitative research checklist (COREQ) was used to improve the transparent reporting of qualitative data. Researcher bias/trustworthiness were mitigated using a researcher, with experience in qualitative research, checking 20% of interview transcripts. Transcripts were checked and edited by participants. Member-checking was used to control for accuracy. Finally, peer debriefing including colleagues, researchers and educators not involved directly in the study, was used to consider different aspects of the findings model of interpretation.

**Results:** Four main themes were identified: 1) osteopathy and its alternative perspective on patients’ perception 2) the osteopaths’ decision making process regarding the selection of treatment approaches; 3) the person’s management through and individualized case treatment model; 4) a renewed person-centred approach setting the treatment in a environment to find fulfilment of individual potential. The participants tailored TTH management to suit patients’ needs and preferences. Treatment strategies resulted highly individual, giving the headache patient a central role within the care process.

**Conclusion:** Osteopaths endorsed a person-centred renewed approach. Although the clinical conditions and disabilities associated with TTH were considered carefully, osteopaths reported how, a more targeted approach at improving and promoting the individual’s wellbeing and symptomatic relief of their symptoms, should be the main aim of osteopathic treatment. Moreover, our findings highlighted the active role of the patient in the process of care and how the osteopath-patient relationship is crucial to create a robust therapeutic alliance.

**Disclosure of Interest:** None Declared

**Tension-Type Headache**

**PO-01-175**

Dynamic Mechanical Hypersensitivity in the Trigeminal Area in Tension Type Headache

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**Objectives:** To explore the association of dynamic algometry for evaluating dynamic mechanical hyperalgesia with headache clinical features and widespread pressure pain sensitivity in subjects with tension-type headache (TTH).

**Methods:** One hundred eighty-eight individuals with TTH (70% women) participated. They were diagnosed of TTH according to the International Classification of Headache Disorders (ICHD-III) criteria. Exclusion criteria included other primary headaches, whiplash, medication overuse headache, fibromyalgia or any neurological disorder. A 1-month headache diary was used to collect clinical data and preventive medication intake Dynamic hyperalgesia was assessed with a dynamic pressure algometry set (Aalborg University, Denmark) consisting of 11 different rollers with fixed levels from 500 g to 5300 g. Each roller was moved at a speed of 0.5 cm/sec over a 60 mm horizontal line covering the temporalis muscle. Dynamic pain threshold (DPT-level of the first painful roller) was determined. As golden standard, static pressure pain thresholds (PPTs) were assessed over temporalis muscle, C5/C6 zygopophyseal joint, second metacarpal and tibialis anterior.

**Results:** Side-to-side consistency between DPT (r = 0.843, P < 0.001) was observed. DPT was moderately associated with widespread PPTs (0.526 > r > 0.656, all P < 0.001).

**Conclusion:** DPT was associated with widespread pressure sensitivity supporting that dynamic pressure hyperalgesia within the trigeminal area is consistent with generalized pressure pain hyperalgesia. These results
suggest that dynamic pressure algometry may be a valid tool for assessing dynamic mechanical pain sensitivity in TTH. Therefore, assessing both static and dynamic deep somatic tissue pain sensitivity may provide new opportunities for differentiated diagnostics and new tool for assessing treatment effects.

Disclosure of Interest: None Declared

**Tension-Type Headache**

**PO-01-176**

The use of Preventive Pharmacological Treatment is Associated with Local Pressure Pain Hyperalgesia in Tension Type Headache

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**Objectives:** To investigate the differences in clinical features and widespread pressure sensitivity according to the use of preventive medication in individuals with tension type headache (TTH).

**Methods:** Individuals with TTH diagnosed according to the International Classification of Headache Disorders (ICHD-III) criteria participated. Exclusion criteria included other primary headaches, medication overuse headache, whiplash, fibromyalgia or any neurological disorder. A 1-month headache diary was used to collect clinical data and preventive medication intake. Pressure pain thresholds (PPTs) over the temporalis, C5-C6 zygapophyseal joint, second metacarpal, and tibialis anterior were assessed.

**Results:** One hundred and forty-four (n = 144) patients (72% women; mean age: 45 ± 13 years; headache frequency: 16 ± 9 days per month; headache intensity: 6.1 ± 1.1; headache duration: 7.4 ± 4.3 hours/attack) participated. Fifty-nine (41%) reported use of preventive medication (62% amitriptyline). Patients taking preventive medication reported longer headache duration and higher headache frequency, but similar intensity, than those not taking medication (P < 0.001). Similarly, those patients taking preventive medication had lower PPT over the temporalis muscle and C5-C6 zygapophyseal joint (P < 0.05) than those patients not taking preventive medication. No significant differences in PPTs over the second metacarpal and tibialis anterior muscles were observed.

**Conclusion:** The current study found that preventive medication intake was related to worse headache frequency and duration and higher local pressure pain hyper-sensitivity in the trigemino-cervical area in patients with TTH. Future studies should investigate if the use of preventive medication intake is able to reduce sensitization mechanisms in TTH.

Disclosure of Interest: None Declared

**Tension-Type Headache**

**PO-01-177**

Comparison of clinical characteristics between chronic tension-type headache patients diagnosed by ICHD-3β original and stricter alternative criteria

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**Objectives:** The purpose of this study was to compare the clinical characteristics of chronic tension-type headache (CTTH) patients diagnosed by International Classification of Headache Disorders-3β (ICHD-3β) original criteria code 2.3 and stricter alternative criteria code A2.3.

**Methods:** Of the 12,920 outpatients in a headache clinic seen by neurologists from 2004 to 2016 in one tertiary teaching hospital in Taipei, Taiwan, 225 (1.7%) patients were diagnosed as CTTH. Among them, all patients fulfilled the ICHD-3β original criteria (ICHD-3β original group), whereas, only 67 (29.8%) fulfilled the stricter alternative criteria. In order to compare these two criteria, this field testing study compared these two groups of CTTH patients, i.e. those who did not fulfill stricter criteria (non-stricter group, n = 158) vs. those who fulfilled stricter criteria (stricter group). The comparisons included the following data if available: demographics, headache profiles, comorbidities, and a battery of rating scales including Hospital Anxiety and Depression Scale (HADS), Migraine Disability Assessment (MIDAS), Pittsburgh Sleep Quality Index (PSQI), and fibromyalgia (FM) questionnaires based on the modified 2010 American College of Rheumatology preliminary diagnostic criteria. Categorical data was
performed by chi-square test and continuous data was performed by independent t-tests.

**Results:** Demographic data showed no difference between 2 groups except that the non-strict group had a higher family history (1st degree relatives) of headache (49.7% vs. 28.8%, $p = 0.005$) than stricter group. In headache profiles, non-strict group had higher intensity of the worst headache in the past year (6.8 ± 2.1 vs. 6.0 ± 2.3, $p = 0.01$), higher intensity of the average headache in the past year (5.4 ± 2.1 vs. 4.4 ± 1.9, $p = 0.03$), and higher frequency of posterior neck pain (43.9% vs. 25.4%, $p = 0.01$) than the stricter group. The non-strict group had higher frequency of coffee or tea or coke drinking than the stricter group (45.8% vs. 27.3%, $p = 0.04$). Moreover, non-strict group had higher HADS score (7.2 ± 6.1 vs. 5.4 ± 3.9, $p = 0.01$), higher widespread pain index (2.8 ± 2.9 vs. 1.9 ± 2.0, $p = 0.001$), and higher symptom severity score (4.9 ± 2.6 vs. 3.9 ± 2.8, $p = 0.02$) than stricter group but not for the scores of the MIDAS or PSQI.

**Conclusion:** Our findings suggested that compared to ICHD-3β original criteria, CTTH patients identified by the stricter criteria appear to have less headache severity and comorbidities. Further study needs to identify this unique headache group.

**Disclosure of Interest:** None Declared
Cluster Headache and Other Trigeminal Autonomic Cephalalgias

EP-02-001

Cluster Headache: Investigating severity of pain, suicidality, personal burden, access to effective treatment, and demographics among a large International survey sample.

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Objectives: This research study examined Cluster Headache, with an emphasis on suicidality, severity of pain, personal burden, and access to effective treatment.

Methods: 1,500 Cluster Headache patients from 51 countries completed an IRB approved Internet based survey consisting of more than 150 questions including psychometric measures of depression and hopelessness, comparison of Cluster Headache pain with other painful conditions (e.g. renal stones, pancreatitis, child birth, migraine, shingles, gunshot wound). Other constructs assessed included personal and financial burden, access to effective treatments, suicidality as well as risk and protective factors, and vocational disability.

Table: Abbreviated and Preliminary:
P3 - Comparing each experience with Cluster Headache attacks, how painful would you rate each on a scale of 1 (least painful) to 10 (most painful)?

<table>
<thead>
<tr>
<th>Field</th>
<th>Mean</th>
<th>Std Deviation</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster Headache attacks</td>
<td>9.66</td>
<td>0.88</td>
<td>0.77</td>
</tr>
<tr>
<td>Child birth</td>
<td>7.16</td>
<td>2.08</td>
<td>4.33</td>
</tr>
<tr>
<td>Migraine</td>
<td>5.40</td>
<td>2.11</td>
<td>4.44</td>
</tr>
<tr>
<td>Shingles</td>
<td>4.43</td>
<td>2.12</td>
<td>4.50</td>
</tr>
<tr>
<td>Kidney Stones</td>
<td>6.61</td>
<td>2.17</td>
<td>4.69</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>7.27</td>
<td>1.47</td>
<td>2.16</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>5.06</td>
<td>2.46</td>
<td>6.04</td>
</tr>
<tr>
<td>Gunshot wound</td>
<td>6.34</td>
<td>1.34</td>
<td>1.80</td>
</tr>
</tbody>
</table>

Results: Respondents ranged from 18 to 99 years of age, with slightly more men than women reporting Cluster Headache diagnosis. Age of onset ranged from childhood to 71 years old.

1. Cluster Headache patients indicated severity of pain was significantly worse than any other identified medical conditions.
2. Suicidality among Episodic Cluster Headache patients (ECH) increased significantly during cluster cycles and among those with Chronic Cluster Headache (CCH). Risk and protective factors were identified.
3. Cluster Headache patients experience significant personal and financial burden, as well as vocational disability.
4. Many patients have difficulty accessing safe and effective treatments.
5. Because of the severity of pain or impact of personal burden, psychological needs are not addressed sufficiently?

Conclusion: Despite the numerous statements regarding the severity of pain, the existing literature seems rather anecdotal and inferred. Consequently we asked specifically if this is the worst pain each subject has experienced and elicited their subjective comparison with other painful experiences. We obtained a sufficiently robust sample size to gather data from people who, in addition to Cluster Headache, have also experienced kidney stones, childbirth, gunshot wounds, migraine, etc. While this approach has not been validated, it is arguable that this approach has provided clearer data than existing pain measures.

Suicidality is significantly elevated among ECH patients who are in cycle as well as ECH patients, as are depression and hopelessness.

Many patients have significant barriers to accessing safe and effective treatments.

Physicians and patients would benefit from increased training in managing this condition and should assess for mental health problems and suicidality.

Disclosure of Interest: L. Schor Conflict with: Autonomic Technologies grant
Cluster Headache and Other Trigeminal Autonomic Cephalalgias

EP-02-002

Cranial parasympathetic activation induces autonomic symptoms but no cluster headache attacks

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3 Autonomic Technologies Inc., Redwood City, United States
4 Department of Clinical Biochemistry, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark

Objectives: To investigate if low frequency (LF) stimulation of the sphenopalatine ganglion (SPG) may increase parasympathetic outflow and provoke cluster headache (CH) attacks in CH patients implanted with an SPG neurostimulator.

Methods: In a double-blind randomized sham-controlled crossover study, 20 CH patients received LF or sham stimulation for 30 min on two separate days. We recorded headache characteristics, cephalic autonomic symptoms (CAS), plasma levels of parasympathetic markers such as pituitary adenylate cyclase-activating polypeptide-38 (PACAP38) and vasoactive intestinal peptide (VIP), and mechanical detection and pain thresholds as a marker of sensory modulation.

Results: In the immediate phase (0–60 min), 16 (80%) patients experienced CAS after LF stimulation, while 9 patients (45%) reported CAS after sham (P = 0.046). We found no difference in induction of cluster-like attacks between LF stimulation (n = 7) and sham stimulation (n = 5) (P = 0.724). There was no difference in mechanical detection and pain thresholds, and in PACAP and VIP plasma concentrations between LF and sham stimulation (P ≥ 0.162).

Conclusion: LF stimulation of the SPG induced autonomic symptoms, but no CH attacks. These data suggest that increased parasympathetic outflow is not sufficient to induce CH attacks in patients.

Disclosure of Interest: None Declared

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

EP-02-003

Injection of onabotulinum toxin A towards the sphenopalatine ganglion – a potential long-term treatment for chronic cluster headache patients?

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2 Department of Neurosurgery
3 Department of Neurology, St. Olavs University Hospital, Trondheim, Norway
4 Department of Neurology, Mayo Clinic, Phoenix, United States

Objectives: The aim of this follow-up study was to investigate long-term outcomes in per-protocol (PP) chronic cluster headache (CCH) patients, 18 and 24 months after participation in the “Pilot study of sphenopalatine injection of onabotulinumtoxinA (BTA) for the treatment of intractable chronic cluster headache” (1).

Methods: This was a prospective observational follow-up study where all PP patients (n = 7) from the pilot study were invited to participate. The primary objective was to evaluate changes in cluster headache (CH) attack frequency 18 and 24 months after the initial BTA injection. Primary and secondary outcome measures are described in Table 1. After the pilot study, responding patients had access to repeated injections at timepoints as needed by patients (minimum 3 months between injections). These were performed with a new technique using percutaneous infrrazygomatic (lateral) injection under local anesthesia on awake patients in an outpatient, office-based setting. Data were collected through headache diaries and questionnaires at months 18 and 24 after the initial BTA injection and were compared to the baseline period in the pilot study. Safety data were collected continuously.

Results: A significant reduction in CH attack frequency, reduction in attacks with severe and unbearable intensity and increase in CH attack-free days was found both at months 18 and 24 compared to baseline (Table 1). Five out of seven patients received repeated treatment during the 24 months and a significant long-term reduction (≥ 50%) in number of CH attacks was found in four out of five patients. Of the remaining two patients, one remained headache-free after the initial injection. The new injection technique was well accepted by all patients.
Abstract number: EP-02-003

Table 1. Primary and secondary outcome measures for baseline and at months 18 and 24 after initial injection with onabotulinumtoxinA towards the sphenopalatine ganglion (n = 7).

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Month 18</th>
<th>Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of attacks of all intensity per week (primary outcome)</td>
<td>14.3 ± 8.9</td>
<td>3.1 ± 3.8 <strong>(0.018)</strong></td>
<td>6.1 ± 4.8 <strong>(0.018)</strong></td>
</tr>
<tr>
<td>Number of attacks, intensity 3 or 4 per month</td>
<td>50.0 ± 38.3</td>
<td>10.1 ± 14.7 <strong>(0.018)</strong></td>
<td>16.6 ± 13.7 <strong>(0.028)</strong></td>
</tr>
<tr>
<td>Number of attacks of all intensity per month</td>
<td>57.3 ± 35.6</td>
<td>12.4 ± 15.2 <strong>(0.018)</strong></td>
<td>24.6 ± 19.2 <strong>(0.018)</strong></td>
</tr>
<tr>
<td>Intensity per attacka</td>
<td>3.50 ± 1.05</td>
<td>2.4 ± 1.8 (0.237)</td>
<td>2.7 ± 1.5 (0.063)</td>
</tr>
<tr>
<td>Duration per monthb</td>
<td>1345.0 ± 793.9</td>
<td>380.7 ± 370.2 (0.075)</td>
<td>552.0 ± 537.2 (0.249)</td>
</tr>
<tr>
<td>Duration per attackb</td>
<td>35.6 ± 24.8</td>
<td>28.2 ± 40.7 (0.753)</td>
<td>30.9 ± 44.0 (0.917)</td>
</tr>
<tr>
<td>CH-free days per month</td>
<td>4.2 ± 5.9</td>
<td>19.1 ± 9.4 <strong>(0.027)</strong></td>
<td>12.9 ± 8.8 <strong>(0.018)</strong></td>
</tr>
<tr>
<td>Triptan doses per monthc</td>
<td>91.3 ± 49.1</td>
<td>19.5 ± 22.0 (0.068)</td>
<td>53.5 ± 42.4 (0.068)</td>
</tr>
</tbody>
</table>

Results are presented as mean ± SD. P-values ≤ 0.05 are depicted in bold.

aCategorical intensity scale: Grade 1: mild; Grade 2: moderate; Grade 3: severe; Grade 4: unbearable.
bMinutes.
cFour of seven patients use triptans as acute treatment.

CH: Cluster headache.

who got repeated treatment and the AEs observed in two out of five patients were transient and experienced as acceptable by the patients.

**Conclusion:** These 24 month results suggest that treatment with BTA injections towards the SPG may be an effective long-term treatment for intractable CCH patients. Randomized, placebo-controlled trials on a larger population, with long-term follow-up are needed to confirm the effect of BTA injections towards the SPG in CCH.

**Disclosure of Interest:** I. Aschehoug: None Declared, D. Bratbak Conflict with: This work was supported by The Liaison Committee between the Central Norway Regional Health Authority and Norwegian University of Science and Technology (grant number 12/9996); Joint Research Unit between St. Olavs Hospital and Norwegian University of Science and Technology (grant number 9885); and NTNU Discovery (grant number 244278)., Conflict with: Dr. Bratbak, NTNU and St. Olavs Hospital, may benefit financially from a commercialisation of the proposed treatment through future possible intellectual properties.

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

**EP-02-004**

Chronorisk in cluster headache: A tool for individualized therapy? Results from the Danish cluster headache survey

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**Objectives:** Cluster headache (CH) attacks occur with a high degree of predictability yet we still know very little of what influences the timing of these attacks. We aimed to describe the 24 hour attack distribution (chronorisk) in subgroups of well characterized CH patients.

**Methods:** CH patients (n = 351) from the Danish CH-survey aged 18–65 years, diagnosed according to ICHD-II, completed a questionnaire and structured interview. Patients reported the most common hours of attacks and a chronorisk distribution (% of all attacks reported for each hour) of each subgroup was calculated. To identify periods of increased attack risk and to disentangle overlapping events, a multi modal Gaussian fit was calculated. Only peaks > 3% were included in the analysis. The Gaussian model was limited to maximum 5 modes. The Pittsburgh
Sleep Quality Index (PSQI) was used to evaluate sleep quality and included patients with attacks within the last month. **Results:** The Gaussian model identified three peaks of attacks at 21:41, 02:02 and 06:23 ($R^2 = 0.97$) for patients reporting diurnal rhythmicity in attacks ($n = 286$, 82%). Episodic patients had their nightly peak > one hour earlier than chronic patients (01:28 vs. 02:33), however there was no difference in the morning peak. Furthermore, chronic patients experienced 2 daytime peaks not seen in episodic patients (11:14 and 15:46). Taking verapamil advanced the nocturnal (01:53 vs. 02:43) and morning peak (06:04 vs. 06:51) compared with patients not taking verapamil. Patients with poor sleep quality (PSQI $>$ 5) had three prominent peaks (21:46, 02:16, 06:03), whereas patients with good sleep quality (PSQI $\leq$ 5) had distinct peaks early in the night and throughout the day. The nocturnal peak was earlier in patients consuming tobacco, alcohol and coffee compared with abstainers (01:56 vs. 02:46, 01:10 vs. 02:07, and 01:48 vs. 03:26). Consuming tobacco and alcohol did not affect the morning peak, whereas the consumption of coffee advanced it (06:07 vs. 06:58). Time asleep varied across the groups. Not smoking and being episodic was associated with significantly earlier time asleep. **Conclusion:** In CH, the chronorisk of diurnal attack occurrence was affected by several factors including phenotype, verapamil, sleep quality, and consuming tobacco, alcohol and coffee. Our findings also suggest that chronic patients have a relatively higher daytime risk of attacks, whereas episodic patients are more vulnerable at night. CH has very distinct chronobiological features and is therefore a ripe target for individualized chronotherapy—the administration of medicine tailored to time of day for maximum therapeutic effect and minimal side effects. **Disclosure of Interest:** N. Lund Conflict with: The Tryg Foundation, M. Barloese: None Declared, B. Haddock: None Declared, A. Petersen: None Declared, R. Jensen Conflict with: The Tryg Foundation

**Cluster Headache and Other Trigeminal Autonomic Cephalalgias**

**EP-02-005**

Non-invasive Vagus Nerve Stimulation for Acute Treatment of Episodic and Chronic Cluster Headache: Pooled Analysis of Data From Two Randomised, Double-blind, Sham-Controlled Clinical Trials

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8Geisel School of Medicine at Dartmouth, Hanover, United States
9NIHR-Wellcome Trust CRF, King’s College Hospital, London, United Kingdom

**Objectives:** Clinical observations and results from recent studies support the use of non-invasive vagus nerve stimulation (nVNS) for the acute treatment of cluster headache. We assessed the efficacy and safety of nVNS as acute cluster headache treatment in a large pooled data analysis. **Methods:** Two prospective, randomised (1:1), double-blind, multicentre, sham-controlled clinical trials were used for our pooled data analysis, which consisted of 252 individuals fulfilling ICHD-II criteria for cluster headache. Both studies required three consecutive 120-second vagal nerve stimulations at attack onset. In ACT2, subjects were permitted to treat with an additional three stimulations if they were not pain free by nine minutes after the initiation of the first treatment. In the ACT1 study, all treatments were applied to the right cervical vagus nerve. In ACT2, the subjects were encouraged to treat ipsilateral to the pain. **Results:** The first-order interaction between treatment group and cluster headache subtype was significant ($P < 0.01$) in models estimating the proportion of patients who achieved responder status at 15 minutes after treatment initiation for the first cluster headache attack (the ACT1 primary endpoint) in the ACT1, ACT2, and pooled populations. In models estimating the proportion of all treated attacks that achieved pain-free status at 15 minutes after treatment initiation (the ACT2 primary endpoint),
the first-order interaction term between treatment group and cluster headache subtype was also significant ($P < 0.05$) in all three populations (i.e., ACT1, ACT2, and pooled). Thus, results are presented overall and by cluster headache subtype. The proportion of patients who achieved responder status at 15 minutes after treatment initiation for the first cluster headache attack (the ACT1 primary endpoint) was significant between the nVNS and sham treatment groups in episodic cluster headache patients in both ACT1 (34% vs. 11%; $P = 0.01$) and pooled analyses (39% vs. 12%; $P < 0.01$) but not in the ACT2 analysis (50% vs. 15%; $P = 0.07$). The proportion of all treated attacks that achieved pain-free status at 15 minutes after treatment initiation (the ACT2 primary endpoint) was significant between the nVNS and sham treatment groups in episodic cluster headache patients in ACT1 (15% vs. 6%; $P < 0.05$), ACT2 (35% vs. 7%; $P < 0.05$), and pooled analyses (24% vs. 7%; $P < 0.01$). There were no significant differences for these endpoints for the total cluster headache population or chronic cluster headache population in ACT1, ACT2, or pooled analyses. There were no serious adverse device effects reported.

**Conclusion:** As the largest investigation of a drug or device for the acute treatment of CH attacks, this pooled analysis supports the use of nVNS as a viable, safe, and effective acute treatment option in patients with episodic cluster headache. This analysis also provides the impetus for further research to explore the role of nVNS in the treatment of patients with chronic cluster headache.

**Disclosure of Interest:** I. de Coo Conflict with: Travel grants from electroCore, LLC; J. Marin Conflict with: Honoraria and travel grants from electroCore, LLC; S. Silverstein Conflict with: Consultancy and advisory board fees from Alder Biopharmaceuticals Inc., Allergan, Inc., Amgen, Inc., Avanir Pharmaceuticals, Inc., Depomed, Inc., Dr. Reddy’s Laboratories Ltd., eNeura Inc., Ipsen Biopharmaceuticals Inc., Medscape LLC, Medtronic, Inc., Mitsubishi Tanabe Pharma America, Inc., National Institute of Neurological Disorders and Stroke, St. Jude Medical, Inc., Supernus Pharmaceuticals, Inc., Teva Pharmaceutical Industries Ltd., and Trigemina, Inc., D. Friedman Conflict with: Grant support from Lilly, Merck & Company, and Autonomic Technologies, Conflict with: Consultancy for Allergan, Avanir, and Lilly, Conflict with: On the speaker’s bureau for Allergan, Avanir, Supernus, and Teva Pharmaceuticals, Conflict with: On the advisory board for Avanir, Supernus, and Teva Pharmaceuticals., C. Gaul Conflict with: Honoraria from Allergan; electroCore, LLC; St. Jude Medical; Grünenthal; Desitin; Bayer; Boehringer Ingelheim; Autonomic Technologies; Reckitt Benckiser; Ratiopharm GmbH; Novartis; Lilly Deutschland; and Hormosan, A. Tyagi Conflict with: Honoraria from Allergan and electroCore, LLC, E. Liebler Conflict with: electroCore, LLC, Conflict with: electroCore, LLC, S. Tepper Conflict with: Stock options from Autonomic Technologies, Inc. (ATI), Conflict with: Research grants/support from Alder Biopharmaceuticals, Allergan, Inc., Amgen, Inc., Avanir Pharmaceuticals, Inc., Dr. Reddy’s Laboratories Ltd., electroCore, LLC, eNeura Inc., Scion NeuroStim, LLC, Teva Pharmaceutical Industries Ltd., and Zosano Pharma Corporation, Conflict with: Consultancy fees from Acadora Therapeutics, Inc., Alder Biopharmaceuticals, Allergan, Inc., Amgen, Inc., Autonomic Technologies, Inc. (ATI), Avanir Pharmaceuticals, Inc., Biovision Technologies, LLC, Dr. Reddy's Laboratories Ltd., electroCore, LLC, eNeura Therapeutics, Pernix Therapeutics, Pfizer, Inc., Scion NeuroStim, LLC, Teva Pharmaceutical Industries Ltd., and Zosano Pharma Corporation, Conflict with: Royalties from Springer, M. Ferrari Conflict with: Research support from the Netherlands Organisation for Scientific Research (NWO); the European Community; ZonMw; and the Dutch Heart Foundation, Conflict with: Consultancy fees from Medtronic, Conflict with: Member of the Editorial Board for Cephalalgia, P. Goadsby Conflict with: Grants from Allergan, Amgen, Eli Lilly and Company, Conflict with: Personal fees from Akita Biomedical; Alder Biopharmaceuticals; Allergan; Amgen; Autonomic Technologies; Avanir Pharmaceuticals; Cipla Ltd; CoLucid Pharmaceuticals, Inc.; Dr. Reddy’s Laboratories; electroCore, LLC; Eli Lilly and Company; eNeura; Novartis; Pfizer Inc; Promius Pharma; Quest Diagnostics; Scion; Teva Pharmaceuticals; Trigemina, Inc.; Medico-Legal Journal; Journal Watch; UpToDate; and Oxford University Press. In addition, Dr. Goadsby has a patent for magnetic stimulation for headache pending assigned to eNeura.

**Comorbidity of Primary Headaches**

**EP-02-006**

Framingham cardiovascular risk estimate scores in women with migraine; the importance of lifetime changes

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2Institute of Public Health, Charité-Universitätsmedizin, Berlin, Germany
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**Objectives:** Migraine has consistently been reported to be associated with increased risk of cardiovascular disease (CVD) events. It is, however, not yet clear to what extent increased cardiovascular risk profile is associated with migraine status. Further, in most studies the development of migraine during follow-up was not considered. We studied the cross-sectional association of migraine status with vascular risk profiles and the prospective association with the development of migraine in women.

**Methods:** Female health professionals (Women’s Health Study, n=27,604, age ≥ 45 years at baseline) without a history of CVD, cancer, or other major diseases and who provided a blood sample at baseline were enrolled in the study. The presence or development of migraine was assessed by questionnaire. Women were classified as having ‘no migraine’ (reference group), ‘history of migraine’ (have experienced migraine in the past but did not experience any migraine attacks in the year prior to inclusion in the Women's Health Study), ‘migraine at baseline’ (active migraine at inclusion) or ‘incident migraine’ (presentation of migraine after inclusion in the study).

Framingham risk scores estimating ten-year cardiovascular disease risk were calculated at baseline to classify women in vascular risk classes. We used multinominal logistic regression models to calculate odds ratios (ORs) of the association between migraine status and Framingham risk score categories.

**Results:** A total of 1499 reported history of migraine and 3575 having active migraine at baseline. Of the 21,790 women not reporting migraine at baseline, 740 women reported migraine during follow-up. Women with a history of migraine only were more likely to have a Framingham risk score ≥10 at baseline (OR 1.74, 95% CI 1.38 to 2.18).

In contrast, women with active migraine at baseline (OR 1.52, 95% CI 1.28 to 1.80), and women with newly developed migraine at follow-up (OR 1.25, 95% CI 1.05 to 1.49) had a decreased risk of having a Framingham risk score ≥10. For risk scores <10, a similar pattern was observed.

**Conclusion:** Framingham risk scores are only increased in women with a history of migraine compared with women not reporting migraine. Our results suggest that (i) lifetime changes in migraine status should be considered when studying association with the vascular system, and (ii) that a relatively healthy cardiovascular system, as determined by the Framingham cardiovascular risk score, appears to be associated with having active migraine or to predict development of migraine in the future.

**Disclosure of Interest:** None Declared

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**Comorbidity of Primary Headaches**

**EP-02-007**

**CLINICAL CHARACTERIZATION OF VISUAL SNOW**

Francesca Puledda1,*, Tze Lau1, Christoph Schankin2 and Peter J. Goadsby1

1Headache Group, Department of Basic and Clinical Neuroscience, King’s College London, and NIHR-Wellcome Trust King’s Clinical Research Facility, King’s College Hospital, London, UK, King’s College London, London, United Kingdom

2Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

**Objectives:** Patients with Visual Snow suffer a pan-field, dynamic visual disturbance described as continuous TV-static-like tiny flickering dots. The proposed diagnostic criteria require at least two additional visual symptoms from: palinopsia (afterimages and trailing), entoptic phenomena (floaters, blue field entoptic phenomenon, photopsia, self-light of the eye), photophobia and nystagmus (I).

**Methods:** Visual Snow patients were characterized clinically with regard to the current criteria. An online survey was prepared in collaboration with the patient group Eye-on-Vision. Patients were directed to the site after they contacted us by email asking to be involved in research. The study was approved by the KCL Research Ethics Panel.

**Results:** Of n=636 patients contacting the group, n=570 matched the diagnostic criteria for Visual Snow; data is reported for these patients. The female to male ratio of the cohort was 1:1.1 and mean age of 29±10 years. The mean age of symptom onset was 13±13 years and 38.7% of subjects reported symptoms for their entire lifetime (data available for n=323). Subjects presented with black and white (n=317; 56%), colored (n=249; 44%), flashing (n=253; 45%) and transparent (n=297; 52%) static, with an average of two types of static reported per patient. Floaters (n=486) were the most common associated symptom, followed by afterimages (n=467) and photophobia (n=446). The non-visual symptom tinnitus was reported by 74% of patients. Data on headache comorbidity was available for n=226 subjects, of which 83% reported at least one migraine episode in the past.

**Conclusion:** The data confirm earlier work on this unrecognized disorder and extend the analysis of the overlapping symptoms present in a wide range of subjects. Visual Snow can be a highly disabling syndrome that is now becoming better understood as it is recognized and systematically studied.

**References**

Disclosure of Interest: F. Puledda: None Declared, T. Lau: None Declared, C. Schankin: None Declared, P. Goadsby Conflict with: Dr. Goadsby reports grants and personal fees from Allergan, Amgen, and Eli-Lilly and Company; and personal fees from Akita Biomedical, Alder Biopharmaceuticals, Autonomic Technologies Inc, Avanir Pharma, Cipla Ltd, Colucid Pharmaceuticals, Ltd, Dr Reddy’s Laboratories, eNeura, Electrocore LLC, Novartis, Pfizer Inc, Promius Pharma, Quest Diagnostics, Scion, Teva Pharmaceuticals, Trigemina Inc., Scion; and personal fees from MedicoLegal work, Journal Watch, Up-to-Date, Oxford University Press; and in addition, Dr. Goadsby has a patent Magnetic stimulation for headache pending assigned to eNeura.

Comorbidity of Primary Headaches

EP-02-008

White Matter Hyperintensities in Migraine: Clinical Significance and Central Pulsatile Hemodynamic Correlates

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2Department of Neurology, Neurological Institute, Taipei Veterans General Hospital
3Cardiovascular Research Center, National Yang-Ming University, Taipei, Taiwan, Republic of China

Objectives: To explore the role of central pulsatile hemodynamics in the pathogenesis of cerebral white matter hyperintensities (WMHs) in young migraine patients.

Methods: Sixty patients with migraine, 20 to 50 years old, without overt vascular risk factors and 30 demographically-matched healthy controls were recruited in this prospective study. Cerebral WMHs volume was determined by T1-weighted magnetic resonance imaging with CUBE-fluid-attenuated-inversion-recovery sequences. Central systolic blood pressure (cSBP), carotid-femoral pulse wave velocity (cf-PWV), and carotid augmentation index (AI) were measured by applanation tonometry. Carotid pulsatility index (CPI) was derived by Doppler ultrasound carotid artery flow analysis.

Results: Compared to controls, migraine patients had a higher WMHs frequency (OR, 2.75; P = 0.04) and greater WMHs volume (mean volume, 0.174 vs 0.049, cm³, P = 0.04). Multivariable regression analysis showed that WMHs volume in migraine patients was positively associated with cSBP (P = 0.04) and cf-PWV (P < 0.001), but negatively associated with CPI (P = 0.04) after controlling for potential confounding factors. The interaction effects observed indicated that the influence of cf-PWV (P < 0.001) and cSBP (P = 0.03) on WMHs formation was greater for the lower-CPI subgroup of migraine patients. WMHs volume in migraine patients increased with decreasing CPI and with increasing cSBP or cf-PWV levels.

Conclusion: WMHs are more common in patients with migraine than in healthy controls. Central pulsatile insults in the presence of low intracranial artery resistance may predispose patients with migraine to WMHs formation.

Disclosure of Interest: None Declared

Comorbidity of Primary Headaches

EP-02-009

A DIARY STUDY IN VISUAL SNOW – SYMPTOM VARIATION OVER 30 DAYS

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2Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Objectives: Patients with Visual Snow suffer a pan-field, dynamic visual disturbance consisting of tiny flickering dots resembling the “static” of a badly tuned analogue television. The symptoms are continuous and can persist over years. Proposed diagnostic criteria require at least two additional visual symptoms from: palinopsia, entoptic phenomena, photophobia and nyctalopia (1). In this study we wanted to monitor the symptoms over time of Visual Snow as well as to further characterize their variation in certain lighting conditions.

Methods: A questionnaire was prepared in collaboration with the patient group Eye-on-Vision and sent to subjects who had expressed an interest in research by directly contacting our study team. Patients were required to fill in a daily symptom scale for 30 days, scoring seven different parameters aimed at describing the static. These were static density, speed, colour, size, level of visibility on different surfaces, time variation during the day and level of distraction caused. Patients were also asked to give a
one-off score from 1 to 7 to six different lighting conditions (outdoor sunny, outdoor cloudy, outdoor rainy, outdoor night-time, indoor, fluorescent) to indicate their effect on visual symptoms. The study was approved by the KCL Research Ethics Panel. Data were analysed using non-parametric methods.

Table: Average of main values of static parameters across all patients:

<table>
<thead>
<tr>
<th>Analyzed parameter</th>
<th>Score range</th>
<th>Median</th>
<th>Interquartile Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Static Density</td>
<td>0–6</td>
<td>3</td>
<td>2–4</td>
</tr>
<tr>
<td>Static Speed</td>
<td>0–4</td>
<td>3</td>
<td>2–4</td>
</tr>
<tr>
<td>Surface dependence</td>
<td>0–4</td>
<td>4</td>
<td>3–4</td>
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<tr>
<td>Distraction</td>
<td>0–4</td>
<td>3</td>
<td>3–4</td>
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<tr>
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<tr>
<td>Size</td>
<td>0–5</td>
<td>2</td>
<td>1–2</td>
</tr>
</tbody>
</table>

Results: Ninety patients returned the 30-day diary. Table I shows the main values of static parameters across all patients. Of the different lighting conditions examined, outdoor sunny environments were considered as having the best effect on symptoms (median = 5, IQR = 3–6), while night-time was given the lowest scores (1, 1–3). A related-samples Friedman’s ANOVA showed that the difference between scores was significant (p < 0.001). Spearman rank correlation analysis demonstrated the level of distraction that the static caused was found to correlate at a significant level with the size (rs = 0.34, p < 0.001) and density (rs = 0.36, p < 0.001) of the static itself.

Conclusion: Visual Snow is a highly disabling syndrome, for which there is no clearly identified treatment. It presents a relatively constant symptomatology in most subjects and it appears to be worsened by certain lighting conditions, particularly in the context of low natural light.

References

Disclosure of Interest: F. Puledda: None Declared, F. Greenwood: None Declared, T. Lau: None Declared, C. Schankin: None Declared, P. Goadsby Conflict with: Dr. Goadsby reports grants and personal fees from Allergan, Amgen, and Eli-Lilly and Company; and personal fees from Akita Biomedical, Alder Biopharmaceuticals, Autonomic Technologies Inc, Avanir Pharma, Cipla Ltd, Colucid Pharmaceuticals, Ltd, Dr Reddy’s Laboratories, eNeura, Electrocore LLC, Novartis, Pfizer Inc, Promius Pharma, Quest Diagnostics, Scion, Teva Pharmaceuticals, Trigemina Inc., Scion; and personal fees from MedicoLegal work, Journal Watch, Up-to-Date, Oxford University Press; and in addition, Dr. Goadsby has a patent Magnetic stimulation for headache pending assigned to eNeura.

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and frequency of pain, and impact on quality of life) was significantly different comparing OSA or sOSA and non-OSA groups. Even the OSA women's parameters of sleep study were not different comparing headache or morning headache and non-headache subgroup.

**Conclusion:** There were no differences in primary headaches frequency or headache characteristics among women with or without obstructive sleep apnea OSA.

**Disclosure of Interest:** None Declared

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**Comorbidity of Primary Headaches**

**EP-02-011**

**BURDEN OF HEADACHE DISORDERS AT ATTENTION DEFICIT HYPERACTIVITY DIAGNOSED CHILDREN AND THEIR PARENTS**

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**Objectives:** Attention deficit and hyperactivity disorder (ADHD) is common among children and adolescents with a worldwide prevalence of 5.3% and is considered to be an important factor leading to poor academic performance and poor quality of life. Headache is one of the most common chronic disorder with a prevalence of 10–20% in the school-age population and often accompanied by severe impairments, including low quality of life, low emotional function, school absenteeism, and poor academic performance. The prevalence of ADHD among children with headache are still contradictory and the prevalence of headache disorders in ADHD is not well studied. The clinical study aimed to evaluate burden of primary headache among ADHD children and parents and results compared age and sex matched healthy controls.

**Methods:** The study comprised children and adolescents aged 6–18 years with ADHD according to DSM-5, healthy controls and parents of these 2 groups were referred by the child and adolescent psychiatrist for neurological assessment to the neurologist at Mersin University Medical Faculty during drug navy period for patients. Both the interview and the questionnaire included questions regarding demographics, patients' medical history, headaches characteristics, and other medical history obtained by experienced neurologists and psychiatrists. Headache diagnosis based to ICHD-3 beta criteria.

**Results:** The study group comprised of 117 ADHD children and 111 age and sex matched healthy controls. Median of age was 11 years (6–18) in ADHD group and 12 (8–16) years for healthy controls. Headache was common for both groups and was significantly more common in ADHD patients (59.0% & 37.8%) (p = 0.002). While episodic and chronic migraine found significantly common in ADHD children, frequent episodic TTH was common in control group. The most frequent diagnosis was episodic migraine for ADHD and episodic TTH for control group. The overall prevalence of migraine for ADHD group estimated 26.5%, and 9.9% for healthy controls.

We analyzed characteristics of mothers of ADHD (ADHD-M) and healthy controls mothers (HC-M) headache. Primary headache disorders was significantly more common for ADHD-M (90.5% & 65.6%). While migraine, particularly chronic migraine was more common in ADHD-M, episodic tension type headache was more common at health controls mothers (HC-M). The overall prevalence of migraine for ADHD-Ms was 72% and estimated 42.9% for HC-Ms. The analyses of the fathers of study group performed. The prevalence of headache was similar at two groups. The most common headache disorder was infrequent TTH at ADHD fathers and frequent TTH at control groups' fathers. The overall prevalence of migraine for ADHD fathers estimated 21% and was %13.7 for healthy controls fathers. Chronic migraine was significantly more common at ADHD fathers.

**Conclusion:** We observed headache is more prevalent in ADHD children than controls and also ADHD-mothers have more common headache. Migraine and chronic migraine is more prevalent in them, while tension type headache was more common in mothers of healthy controls. Knowledge of common biologic systems involved would not only help physicians provide better care for their patients but may also provide some clues regarding sources of heterogeneity of ADHD.

**Disclosure of Interest:** None Declared

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Genetics and Biomarkers of Headache Disorders

EP-02-012

Reproducible activation of the PAC1-receptor via maxadilan as target-engagement model in humans

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Objectives: Maxadilan is a potent vasodilator peptide, isolated from the sand fly Lutzomyia longipalpis, which activates the mammalian PAC1 receptor, a promising target for migraine therapy. Therefore, maxadilan is suggested as a target-engagement tool to study PAC1 antagonists. The objectives of our study were: (1) to determine, as a first in human study, the dose response, safety and time course of the dermal blood flow (DBF) after intradermal (ID) injections of maxadilan in the human forearm, and (2) to assess the inter-arm and inter-period reproducibility of this response.

Methods: This was a single-center, open-label, placebo-controlled study in healthy subjects (age 18 to 45 year). The study consisted of 2 parts: dose-finding (n = 10) and reproducibility (n = 10). Study visits started with acclimatization for 30 minutes in a temperature controlled room before baseline. Laser Doppler Imaging (LDI) scans were performed with a PIMIII Laser Doppler Imager (Perimed®). A rubber O-ring was used to delineate the region of interest (ROI) around the injection site. The wheal and flare response was assessed using: (1) LDI, (2) measurement of the largest and smallest diameter with a ruler, and (3) photography-based software (Java®). Maxadilan was injected ID in the volar surface of the forearm and measurements were performed every 10 minutes for 1 hour and at 90, 120 and 180 minutes post-injection. To assess reproducibility, the concordance correlation coefficient (CCC), Bradley-Blackwood test (BB-test) and sample size calculations (SSC) were used.

Table:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Expressed as</th>
<th>Test-Retest</th>
<th>CCC</th>
<th>SSC 50%</th>
<th>BB-test</th>
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<tr>
<td>DBF in the ROI measured with LDI</td>
<td>AUC0–180 (PU*min)</td>
<td>L-R V1 / V2</td>
<td>0.88 / 0.75</td>
<td>4 / 6</td>
<td>0.4 / 0.8</td>
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<td></td>
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<td>V1-V2 L / R</td>
<td>0.77 / 0.71</td>
<td>6 / 7</td>
<td>0.9 / 0.4</td>
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<td></td>
<td>T60 (PU)</td>
<td>L-R V1 / V2</td>
<td>0.9 / 0.8</td>
<td>4 / 6</td>
<td>0.8 / 0.2</td>
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<td></td>
<td></td>
<td>V1-V2 L / R</td>
<td>0.69 / 0.59</td>
<td>8 / 9</td>
<td>0.6 / 0.5</td>
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<td>Flare area measured with LDI</td>
<td>AUC0–180 (mm²*min)</td>
<td>L-R V1 / V2</td>
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<td>12 / 14</td>
<td>0.2 / 0.9</td>
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<td></td>
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<td>V1-V2 L / R</td>
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<td>21 / 16</td>
<td>0.05 / 0.3</td>
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<td>Flare area measured with ruler</td>
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<td>L-R V1 / V2</td>
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<td>0.1 / 0.1</td>
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<td>V1-V2 L / R</td>
<td>0.06 / −0.28</td>
<td>18 / 27</td>
<td>0.09 / 0.1</td>
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<tr>
<td>Flare area measured with photography</td>
<td>AUC0–180 (mm²*min)</td>
<td>L-R V1 / V2</td>
<td>−0.21 / 0.29</td>
<td>8 / 16</td>
<td>0.02 / 0.01</td>
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<tr>
<td></td>
<td></td>
<td>V1-V2 L / R</td>
<td>0.029 / −0.09</td>
<td>11 / 31</td>
<td>0.9 / &lt;0.001</td>
</tr>
</tbody>
</table>

L: Left, R: Right, V1: visit 1, V2: visit 2. BB-test: p-value < 0.05 indicates evidence of unequal means or unequal variances between 2 groups.

Conclusion: ID injections of maxadilan induce reproducible changes in DBF over time and between arms when measured with LDI in the ROI. This study provides an appealing new target-engagement biomarker for the study of PAC1 receptor antagonists in early clinical development studies.

Disclosure of Interest: None Declared
Elevated circulating endothelial-associated microRNAs in migraine patients

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Objectives: Evidence of vascular dysfunction in migraine is increasing. MicroRNAs (miRs) have emerged as important regulators related to vascular endothelial functions. This study was to explore whether endothelial-associated miRs alterations occurred in migraine patients.

Methods: Thirty patients with migraine, aged 20 to 50 years old, without overt vascular risk factors and 30 sex- and age-matched healthy controls were recruited. Abundance of four endothelial-associated miRs (miR-155, miR-126, miR-21, Let-7g) were quantified by quantitative real-time PCR and expressed by fold changes (2-ΔΔct) in relative to the average miR levels in the control group. The concentrations of three circulating biochemical factors implicated in the endothelial functions were measured by enzyme-linked immunosorbent assay. The miRs levels were correlated with headache profiles as well as syncope in migraine patients.

Results: Compared to controls, migraine patients were associated with upregulated expression of miR-155 (6.17-fold, P = 0.018), miR-126 (6.17-fold, P = 0.013), Let-7g (7.37-fold, P = 0.005) and plasminogen activator inhibitor-1 level (P = 0.015). Migraine patients with all 6 migrainous symptoms (unilateral, throbbing, aggravation by physical activities, moderate or severe intensity, nausea/vomiting, photophobia and phonophobia) had the higher expression of miR-155 (P = 0.009), miR-126 (P = 0.008), miR-126 (P = 0.046) and Let-7g (P = 0.028) than those without. Increased miR-155 (P = 0.041) and miR-126 (P = 0.041) were associated with numbers of syncope in the past year in migraine patients.

Conclusion: Circulating levels of endothelial-associated miRs are significantly increased in migraine patients, indicating a potential interplay between endothelial dysfunction and migraine pathogenesis.

Disclosure of Interest: None Declared

Increased thrombophilic predisposition in premenopausal females with chronic migraine

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Objectives: Migraine is associated with an increased risk for cardiovascular diseases (CVD), especially in women aged less than 45 years. Although the pathophysiological mechanisms linking migraine and CVD are still unclear, coagulation abnormalities have been regarded as a logical link. However, the majority of the studies investigating the procoagulant status of migraneurs focused on the presence of inherited thrombophilic factors with inconsistent results that, together with the high costs of laboratory testing, precludes a universal screening in favour of a selective history-based one. Therefore, the present study was designed to explore the thrombophilic potential of patients with migraine using a novel standardized assay for globally screening the patient thrombophilic state in a large, unselected, carefully clinically characterized population of episodic and chronic migraneurs.

Methods: Thrombophilic predisposition was evaluated in a cohort of 550 migraneurs (448 females, 102 males) using an easy-to-run and commercially available activated protein C (APC)-dependent thrombin generation assay [HemosIL ThromboPath (ThP)]. The assay is characterized by an overall sensitivity of 95% to all protein C pathway abnormalities (either acquired or inherited) and has been proposed as a potential screening tool in thrombophilia assessment. Association analysis of APC function with migraine clinical features was also investigated.

Results: APC function was impaired in 17% of migraneurs compared with 9% of otherwise healthy individuals (p = 0.037). Overall, ThromboPath correlated with age (Rs = 0.132, p = 0.002), female sex (Chi-square = 4.3,
photophobia and hemiparesis. FHM symptomology possibly affecting the individual pro-coagulant status. None of the tested variables associated with APC function in the female cohort. Conversely, pre-menopausal status (OR = 2.86, 95%CI: 1.58–5.18, p = 0.0005) and oral contraceptive/hormone replacement treatment (OR = 3.74, 95%CI: 1.28–10.9, p = 0.015) were associated with impaired APC function in the female cohort, independently of major cardiovascular risk factors, or migraine features.

Conclusion: Premenopausal females with near-daily chronic migraine (>25 day/months) revealed a thrombo-philic predisposition, possibly due to impaired APC function, which might increase cardiovascular risk. Accordingly, we suggest a scrupulous attention to concomitant ischemic risk conditions and an accurate choice of acute/prophylactic migraine treatments in these patients. ThromboPath, for its part, might represent a first-step screening assay to investigate the thrombophilic potential in at risk migraineurs, providing the opportunity to rationalize the use of expensive individual assays.

Disclosure of Interest: P. Barbanti: None Declared, P. Ferroni: None Declared, C. Aurilia: None Declared, G. Egeo: None Declared, L. Fofi: None Declared, F. La Farina: None Declared, M. G. Valente: None Declared, L. De Marchis: None Declared, A. Spila: None Declared, R. Palmirota: None Declared, D. Della Morte: None Declared, F. Guadagni Conflict with: Partially supported R. Palmirotta: None Declared, D. Della Morte: None Declared, L. De Marchis: None Declared, A. Spila: None Declared, R. Palmirota: None Declared, F. Guadagni Conflict with: Partially supported

Genetics and Biomarkers of Headache Disorders

EP-02-015
Identification of Novel FHM Genes by Whole Exome Sequencing

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Objectives: Familial Hemiplegic Migraine (FHM) is an autosomal dominant neurological condition with attacks characterised by severe head pain, nausea, aura, phono/photophobia and hemiparesis. FHM symptomatology commonly overlaps with a number of similar neurological disorders, diagnostic success rates are low (<25%), and our understanding of the pathophysiological consequence of the geno-phenotype associations limited. The disease is considered to be a channelopathy, with mutations in several ion channel genes (CACNA1A, ATP1A2 and SCN1A) shown to be causative in large FHM family studies. In an effort to identify novel mutations causing FHM, we are performing Whole Exome Sequencing (WES) in a cohort (n = 209) of clinically suspected and genetically undiagnosed (ie negative for the known FHM1, 2 and 3 genes) FHM patients. Variant prioritisation analysis and in-silico prediction methods are being used to identify novel candidate mutations for further characterisation and functional assessment.

Methods: WES of patient DNA samples has been performed using the Ion ProtonTM platform. Ion AmpliSeq™ Exome RDY – OT2 kits were used for exome capture and preparation and libraries quantified with Agilent High Sensitivity DNA kits. Prepared libraries were loaded on chips using Ion PI™ Hi-Q™ Chef reagents and the Ion Chef™ for 200 bp read NGS. WES data was analysed using an in-house bioinformatic pipeline. Briefly, first pass analysis removed common variants and functionally insignificant variants based on minor allele frequencies (<1%) and predictive functional scores (SIFT <0.05; Polyphen >0.80). Second pass analysis removed hotspot variants based on comparisons with unrelated controls. Benign variants reported in ClinVar were also removed. Priorities were placed on novel variants, indels and frameshift mutations. Third pass analysis classified variants based on their gene ontology into groups including vasogenic; neural and CNS; ion channels and metals; and hormones and the immune system. Short-listed variants were assessed based on IGV observation and read coverage with likely false positives (coverage <20x) removed. The remaining variants were checked against frequencies reported in the ExAC and gnomAD databases. Given the variations in phenotypic presentation and the polygenic nature of FHM, each sample was analysed in three ways: independently, according to symptomology and as a cohort. All candidate gene mutations on n = 23 cases to date, have been validated using Sanger Sequencing.

Results: Data was classified according to gene mechanism and FHM symptoms and reaffirmed the causative role of previously associated pathways: namely action potential homeostasis regulated by ion channels and enzyme production pathways indirectly involving mitochondrial influence. Independent analysis has to date identified 32 variants previously implicated in neurological disorders, including spinocerebellar ataxia, epilepsy and spastic paraplegia. Symptomology analysis has to date identified a plausible mutation in a physiologically relevant gene defined by amino acid changing, disease causing and low allele frequency in silico prediction status. Cohort analysis has to
date identified an additional novel causative candidate with a potential disease causing amino acid changing variant in a transmembrane receptor regulatory protein.

**Conclusion:** These data confirm the power of WES, variant prioritization strategies and in-silico prediction methods to identify novel causative mutations for FHM. The identified mutations will be validated for pathogenicity using a two-staged functional approach using *in vitro* models. Further advances in these efforts will provide improved FHM diagnostics by substantially increasing the rate of diagnostic success toward improved patient outcomes.

**Disclosure of Interest:** None Declared

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**Genetics and Biomarkers of Headache Disorders**

**EP-02-016**

**Serum Interleukin-6 and Interleukin-18 levels in migraineurs**

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²Division of Neurology, Matsue Medical Center, Matsue, Japan

**Objectives:** There are some evidences suggesting that an immunologic dysfunction has been hypothesized to be involved in migraine pathogenesis. It is not yet clearly understood what immunological mechanism leadings to migraine headaches. The aim of this study was to investigate the serum Interleukin-6 (IL-6) and Interleukin-18 (IL-18) levels in patients with migraine.

**Methods:** IL-6 and IL-18 levels in serum were measured in 32 patients with migraine with aura (MA; 12 males and 20 females, average age: 32.8 years), 68 patients with migraine without aura (MO; 15 males and 53 females, average age: 37.3 years) and 15 patients with tension-type headache (TH; 4 males and 11 females, average age: 55.3 years). Thirty one normal healthy volunteers composed the control group (CTL; 11 males and 20 females, average age 37.9 years). IL-6 and IL-18 levels in serum were determined respectively using chemiluminescence enzyme immunoassay and latex immunology turbidimetric method. Comparisons among MA, MO, TH and CTL groups were assessed by the analysis of multivariate statistics. Acute phase (AP) and intermittent phase (IP) cases were defined respectively as the day of migraine attack and the other days after migraine attack and compared by the analysis of multivariate statistics. And difference between with medication overuse headache (with-MOH) and without MOH (without-MOH) groups were analyzed.

**Results:** Mean IL-6 levels in serum were 9.8 pg/mL in the patients with MA, 5.2 pg/mL in the patients with MO, 1.3 pg/mL in the patients with TH and 5.6 pg/mL in CTL. IL-6 level in the patients with MA was significantly higher than in the MO, TH and CTL (\(p = 0.0385\)). Mean IL-18 levels in serum were 185.7 pg/mL in the patients with MA, 227.5 pg/mL in the patients with MO, 204.9 pg/mL in the patients with TH and 246.8 pg/mL in CTL. IL-18 level in MA, MO, TH and CTL was not significantly different. IL-6 levels at the AP in the patients with MA were significantly higher than them at the IP (\(p = 0.0185\)). IL-6 level in AP/IP with MO and TH was not significantly different. IL-18 level in AP/IP with MA, MO and TH was not significantly different. IL-6 and IL-18 levels at the with-MOH in the patients with MA were significantly higher than them at the without-MOH (\(p = 0.0185, 0.0086\)). IL-6 and IL-18 level in with-MOH/without-MOH with MO and TH was not significantly different.

**Conclusion:** Some cytokines have recently been shown to have pain-mediating functions, in addition to their known immunological functions. Our results suggest that the immunological system relevant to IL-6 is involved in the acute migraine pathogenesis. The chronicity and severity of the migraine pathogenes were associated with not only IL-6 but also IL-18.

**Disclosure of Interest:** None Declared

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**Genetics and Biomarkers of Headache Disorders**

**EP-02-017**

**RNA-Sequencing of Trigeminal Ganglia and Dorsal Root Ganglia gives insight in transcriptomic differences between the trigeminal and spinal system.**

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²Institute of Biological Psychiatry, Mental Health Center Sc. Hans, University of Copenhagen, Roskilde, Denmark

**Objectives:** The trigeminal ganglia (TG) and the dorsal root ganglia (DRG) are homologous handling sensory input involved in nociception, where the TG subserves the head and the DRG subserves the rest of the body. Even though they are homologous, we expect differences due to the fact that several signaling substances (such as
nitroglycerin) cause a headache but are not leading to pain in the rest of the body. To date, very little is known about the differences between the two systems. Insight into the genetic differences between TG and DRG will help to unravel the mechanisms of pain specific to the head or the rest of the body. We therefore aim to reveal the basal gene expression levels in TG and DRG and furthermore, detect genes that show differential expression between TG and DRG.

**Methods:** We RNA-Sequenced the TG and DRG of six naïve rats (Wistar Han) using the Illumina HiSeq2500 technology. After alignment with STAR and read quantification using HTSeq, we detected differentially expressed (DE) genes by using DESeq2, edgeR and limma. Only genes that were detected to be DE in all three methods with a false-discovery rate < 0.05 were regarded to be DE. Post hoc/subsequent filtering was applied based on the coefficient of variation within each tissue, the expression level, and fold change. Detected DE genes were further investigated using pathway analysis (GOSeq) and functional annotation.

**Results:** Using strong filtering ([log Fold Change] > 2 and log2 expression > 5) we detected 64 genes with higher and 55 genes with lower expression in TG than in DRG. The most highly DE gene with higher expression in TG was Nipal4 and several of the DE genes lower expressed in TG were Hox genes. Pathway analysis of the DE genes higher expressed in TG showed an overrepresentation of phospholipase activity (Padj = 0.0047) and genes lower expressed in TG showed an association with tyrosine metabolism (Padj = 0.0142) and phenylalanine metabolism (Padj = 0.0035). Several genes were expressed in only one of the tissues, such as Gabra6 and Gabrd in TG (neurotransmitters in the brain) and Hox genes in DRG. Most pain-associated genes, based on previous studies, were moderately to highly expressed in one or both tissues.

**Conclusion:** We performed a comprehensive analysis of the transcriptomic profiles of TG (trigeminal system) and DRG (spinal system). We used a hypothesis-free approach to detect transcriptomic differences between the trigeminal and spinal system at a first order level, and homed in on the expression profiles of headache-related genes. This study is highly relevant for future pain-related studies.

**Disclosure of Interest:** None Declared
Conclusion: Multiple factors influence olfaction including anatomic, genetic, and sensory processing differences. While many patients with migraine can develop osmophobia or experience migraine triggered by odor, patients with migraine are not very good at predicting their olfactory abilities during migraine. This phenomenon of persons with a sense of hyperacute odor detection having normal or decreased olfactory acuity has been seen in other conditions, such as pregnancy. Specifically patients with EM who predict improved smell during attacks are probably incorrect. CM subjects reporting increased acuity were more likely to be correct but most are not. Changes in autonomic function, limbic system activation or alterations in higher order sensory processing may influence olfactory acuity in migraine.

Disclosure of Interest: M. Marmura Conflict with: Teva, eNeura, Conflict with: Supernus, Teva

Genetics and Biomarkers of Headache Disorders

EP-02-019

S100B protein, a marker of trigemino-vascular system glial activation, is not increased in chronic migraine

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²Neurology, Univ. Hospital Marqués de Valdecilla and IDIVAL, Santander, Spain

Objectives: S100B protein is a marker of the activation of glial cells. Theoretically, S100B protein could be released in case of trigemino-vascular system (TVS) activation and contribute to sensitization of pain pathways in chronic migraine (CM). S100B levels have been studied in migraine with contradictory results. The aim of this study was to analyze serum levels of S100B protein as a possible biomarker of the glial TVS activation in CM.

Methods: We determined by ELISA and in peripheral blood samples interictal S100B levels in 48 CM patients. As control groups S100B levels were also measured in 20 patients with episodic migraine (EP), 22 with cluster headache (CH) and in 29 matched healthy volunteers (HV) with no headache history.

Results: S100B levels in CM patients (21.9 ± 9.9 pg/mL) were not significantly different when compared to those of EM patients (26.7 ± 26.4 pg/mL), CH patients (22.4 ± 7.8 pg/mL) or HV (20.6 ± 8.3 pg/mL).

Conclusion: In contrast to other pain-producing peptides, such as CGRP, interictal, peripheral serum level of S100B protein does not seem to be a useful biomarker of glial TVS activation in CM.

(This work was supported by the PI14/0020FISSS grant (Fondos Feder, ISCIII, Ministry of Economy, Spain)

Disclosure of Interest: None Declared

Headache and Gender

EP-02-020

Headache in pregnant women at the emergency service: etiologies, predictors and usefulness of the ICHD 3B criteria.

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Objectives: To determine the main etiologies, predictors and usefulness of ICHD 3 B criteria to differentiate primary from non -primary headaches in pregnant women at the ER.

Methods: Cross-sectional study comparing the prevalence of ICHD 3 B fulfilled criteria, associated symptoms, history of headache and demographic features between primary vs non primary headaches.

Table:

<table>
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<th>Variable</th>
<th>OR</th>
<th>CI 95%</th>
<th>p</th>
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<tr>
<td>Migraine history</td>
<td>2.65</td>
<td>1.18–5.94</td>
<td>0.013</td>
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<tr>
<td>Similar episodes</td>
<td>6.4</td>
<td>2.78–14.0</td>
<td>&lt;0.001</td>
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<td>ICHD 3B criteria probable</td>
<td>12.5</td>
<td>3.5–50.8</td>
<td>&lt;0.001</td>
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<td>ICHD 3 B criteria Definitive</td>
<td>102</td>
<td>13.1–802</td>
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<td>Osmophobia</td>
<td>NS</td>
<td>NS</td>
<td>0.10</td>
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<tr>
<td>Phosphenes</td>
<td>4.2</td>
<td>1.5–11.68</td>
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<td>Epigastralgia</td>
<td>4.83</td>
<td>1.08–21.62</td>
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</table>

Results: Headache was responsible for 152 (5.2%) out of 2952 admissions. Median age was 25.4 years, IQR (25%–75%): 23–28, range 13–43. Primary, non-primary and unclassified headaches were 68.2%, 26.2% and 5.6% respectively. Migraine and headache associated to hypertensive disorders were the most frequent etiologies for primary and non-primary groups 91.6% and 31.4% respectively.

Factors associated to primary headaches were ICHD 3B fulfilled criteria OR:102, (IC95%13.1–802) p <0.001, history of migraine OR2.85 (IC 95% 1.18–5.94) p:0.013, history of similar episodes OR6.4 (IC 95% 2.78–14.0) p <0.001 and description of phosphenes OR:4.2 (IC 95% 1.5–11.68) p:0.02.

Factors associated to non-primary etiologies were fever (OR12.8 IC 95%1,38–119) p:0.016, median blood pressure over 106.6 (OR:2.6 IC 95%1.7–3.5) p:0.03

Conclusion: ICHD 3 B criteria could be useful to differentiate primary from non-primary headaches. This

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Methods: Participants were 750 individuals with migraine being associated with severity of a migraine. Possible “triggers” of migraine onset as opposed to pared in terms of which risk factors were identified as person analyses. These two analytic techniques were compared to identify severity that is tailored for intensive within-person analyses. These two analytic techniques were compared in terms of which risk factors were identified as possible “triggers” of migraine onset as opposed to being associated with severity of a migraine.

Objectives: The present investigation compares the strengths and limitations of two distinct analytic approaches to understand both incidence and severity patterns within individuals in relation to daily exposure to a wide spectrum of risk factors that included emotions, sleep qualities, environmental and weather, lifestyle, and diet. The two approaches used were Cox regression to define incidence and a form of hierarchical linear modeling to identify severity that is tailored for intensive within-person analyses. These two analytic techniques were compared in terms of which risk factors were identified as possible “triggers” of migraine onset as opposed to being associated with severity of a migraine.

Results: Overall, a greater number of risk factors were associated with severity of migraine headaches (MMTA) than incidence of migraines (Cox regression). However, Cox regression also detected unique triggers that were associated only with incidence (not severity) of migraine attacks. Consistent with past evidence, the profile of risk factors that were associated with incidence and severity of migraines varied considerably among patients, demonstrating that comprehensive clinical research on migraines requires analytics at the N = 1 level.

Conclusion: Cox regression of migraine incidence and MMTA of migraine severity each provide unique insights regarding within-person patterns and correlates of migraine attacks. The power to detect associations may be greater for MMTA by virtue of the continuous pain severity outcome rather than the binomial outcome used in Cox regression. However, the fact that Cox regression detected unique risk factors for occurrence of migraine headaches suggests that different risk factors are associated with occurrence of migraine attacks versus severity of migraine pain.


Headache Classification

EP-02-022

Individual Differences in the Relation of Migraine and Menstruation: Examining the ICHD-3-beta Time Window

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2Curelator, Inc., Cambridge
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4Barts and The London School of Medicine and Dentistry, London, United Kingdom

Objectives: Though the role of menses as a migraine trigger is well-known, most studies have focused on group level analyses that do not assess within person associations between menses and migraine. Herein, we use individual daily diary data to explore both inter- and
intra-individual differences in the perimenstrual occurrence of migraine.

Methods: Individuals with migraine were identified by clinician referral or via the internet and registered to use a novel digital platform (Curelator HeadacheTM). Participants completed baseline questionnaires and then entered daily data on headache occurrence, symptoms and potential trigger factors. Migraine days were defined by applying the ICHD-3beta (b) case definition to reported and potential trigger factors. Migraine days were defined by comparing the relative odds of having a migraine on PMD in the ICHD-3b time window to days outside the window (odds ratios [OR] > 1 indicate increased risk). Models quantified each woman’s risk by comparing the relative odds of having a migraine on PMD in the ICHD-3b time window to days outside the window (odds ratios [OR] > 1 indicate increased risk).

Results: Among 82 menstruating females, the age range was 15 to 53 years (mean = 34.4 years old). Women reported on a median of 159.5 days, 6 menstrual cycles, and 47.5 migraine days. Almost one-fifth of the sample (18.3%) used contraceptive pills. Women varied substantially in the association of migraine with menses. We next classified individuals into three migraine risk categories based on their individual OR (“Low” OR < 1: n = 28, 34.2%; “Moderate” 1 < OR < 3.47 : n = 48, 58.4%; “High” OR ≥ 3.47: n = 6, 7.3%). Importantly, there were individual differences in migraine risk within each of the three broad risk classifications. Lastly, n of 1 individual plots showed substantial individual differences in relation of migraine to menstruation.

Conclusion: This study shows that even within broader risk groups, there is still substantial individual variability in PMA risk based on the ICHD-3b time window. A limitation of this study is that it does not consider alternative PMA time windows. It is plausible that expanding the PMA time window beyond 5 days could provide further insights into inter- and intra-individual differences in migraine related to hormonal changes. The current study suggests a limitation in applying, aggregate, one-size-fits-all assumptions to all patients.


Headache Classification

EP-02-023

Evaluation of the Identify Chronic Migraine (ID-CM) screener in an accountable care organization

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Objectives: The objective of this analysis was to assess the sensitivity and specificity of the Identify Chronic Migraine (ID-CM) screener using a physician-administered Semi-structured Diagnostic Interview (SDI) as the gold standard for CM diagnosis.

Methods: Eligible patients were enrolled in an accountable care organization, had at least 12 months of complete medical and pharmacy claims data, and had at least 1 medical claim with an ICD-9/10 code for migraine (346.xx/G43.xxx) in the 12 months prior to the study enrollment date. The ID-CM was then administered by e-mail, in person, or over the telephone to all eligible patients. The ID-CM is based primarily on 30-day patient recall and consists of 12 questions that assess headache frequency, headache symptoms, medication use for headache, interference with activities due to headache, and planning disruption due to headache. Additionally, a SDI was administered by telephone to a subset of eligible patients by a physician trained to reliably administer the tool. The SDI assesses headache symptoms, frequency, disability, and medication use based on 30-day and 90-day patient
Recall. The SDI is scored in two ways: (1) A computer-based algorithmic diagnosis based on ICHD-3β criteria for migraine and modified Silberstein-Lipton criteria for CM; (2) A physician-based diagnosis taking into account the above criteria and clinical judgment. In the event that the algorithmic and physician diagnosis disagreed, a headache expert adjudicated the disagreement and assigned a final diagnosis of CM or non-CM. Although all included patients were administered the ID-CM, only those that were administered the SDI were included in order to have a gold standard with which to compare the ID-CM results. Additionally, migraine patients with a previous CM diagnosis based on an ICD-9/10 code (346.7x/G43.7xx) were excluded. Two-by-two tables that compared ID-CM and SDI classifications of CM status were used to assess sensitivity and specificity of the ID-CM.

Results: The analysis of the ID-CM included 120 patients with a migraine diagnosis who completed the ID-CM and the SDI. Based on the ID-CM findings, 61 (51%) met criteria for CM while 59 (49%) did not meet criteria for CM. Using the SDI as the diagnostic gold standard for CM, the ID-CM had a sensitivity of 73% (55/75) and a specificity of 87% (39/45).

Conclusion: An accurate diagnosis of CM is required in order to optimize treatment for the condition. Based on the SDI as the gold standard for CM diagnosis, the ID-CM demonstrated acceptable sensitivity and good specificity in determining CM status. The results support previous findings on the validity of the ID-CM screener, and the real-world utility of the ID-CM as a simple yet accurate tool to identify CM patients.

Disclosure of Interest: J. Yu Conflict with: Allergan, Conflict with: Allergan, J. Pavlovic Conflict with: Honoraria from Allergan and the American Headache Society, S. Silverstein Conflict with: His employer receives research support from Allergan, Inc.; Amgen; Cumberland Pharmaceuticals, Inc.; ElectroCore Medical, Inc.; Labrys Biologics; Eli Lilly and Company; Merz Pharmaceuticals; and Troy Healthcare Consultant; Alder Biopharmaceuticals; Allergan, Inc.; Amgen; Avanir Pharmaceuticals, Inc.; eNeura; ElectroCore Medical, LLC; Labrys Biologics; Medscape, LLC; Medtronic, Inc.; NeuraLieve; NINDS; Pfizer, Inc.; and Teva Pharmaceuticals, M. Reed Conflict with: Managing Director of Vedanta Research, which has received research funding from Allergan, Amgen, CoLucid, Dr. Reddy’s Laboratories, Enzo Pharmaceuticals, GlaxoSmithKline, Merck & Co., Inc., NuPathes, Novartis, and Ortho-McNeil, via grants to the National Headache Foundation. Vedanta Research has received funding directly from Allergan for work on the CaMEO Study. S. Kawahara Conflict with: Steve Kawahara, PharmD, in the past 12 months, has served as a consultant and received consulting fees from DaVita medical Group., R. Cowan: None Declared, F. Dabbous: None Declared, K. Campbell Conflict with: Allergan, Conflict with: Allergan, R. Pulicharam Conflict with: served as a consultant and received consulting fees from DaVita medical Group., H. N. Viswanathan: None Declared, R. Lipton Conflict with: eNeura Therapeutics, Conflict with: NIH, Conflict with: Alder, Allergan, American Headache Society, Amgen, Autonomic Technologies, Avanir, Biohaven Inc, Boston Scientific, Colucid, Dr. Reddy’s, Electrocore, Eli Lilly, eNeura Therapeutics, Glaxo, Merck, GlaxoSmithKlein, Pfizer, Teva, Vedanta, Conflict with: Served on the editorial board of Neurology and as senior advisor to Headache. Received support from the Migraine Research Foundation and the National Headache Foundation. He has reviewed for the NIA and NINDS. Receives royalties from Wolff’s Headache, 8th Edition, Oxford Press University, 2009 and Informa

Headache Classification

EP-02-024

Prolonged migraine aura: new insights from a prospective diary-aided study.

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Objectives: To characterize the phenotype of prolonged aura (PA), i.e. an aura that includes at least one symptoms lasting for >1 hr

Methods: We recruited 224 consecutive patients affected by migraine aura attending the Headache Centers of Pavia and Trondheim. Patients were asked to describe each aura symptom (AS) [visual symptom (VS), sensory symptoms (SS) and dysphasic symptoms (DS)] with their own words in a dedicated free-text box in a diary. They also were asked to insert the time of onset/end of AS and of the painful phase. Once the patient had recorded three attacks, they returned for a follow-up visit and the diaries were discussed with the neurologist. The features collected for every aura were: presence of VSS/SSS/DSs, number of elementary visual disturbances, presence of positive and/or negative visual disturbances and/or disturbance of visual perception (DVP) (Viana et al 2016a), and presence of headache.

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Results: Seventy-two patients completed the diaries during three consecutive auras for a cumulative number of 216 auras recorded. Out of 216 auras, 38 (17%) were PA. Out of 72 patients, 19 (26%) have at least one PA. PA had the following characteristics: VSs were present in 37 auras (97%), SSs in 26 (68%), DSs in 12 (31%). Median duration of VSs was 135 min (IQR 630), for SSs was 180 min (IQR 390), for DSs was 70 min (IQR 35). Ten PA (26%) had three symptoms, 19 PA (50%) had two symptoms and 9 PA (23%) had one symptom. One PA had three symptoms prolonged (>1 hr), six PA had two symptoms prolonged (VS + SS = 5, VS + DS = 1), 31 PA had only one symptom prolonged (VS = 19, SS = 11, DS = 1). All PA were associated to headache. With respect to VSs, 23 (60%) had positive features, 12 (31%) negative features and 19 (50%) included DVP. When comparing PA with the other auras (n = 178) with respect to the presence of VSs and/or SSs and/or DSs, total number of AS, number and type of elementary visual disturbances, and presence of headache, we found PA was characterized by a higher total number symptoms (p < 0.001), a higher frequency of SSs (p < 0.001) and a higher frequency of DSs (p < 0.001). No other differences were found. We performed the same analysis comparing auras including at least one AS lasting for >2 hrs (PA > 2, n = 23) with the remaining ones (n = 193) and auras including at least one AS lasting for 4 hrs (PA > 4, n = 14) with the remaining ones (n = 202). In the first comparison the only differences were a higher frequency of SSs and a higher number of aura symptoms in PA > 2 (p = 0.001 and p = 0.005, respectively) and in the second comparison the only difference was a higher number of aura symptoms in PA > 4 (p = 0.043). With respect to the duration of each AS of all auras, when considering them as a whole (n = 297), 46 AS (15%) lasted for more than one hr, 25 AS (8%) lasted for more than two hrs, 15 (5%) lasted for more than 4 hrs. Conclusion: Prolonged aura is quite common (17% of all auras) and phenotypically differs from the other auras only for a higher number of non-visual symptoms (non-VSs). This latter finding is not surprising if we consider that an AS with a longer duration is likely related to a cortical spreading depression (CSD) that proceeds along a longer path on the respective brain area. Such CSD therefore will involve more easily other adjacent brain areas, conferring a higher number of non-VSs to PA. The substantial phenotypical similarities between PA and the other auras is maintained also when we increase the limit of duration to 2 and/or 4 hrs. This finding should lead to a discussion of the term “prolonged aura” and how long its duration should be.

Disclosure of Interest: None Declared

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Headache Classification

EP-02-025
Field testing the ICHD 3 beta diagnostic criteria of vestibular migraine
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Objectives: To determine the diagnostic accuracy of the ICHD3 diagnostic criteria for vestibular migraine in a real-world clinical setting.

Methods: 130 patients with vestibular migraine were re-evaluated by telephone interview with the new ICHD 3 beta diagnostic criteria. The initial diagnosis was made during outpatient consultation in a tertiary dizziness clinic. As control group 30 patients with a clinically confirmed diagnosis of migraine with or without aura were also re-evaluated using the same questionnaire. The initial diagnosis was made in a tertiary headache center. The Mean age was 46.3 +/- 14 years and 75% of participants were women.

Results: The ICHD 3 beta criteria showed a sensitivity of 76.5 % and a specificity of 72.5%. Only 50% of patients had a temporal association of headache and vestibular symptoms. Most important diagnostic factors were the total amount of endured vertigo attacks (≥5), presence of one of the following specific vertigo characteristics (internal, external, spontaneous, visual vertigo, positional vertigo and aggravation by head movement), the presence of headache, at least 2 out of 4 migraine criteria (unilateral location, pulsating character, moderate to severe pain intensity, aggravation by physical activity), phono-/photophobia, nausea/vomiting, and aura (visual, sensible, aphasia).

Conclusion: The sensitivity and specificity of the proposed vestibular migraine diagnostic criteria were comparable to other ICHD diagnostic criteria, but may be reduced to a few key criteria.

Disclosure of Interest: None Declared

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Headache Classification

EP-02-026

Migraine in Children Under the Age of 7 Years: limits of new classification.

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Objectives: migraine is a common problem in childhood. The new classification criteria, defined by the International Headache Society (IHS), have few references for children, especially for the preschool age. Aim of this study is to evaluate if it is possible to classify a population of children under 7 years old with migraine using ICHD-3Beta criteria and compare these criteria to those were previously used

Methods: in this retrospective study we identified 74 children younger than 7 years, referred to our Headache Centre and classified as “migraine without aura (Mwo) patients” in the previous studies. We’ve reevaluated every characteristic of each of them, according to ICHD-3Beta criteria and comparing the results with those obtained using a different classification’s systems

Results: in our study the application of different classification’s criteria changed the percentage of Mwo diagnosis. In particular, when Winner’s criteria and ICHD-II criteria were used, the prevalence of Mwo was 85.1%, by contrast, using ICHD-3Beta, it changed to 55.4%; in addition, in Valquist 1955 to in IHS1988, the prevalence changed to 33.8% and 71.6%, respectively. Moreover, according to the ICHD-II criteria, a 14.9% of patients had a diagnosis of ‘probable migraine’ but when ICHD-3 beta criteria were used it changed to 25.6% and 18.9% of patients remained undiagnosed

Conclusion: Our results showed that the ICHD-3Beta owned a low sensitivity and specificity for Mwo rather than ICHD-II; that because the first is too restrictive and it is very poorly suited to Mwo in children

Disclosure of Interest: None Declared

Headache Classification

EP-02-027

Prospective testing of ICHD-3 beta diagnostic criteria for migraine with aura and migraine with typical aura in patients with transient ischemic attacks

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Objectives: The International Classification of Headache Disorders 3rd edition beta (ICHD-3 beta) gave alternative diagnostic criteria for 1.2 migraine with aura (MA) and 1.2.1 migraine with typical aura (MTA) in the appendix. The latter were presumed to better differentiate transient ischemic attacks (TIA) from MA. The aim of the present study was to field test that.

Methods: A neurologist interviewed soon after admission 120 consecutive patients diagnosed with TIA after MRI with DWI scans (n = 112) or CT (n = 8). Semi-structured interview forms addressed all details of the TIA episode and all information necessary to apply the ICHD-3beta diagnostic criteria for 1.2, 1.2.1, A1.2 and A1.2.1.

Results: Requiring at least one identical previous attack, the main body and the appendix criteria performed almost equally well. But requiring only one attack, more than a quarter of TIA patients also fulfilled the main body criteria for 1.2. Specificity was as follows for one attack: 1.2: 0.73, A1.2: 0.91, 1.2.1: 0.88 and A1.2.1: 1.0. Sensitivity when tested against ICHD-2 criteria were 100% for the main body criteria (because they were unchanged) and 96% for A1.2 and 94% for A1.2.1

Conclusion: The appendix criteria performed much better than the main body criteria for 1.2 MA and 1.2.1 MTA when diagnosing one attack (probable MA). We recommend that the appendix criteria should replace the main body criteria in the ICHD-3.

Disclosure of Interest: None Declared

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**Headache Disorders in Children and Adolescents**

**EP-02-028**

**A Comparison of Placebo Responders with Non-responders in the Zolmitriptan Nasal Spray Adolescent (TEENZ) Study**

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**Objectives:** To compare the reported baseline patient demographics, migraine headache characteristics, and pre-study use of preventive migraine medications in adolescent (aged 12–17 years) placebo responders versus non-responders in the Zolmitriptan Nasal Spray (ZNS) TEENZ Study.

**Methods:** The TEENZ Study was a global, multicenter, randomized, double-blind, parallel-group study of ZNS compared with placebo that was designed to assess the safety and tolerability of ZNS for the acute treatment of migraine headache in adolescents (NCT01211145). Patients (12–17 years old) with an established diagnosis of migraine with or without aura by the International Classification of Headache Disorders were enrolled if they reported an at least 1-year history of having a minimum of 2 moderate to severe migraines per month, each lasting at least 3 hours, prior to study enrollment. The study design included a single-blind run-in period during which subjects treated a single attack with 1 dose of placebo. During the run-in period, 38% of subjects responded to placebo. Non-responders were then randomized to ZNS or matching placebo. In this post-hoc analysis, the baseline demographic, headache, and preventive medication use characteristics of the placebo responders are compared to those subjects who did not respond to placebo during the run-in period.

**Results:** For the 325 subjects responding to placebo and the 784 subjects not responding to placebo, demographic characteristics such as age, gender, race, and body mass index (BMI) were similar. Additionally, migraine characteristics—age of onset of first migraine attack, average number of migraines and non-migraine headaches per month, duration of typical untreated migraine, and type of migraine—were also similar. Occurrence of the associated migraine symptoms of photophobia and phonophobia was similar between the two groups of migraineurs, but the placebo non-responders reported the associated symptoms of nausea and vomiting more frequently than the placebo responders (nausea 87% vs 75%, p < 0.0001; vomiting 48% vs 36%, p = 0.0003). Finally, as compared to the non-responders, more placebo responders were using preventive migraine medications (21% vs 13%, p = 0.0007).

**Conclusion:** In this exploratory analysis there were no remarkable differences in demographics and migraine characteristics of placebo responders compared to placebo non-responders. Non-responders reported a higher incidence of nausea and vomiting accompanying their typical migraine and less use of preventive migraine medications; both of these factors may be related to headache severity.


**Headache Disorders in Children and Adolescents**

**EP-02-029**

**Correlation between red flags in pediatric headache and abnormalities on neuroimaging studies in emergency department: preliminary data.**

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**Objectives:** Headache is a common cause of access to pediatric emergency department. To date in literature we don’t have clear evidence about when Brain Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are necessary. Aim of this study is to explore and verify the relationship between the presence of red flags and neuroimaging abnormalities in pediatric headache.

**Methods:** We collected clinical data of 400 children (195 males and 205 females) aged from 1 to 17 years old admitted in emergency department from October 2015 to September 2016. We used a predetermined list of red flags (acute onset, associated symptoms, abnormal neurologic examination and others) and we evaluate the number of children underwent neuroimaging studies (CT or MRI).

**Results:** We found that 400 (1.23%) of children admitted in emergency department suffering with headache. The age
range more interested was 6-12 years old children. As preliminary result we found that 265/400 (66.25%) showing one or more red flags at the access to hospital, 164/265 (61.8%) of these was investigated with neuroimaging studies. Children who had just one red flag presented with positive CT in 25.23% of cases, those ones who had two or more red flags showed in 74.7% altered CT.

**Conclusion:** These preliminary results show that there is a significant relationship between red flags and anomalies on neuroimaging studies in pediatric population suffering headaches (especially when red flags are more than one), which support the potential role of red flags like predictors.

**Disclosure of Interest:** None Declared

**Headache Disorders in Children and Adolescents**

**EP-02-030**

**Usefulness of an Algorithm for Primary Headache Diagnosis in Children and Adolescents**

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**Objectives:** The primary objective of this project was to develop and utilize an algorithm for primary headache diagnosis in children and adolescents in order to standardize and improve pediatric care and minimize practice variation. Improving and standardizing the diagnosis of primary migraine headaches in children can directly affect the quality and cost of pediatric headache care. The goal of this specific algorithm was to increase the accuracy of headache diagnosis to more than 80% of patients receiving the correct diagnosis by utilizing ICHD3 (International Classification of Headache Disorders 3 Beta) criteria.

**Methods:** A team of headache specialists, nurse practitioners, nurses, data analysts, and business specialists developed an algorithm based on available scientific evidence. The algorithm was presented to all general neurology faculty to review and provide feedback and final consensus was received prior to testing. The testing was done in limited general neurology clinics for further feedback, and the algorithm was adjusted according to process improvement models (plan-do-study-act/PDSA cycle) and tests of change. Patients presenting with a chief complaint of headache received a headache questionnaire and the provider independently evaluated and diagnosed the patients. Those charts were then reviewed by headache specialists to see if the algorithm was followed and correct diagnosis was attained. The testing cycle continued for 3 months and then the algorithm was spread to all general neurology clinics. The following information was gathered: number of providers following the algorithm; percentage of appropriate diagnosis as by ICHD3 criteria; percentage of appropriate testing ordered; and cost per headache visit.

**Results:** Correct diagnosis of primary headache by ICHD3 criteria in a pediatric neurology clinic improved from 72% at initiation of the project to 90% and the appropriate testing ordered improved from 80% to 94%.

By the end of the 6 months, 94% of the providers were correctly implementing the algorithm on a regular basis. The cost of headache care was a secondary analysis. The initial cost was lower in the summer months and increased in the fall when school started. The impact of the algorithm on cost was limited due to the seasonal variation of headache. A year-long tracking will be needed to evaluate improvement in cost benefit due to the algorithm.

**Conclusion:** Standardization of primary headache diagnosis is the first step in this project to improve headache care delivery. The algorithm improved the diagnosis of headache in general neurology clinics. Expanding the algorithm to primary care providers and pediatric emergency rooms would have a greater impact on headache evaluation, diagnosis, and treatment. This should result in an improvement of care delivery and outcome with expected positive long term effects on the cost of headache care throughout the health system.

**Disclosure of Interest:** None Declared

**Headache Education for Clinicians and Patients**

**EP-02-031**

**Headache interest in US academic neurology leadership: a cross-sectional study**

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**Objectives:** Headache disorders are exceedingly common, debilitating neurological conditions, and there is a striking paucity of headache specialists nationally. However, headache education is underrepresented in the curriculum of neurology residency programs and few neurology residents elect to pursue headache medicine fellowships. We aimed to explore the possibility that a low degree of headache interest among neurology department chairs and residency program directors (PDs) belies this mismatch.

**Methods:** We performed a cross-sectional analysis of chairs and PDs associated with accredited neurology
residency programs. Data sources included the accredited program list, faculty profiles on institutional webpages, Doximity profiles, the American Headache Society (AHS) membership directory, and the roster of United Council for Neurologic Specialties (UCNS) headache diplomates. A headache interest was deemed to be present with the presence of a declared headache or concussion interest, active AHS membership, or UCNS certification.

Results: Our review included 137 residency programs comprising 127 department chairs, 132 PDs, and 5 faculty who were both chairs and PDs. Of all faculty, 62 (23.5%) were women. Headache expertise was declared by 10 (7.6%) chairs and 13 (9.5%) PDs. Headache fellowship training was pursued by 1 (0.8%) chair and 5 (3.6%) PDs, and among all faculty was the 10th most common subspecialty fellowship pursued. Three (2.3%) chairs and 7 (5.1%) PDs were AHS members. Seven (5.3%) chairs and 10 (7.3%) PDs were UCNS headache certified. An overall headache interest was present in 29 (11.0%) faculty, including 14 (10.6%) chairs and 15 (10.9%) PDs. A graduate degree aside from an MD (e.g. PhD, MPH) was more likely to be achieved in faculty without a headache interest (29.4%) than faculty with a headache interest (6.9%, \( p = 0.0076 \)). Residency programs where either the chair or PD had a headache interest were just as likely to feature a UCNS headache fellowship program than programs without chair or PD headache interest (25.0% vs 23.0%, \( p = 0.83 \)).

Conclusion: Current neurology department chairs and residency PDs have low rates of headache interest, which may influence the emphasis of headache education in neurology training. Headache interest is associated with lower rates of other graduate degrees, and future analysis should examine if academic faculty interested in headache are less likely to be in leadership positions because of a lack of research funding, opportunities or accomplishments.

Disclosure of Interest: M. Robbins Conflict with: eNeura, Inc. (site PI for clinical trial; funds to institution), N. Rosen Conflict with: Curelator, Conflict with: Allergan, Curelator, Eli Lilly, Promius, Supernus, Conflict with: Allergan, Avanir

Headache Education for Clinicians and Patients

EP-02-032

National awareness campaign for medication-overuse headache in Denmark

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Objectives: Overuse of acute pain medication for headache plays a major role in transforming episodic headache to chronic forms. One aspect of preventing medication-overuse headache (MOH) is to increase the public’s awareness of the disorder. It is also important to increase healthcare professionals’ awareness in order to improve their skills in counselling patients on pain medication use, and to promote rational prescription of pain medication. The objective is to describe the implementation of the Danish national awareness campaign for MOH.

Methods: The Danish Headache Center (DHC), the Association of Danish Pharmacies, and the Migraine and Headache Patient Organization, planned and implemented a national awareness campaign in the autumn of 2016. Target groups were the general public, general practitioners and pharmacists. The key messages were: 1) overuse of acute pain medication can make headaches worse; 2) MOH prevalence can be reduced through rational use of pain medication; and 3) MOH can be treated. The following campaign components were developed for the general public: online videos, leaflets about MOH, and interviews with expert resource persons for TV, radio and print media outlets; for pharmacists: information and training materials; and for physicians: reviews and case studies in Danish medical journals, and information materials. A survey on knowledge of, and sources of information on MOH, was conducted before and four weeks after the implementation of the campaign. Formative evaluation was conducted.

Results: All planned campaign components were developed and implemented. Online videos were viewed 297,000 times during the campaign period. Four-hundred pharmacies were invited to participate, and received education material. Over 28,000 leaflets were distributed in 400 pharmacies. Two radio interviews were conducted and a television broadcast about headache, including MOH, reached approximately 520,000 persons. Forty articles were published in popular print media, and information about MOH came up at 32 websites and five online news agencies. Three papers in Danish scientific journals for medical doctors, and one scientific paper for
pharmacists were published. There were about 100 visitors at an information table operated by volunteers from a patient organization and DHC staff members at an annual conference attended by about 3000 general practitioners. A survey conducted four weeks after implementation showed minor but encouraging increase in percentage of the general public who knew about MOH (from 31% to 38%).

Conclusion: A concerted campaign for rational use of acute pain medications for headache can be implemented through the involvement of many stakeholders. Long term changes in health behaviors, prescription patterns, and medicine consumption should be continually monitored.


Headache Epidemiology, Outcomes and Burden

EP-02-033

Transmission of migraine in families:
Family-linkage data from the HUNT study.

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Objectives: Migraine is known to run in families. While some clinic-based studies have indicated that migraine is disproportionally transmitted through the maternal line, this has not been examined in a population-based setting. We aimed to clarify the parent-offspring associations of migraine and non-migrainous headache in a large, unselected population, taking into account relevant psychosocial factors.

Methods: We utilized the large, population-based Nord-Trøndelag Health Study (HUNT) from Norway. Headache diagnoses were separated into migraine and non-migrainous headache. Our study sample consisted of 8985 individuals (aged 13–45 years), who had information about headache in at least one parent. We included 8029 mothers and 5726 fathers (aged 21–52 years). In a cross-sectional design, logistic regression was used to calculate odds ratios (OR) with 95% confidence intervals (CI) for offspring headache given parental headache. Potential confounders, including parental education, anxiety, depression, alcohol, smoke, overweight and physical activity, were tested by the Mantel-Haenszel method.

Results: We found a strong association between maternal migraine and offspring migraine, both in daughters (OR 2.46, 95% CI 1.95–3.09) and sons (OR 2.68, 95% CI 1.89–3.80). A weaker, but significant association was also found between paternal migraine and offspring migraine, both in daughters (OR 1.60, 95% CI 1.12–2.29) and sons (OR 1.73, 95% CI 1.08–2.78). For non-migrainous headache, the only significant association was seen between mothers and daughters (OR 1.30, 95% CI 1.11–1.51). None of the psychosocial or demographic factors affected the estimates significantly.

Conclusion: Migraine in parents is strongly associated with migraine in their offspring, with a stronger association for maternal than paternal migraine. A different pattern was seen for non-migrainous headache, where the only significant association was seen between mothers and daughters. This may indicate different causative mechanisms for migraine and non-migrainous headache.

Disclosure of Interest: None Declared

Headache Epidemiology, Outcomes and Burden

EP-02-035

Reducing the Impact of Migraine on Functioning: Results from the STRIVE Trial: A Phase 3, Randomized, Double-Blind Study of Erenumab in Subjects with Episodic Migraine

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Objectives: To evaluate the effect of erenumab, a preventive treatment for migraine in adults, on functional outcomes using the Migraine Functional Impact Questionnaire (MFIQ).

Methods: MFIQ is a newly-developed 31-item patient-reported outcome (PRO) instrument assessing the impact of migraine on functional outcomes over the past seven days. MFIQ was completed at baseline and every 4 weeks for 24 weeks in a phase 3 clinical trial (NCT02456740) where 955 adults with episodic migraine (EM) aged 18–65 years were randomized 1:1:1 to subcutaneous, 1. monthly placebo, 2. erenumab 140 mg, or 3. erenumab 70 mg. MFIQ includes 4 domains: impact on physical function (PF), usual activities (UA), social function (SF), and emotional function (EF). Domain scores range from 0–100 where higher scores indicate greater impact; negative change scores represent reduction in impact.
(improvement). Exploratory endpoints based on MFIQ were evaluated as change from baseline to the last 3 months of the double blind treatment phase (defined as the average of scores in months 4–6 [i.e. weeks 13–24]); primary and secondary endpoints from the trial are reported separately. A generalized linear mixed model with covariates was estimated. Pairwise comparisons of least squares (LS) mean changes from baseline in MFIQ domain scores were assessed for each active treatment vs placebo. P-values are descriptive and not adjusted for multiplicity.

**Results:** Baseline MFIQ scores were similar in erenumab and placebo groups for PF (140 mg: mean ± standard deviation (SD) 36.60 ± 19.42; 70 mg: 37.09 ± 19.48; placebo: 37.78 ± 20.40), UA (140 mg: 29.91 ± 20.26; 70 mg: 31.21 ± 19.05; placebo: 30.10 ± 20.16), SF (140 mg: 29.1 ± 21.37; 70 mg: 31.32 ± 21.59; placebo: 29.92 ± 22.71), and EF (140 mg: 31.57 ± 23.84; 70 mg: 33.59 ± 23.67; placebo: 34.59 ± 34.59) domains. Greater reductions in impact from baseline were observed for each MFIQ domain in erenumab groups compared to placebo. On the PF domain, LS mean changes were −15.14 (95% confidence interval (CI): −16.96, −13.33), p < 0.001 in erenumab 140 mg and −13.72 (−15.54, −11.90), p < 0.001 in erenumab 70 mg compared to the placebo group −9.44 (−11.28, −7.61), indicating greater reduction in impact of migraine on PF. LS mean change scores on the UA domain in the erenumab 140 mg and 70 mg groups were −13.43 (−15.08, −11.78), p < 0.001 and −12.25 (−13.92, −10.59), p < 0.001, respectively, compared to placebo group change of −8.29 (−9.96, −6.62). Changes on the SF domain were −14.49 (−16.24, −12.75), p < 0.001 in erenumab 140 mg and −13.17 (−14.93, −11.42), p = 0.003 in erenumab 70 mg compared to the placebo group −9.50 (−11.26, −7.74). EF domain change scores were −18.38 (−20.30, −16.46), p < 0.001 and −16.43 (−18.36, −14.49), p < 0.001 in the erenumab 140 mg and 70 mg groups, respectively, compared to placebo group change of −11.17 (−13.11, −9.23).

**Conclusion:** Over 24 weeks, compared to the placebo group, subjects with EM who were treated with erenumab 140 mg and 70 mg experienced greater reductions in the impact of migraine on their physical functioning, usual activity, and social and emotional functioning based on the MFIQ, with numerically greater reductions for 140 mg compared to 70 mg. These improvements in multiple aspects of functional outcomes highlight the benefits for patients of treatment with erenumab, extending findings from other efficacy outcomes in the trial.


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**Headache Epidemiology, Outcomes and Burden**

**EP-02-036**

**Study of headache after the Great East Japan Earthquake in Iwate coast area (1) Relationship between headache prevalence and medical and environmental factors**

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3Iwate Medical University, Morioka, Japan

**Objectives:** To investigate prevalence of headache after The Great East Japan Earthquake and factors related to change of prevalence of headache.

**Methods:** In 2011, The Great East Japan Earthquake gave serious damage to the Pacific coast district of Japan. We conducted medical inquiries concerning headaches from 2012 to 2015 among municipalities with the greatest earthquake-related damage in Iwate prefecture including Yamada Town, Rikuzentakata City and Heita District of Kamaishi City. Fifty nine hundred and fifteen individuals in 2012, 5588 individuals in 2013, 5395 individuals in 2014 and 5318 individuals replied inquiries. We
investigated prevalence of headache and compared age, gender, mental factors (stress, nervousness, K6 score and sleep disorder), metabolic syndrome, smoking and drinking habits, daily physical exercise, post-traumatic stress disorder (PTSD)-related factors caused by the earthquake and social network factors (friendship, mutual aid and trust) between the group with and without headache.

Results: Prevalence of headache was gradually decreased (25.4% in 2012, 20.5% in 2013, 19.9% in 2014 and 17.2% in 2015. p < 0.001) significantly. For the investigated period, the significant factors affecting headache were younger age (p < 0.001), female gender (p < 0.001), mental factors (p < 0.001), PTSD-related factors (p < 0.001) and social isolation (p < 0.001 in almost all social network factors); and those avoiding headache were metabolic syndrome (p < 0.001) and drinking habit (p < 0.001). Exercise and smoking habit were not headache-relating factors. Changes in headache prevalence were well correlated with changes of prevalence in mental and PTSD-related factors of the previous year.

Conclusion: Headache prevalence after The Great East Japan Earthquake is affected by mental and PTSD-related factors of the previous year.

Disclosure of Interest: None Declared

Headache Epidemiology, Outcomes and Burden

EP-02-037

Validation of a migraine questionnaire for use in the SAGA cohort study

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Objectives: To describe the validation of a new migraine questionnaire for the SAGA cohort study.

Background: With a target enrollment of 100,000 Icelanders during the next 10 year period, the Stress-And-Gene-Analysis (SAGA) cohort is a population-based longitudinal study of the combined influence of inheritance, psychological stress, and modern lifestyle on various indices of health, including migraine. Participants answer an extensive online Icelandic language questionnaire on various exposures and health measures. Due to a high number of questions in the SAGA questionnaire it is not feasible to use the existing migraine questionnaires, thus, in order to reduce number of questions for participants, we developed a new questionnaire for the SAGA cohort study.

Methods: For validation of the new measure we used data from the SAGA cohort pilot study. Women were recruited through a routine cancer screening program offered to all women in Iceland aged 20–69 years. Men were a random sample (aged 20–69) from the national registry identified by Statistics Iceland. Participants answered an online questionnaire including 16 screening questions on headache symptoms (based on ICHD-3 beta criteria) and 3 questions on headache treatment. In addition, subjects with visual or sensory symptoms were asked 14 questions about their visual symptoms and 15 questions about their sensory symptoms. Participants with and without headache according to the questionnaire, were selected for telephone interview by a neurologist (JHE) during 2015 and 2016 to ascertain migraine based on ICHD-3 beta criteria.

Table: Table. Migraine diagnosed by a neurologist (gold standard) vs. questionnaire in the pilot for the SAGA cohort study

<table>
<thead>
<tr>
<th></th>
<th>Migraine dx by neurol.</th>
<th>No migraine</th>
<th>Total, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine by questionnaire</td>
<td>69</td>
<td>9</td>
<td>78</td>
</tr>
<tr>
<td>No migraine</td>
<td>15</td>
<td>57</td>
<td>72</td>
</tr>
<tr>
<td>Total, n</td>
<td>84</td>
<td>66</td>
<td>150</td>
</tr>
</tbody>
</table>

Results: Of 1398 invited adults, 921 (66%) participated in the study; 402 men (average age 45.6 years, SD 13.2) and 519 women (52.6 years, SD 11.1). Out of the 921 participants, 242 participants with and without headache in the past 12 months, were invited to participate in the validation study, 150 (62.0%) of those subjects were interviewed by a neurologist (JHE). Among participants diagnosed with migraine by the neurologic assessment (n = 84; 56.0%) the questionnaire screened positive for migraine (n = 69) yielding a sensitivity of 82.1% (see Table). Conversely among the 66 individuals free of migraine by the neurologic assessment 57 did not have migraine by questionnaire for specificity of 86.4%. The relative odds of migraine by neurologic assessment given a questionnaire positive for migraine was 29.2 (95% CI: 11.9 to 71.4).
Conclusion: A self-administered screening questionnaire identified migraine with high sensitivity and specificity using a neurologist interview as the diagnostic gold standard.

Disclosure of Interest: None Declared

Headache Epidemiology, Outcomes and Burden

EP-02-038

Alcohol as a risk factor for migraine attacks: an exploration

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2Northwell Health, New York, United States

Objectives: Various types of alcohol have long been suspected as a migraine risk factor (potential trigger) commonly resulting in avoidance and possible impact on quality of life. Numerous studies on alcohol have been inconclusive (1). To explore this question we statistically compare daily intake of alcohol and occurrence of migraine attacks.

Methods: Individuals with migraine registered to use a digital platform (Curelator HeadacheTM) (2) via website or the App Store (iOS only) and answered questions about personal suspected risk factors, including alcohol, and their importance (1 = low; 10 = maximal). They then used Curelator Headache daily for at least 90 days, entering details about headaches and exposure to factors that may affect migraine attack occurrence. Unless users stated that they never drank alcohol, alcohol consumption was collected as a dichotomous variable (yes/no) and also as a continuous variable (type and units of alcohol) daily. After 90 days all factors were analyzed and for each individual the association of alcohol intake with attacks was determined (3).

Results: Of 509 individuals with migraine (Table 1), alcohol was suspected as a risk factor by 328 (64%). Prevalence of consumption of alcohol was significantly different (p < 0.001) between those who did not suspect vs those who did (41% vs 91%). 136 (27%) users did not consume alcohol and 110 (30%) of those who did consume alcohol did not have data of adequate quality for analysis (including lack of data variability, e.g. avoidance of alcohol or too frequent consumption around migraine events) were not included on the analysis. Among the 373 (73%) users who consumed alcohol, comparisons between those who did not suspect versus those who did suspect alcohol as a risk factor were made as follows: adequacy of data for analysis (64% vs 72%); no association found between alcohol and migraine (89% vs 75%); alcohol found as a risk factor associated with increased migraine (6% vs 8%); alcohol found associated with decreased risk of migraine (4% vs 17%). In addition, no association was found between degree of suspicion of alcohol and the percentage of individuals in whom an association was identified.

Conclusion: Despite the common belief that alcohol is a risk factor for migraine, in the majority users no association was found. Interestingly, alcohol intake was less frequent in people not suspecting alcohol. This may be explained as follows: those practicing abstinence would also not suspect alcohol as risk factor. Irrespective of whether a user suspected of alcohol as a risk factor, or the degree of suspicion, in total 78% of users showed no association between alcohol and migraine. Surprisingly, when an association was found it was more often found to be associated with risk reduction (potential protector) than risk increase (potential trigger). The results presented here do not support the hypothesis that alcohol is a major risk factor for migraine.


References
(3) Peris F. Cephalalgia. 2016 May 14

Abstract number: EP-02-038

Table 1. User characteristics and risk factor associations in those suspecting alcohol as a risk factor; those who did not and all users.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Did not consume alcohol</th>
<th>Consumed Alcohol</th>
<th>Adequate data for analysis</th>
<th>Potential trigger</th>
<th>Potential protector</th>
<th>No Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected</td>
<td>328</td>
<td>29 (9%)</td>
<td>299 (91%)</td>
<td>216 (72%)</td>
<td>17 (8%)</td>
<td>37 (17%)</td>
<td>162 (75%)</td>
</tr>
<tr>
<td>Not suspected</td>
<td>181</td>
<td>107 (59%)</td>
<td>74 (41%)</td>
<td>47 (64%)</td>
<td>3 (6%)</td>
<td>2 (4%)</td>
<td>42 (89%)</td>
</tr>
<tr>
<td>Totals</td>
<td>509</td>
<td>136 (27%)</td>
<td>373 (73%)</td>
<td>263 (70%)</td>
<td>20 (7%)</td>
<td>39 (15%)</td>
<td>204 (78%)</td>
</tr>
</tbody>
</table>
**Headache Epidemiology, Outcomes and Burden**

**EP-02-039**

**Migraine is associated with intracranial carotid artery calcification: the Rotterdam Study**

Ke-Xin Wen¹, Daniel Bos¹, M. A. Ikram¹, Oscar H. Franco¹ and Maryam Kavousi¹

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**Objectives:** Migraine has been associated with increased risk of cardiovascular disease. The exact mechanisms remain unclear. We investigate whether migraine is associated with carotid intima media thickness (cIMT) and arterial calcification.

**Methods:** Migraine was assessed by questionnaire in 6961 participants of the Rotterdam Study. Mean cIMT was assessed by ultrasound of the common carotid artery, carotid bifurcation and the internal carotid artery. 6157 participants had data on both migraine and cIMT. Arterial calcification of the coronary arteries, aortic arch, and extracranial and intracranial carotid arteries was assessed by computed tomography. 1856 participants had data on migraine and arterial calcification. Analyses were performed using linear regression with adjustment for age, sex and cardiovascular risk factors.

**Results:** In the population for analysis of cIMT, 980 persons (15.9%) had migraine and the mean age was 60.6 years (standard deviation 7.5). In the population for analysis of arterial calcification, 279 persons had migraine (15.0%) and the mean age was 67.4 years (standard deviation 5.8). Migraine was associated with lower mean cIMT (unstandardized beta coefficient −0.01 (95% confidence interval (CI) −0.02, 0.00)) and lower intracranial carotid artery calcification score (−0.19 (95% CI −0.29, −0.08)). There was no association with coronary artery, aortic arch or extracranial carotid artery calcification.

**Conclusion:** Migraine is associated with lower cIMT and lower arterial calcification in the intracranial carotid artery, but not with calcification in the other arterial vessels. This suggests that there is less atherosclerosis in the intracranial carotid artery in persons with migraine compared to persons without migraine. More studies are needed to investigate the mechanism and implications.

**Disclosure of Interest:** None Declared

**Headache Pathophysiology - Basic Science**

**EP-02-040**

**PACAP, CGRP and Headache Targets in the Trigeminal Sensory Ganglion in Rats and Humans based on Immunohistochemistry**

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²Vascular Experimental Research, Clinical Sciences, Lund University, Lund, Sweden

**Objectives:** Trigeminal ganglion (TG) activation and sensitization are well-established as pathophysiological effects in primary headache disorders, especially in migraine. Release of neurotransmitters, e.g. calcitonin gene related peptide (CGRP) and pituitary adenylate cyclase activating peptide (PACAP) by sensory ganglia, is considered a mechanism involved in cranial pain processing. Several therapeutic agents have shown efficacy in treating headache patients, however, with individual effects. The aim of this study was to investigate expression of PACAP and relate it to CGRP, vasoactive intestinal peptide (VIP)/PACAP receptors 1/2 (VPAC1/2), PACAP type I receptor (PAC1), 5-hydroxytryptamine receptors 1B/1D/1F (5-HT1B/1D/1F) and Onabotulinum toxin A (Botox) signaling elements synaptic vesicle glycoprotein 2 (SV2-A) and

**Abstract number:** EP-02-039

**Table.** Difference in carotid intima-media thickness or log-transformed calcification scores between persons with and without migraine.

<table>
<thead>
<tr>
<th></th>
<th>n/N</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid intima-media thickness</td>
<td>980/517</td>
<td>−0.01 (−0.02, −0.01)</td>
<td>−0.01 (−0.02, 0.00)</td>
</tr>
<tr>
<td>Coronary artery calcification</td>
<td>271/1561</td>
<td>−0.09 (−0.23, 0.40)</td>
<td>−0.05 (−0.18, 0.07)</td>
</tr>
<tr>
<td>Aortic arch calcification</td>
<td>279/1574</td>
<td>−0.06 (−0.18, 0.07)</td>
<td>−0.04 (−0.15, 0.08)</td>
</tr>
<tr>
<td>Extracranial carotid artery calcification</td>
<td>279/1576</td>
<td>−0.14 (−0.26, −0.02)</td>
<td>−0.10 (−0.22, 0.01)</td>
</tr>
<tr>
<td>Intracranial carotid artery calcification</td>
<td>279/1563</td>
<td>−0.21 (−0.32, −0.11)</td>
<td>−0.19 (−0.29, −0.08)</td>
</tr>
</tbody>
</table>

Values given are difference in mean carotid intima-media thickness or log-transformed calcification scores and accompanying 95% CI for persons with migraine compared to persons without migraine. n = number of persons with migraine; N = number of persons without migraine. Model 1: adjusted for age, sex and cohort. Model 2: additionally adjusted for body-mass index, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein, smoking, blood-pressure lowering medication use, lipid-lowering medication use, prevalent diabetes, and a history of cardiovascular disease.

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synaptomal-associated protein 25 kDa (SNAP25) in rat and human TG. Revealing the neurotransmitter and therapeutic target localizations might increase the understanding of sites of action and mechanisms related to headache therapy.

**Methods:** Using rat as a model, TG from Sprague-Dawley male rats, but also human TG, were dissected and processed for immunohistochemistry. Microscopically, single-labelling in rats and humans and double-labelling in rats were used to evaluate immunoreactivity in the various cells types.

**Results:** Expression of PACAP, CGRP and selected headache targets were detected in rat and human TG. PACAP receptors were confined to neurons and satellite glial cells (SGCs), however with variability between subtypes. For the 5-HT receptors, the immunoreactivity was consistently expressed on neuronal cell bodies and fibers with the following frequency for humans: 5-HT1D > 5-HT1B > 5-HT1F, SNAP25 was primarily expressed in SGCs in humans and neurons in rats while SV2-A was confined to SGCs and some neurons in both species. PACAP38 colocalized with CGRP in many neuronal cell bodies and fibers. Some PACAP38-positive cells, neurons and SGCs, also expressed PAC1, VPAC2, 5-HT1B, 5-HT1D, 5-HT1F, SNAP25 and SV2-A. Generally, VPAC1 was detected in SGCs surrounding neuronal cell bodies some expressing PACAP38.

**Conclusion:** Our study revealed colocalization and possible signaling mechanisms between neurotransmitters and headache targets thus potential sites of actions for anti-headache drugs such as PACAP receptor antagonists, Lasmiditan and Botox in humans acting through the sensory nervous system. Further, the results indicate the value of using the rat as a model for investigating the therapeutic targets in question.

**Disclosure of Interest:** None Declared

**Headache Pathophysiology - Basic Science**

**EP-02-041**

**Distribution of CGRP and CGRP receptor components in the rat brain**

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**Objectives:** The present study was designed to comprehensively map the distribution of CGRP and its receptor elements CLR and RAMPI in the rat brain in order to provide an overview of their localization in fibers and cells to add to the discussion of migraine/headache pathogenesis.

**Methods:** Sagittal rat brain sections spanning over 0.5 mm to 1.5 mm lateral to the midline were immunohistochemically processed with specific antibodies against CGRP and RAMPI/CLR.

**Results:** In the entire brain volume investigated, CGRP was consistently found in neuronal cell somata, while the receptor components were almost exclusively found within fibers.

In the cerebrum cortex, the density, size and morphology of CGRP immunoreactive fibers indicate that all cortical neurons were positive for CGRP. Thin RAMPI immunoreactive fibers were found spanning through the entire cortex, but also traversing through cortex in layer I and III. In the hippocampal CA3 region, the cytoplasm of the pyramidal cells displayed intense immunoreactivity in a similar way as was seen in the cerebral cortex. The extension of RAMPI immunoreactive fibers indicated that it was the mossy fibers (originating from the dentate granule cells) that were stained and not the dendritic tree of the pyramidal cells.

The thalamic and hypothalamic nuclei showed intense CGRP immunoreactivity. The RAMPI immunohistochemistry showed similar pattern for all nuclei with a tight mass of positive slender processes.

In all brain stem nuclei, CGRP immunoreactivity was present in the neuronal cell somata, but not in the fibers. RAMPI staining was found in slender fibers and, in addition, in the neuronal cell somata to a varying degree. CLR immunoreactivity was found in stubby fibers, cell somata and in vessels.

In a few regions of the examined volume of the brain, CGRP positive fibers were found. However, in the septal nucleus, pearl-like CGRP immunoreactive fibers, often also seen in TG and SPG, were found. In addition, neuronal cell somata were CGRP immunoreactive.

**Conclusion:** It is widely accepted that migraine involves trigeminovascular pathways as well as the brain stem, and nuclei of the thalamus and hypothalamus. Here we describe the distribution of CGRP and CLR/RAMPI in a lateral slice of the entire brain. Clearly, further in depth analysis should be performed to understand the role of the CGRP system in general and other peptides and their receptors in the brain. However, we provide a careful interpretation of the immunoreactivity of the particular antibodies and thereby add to the understanding of CGRP and its receptor components in the CNS.

**Disclosure of Interest:** None Declared
Methods:
We used a MOH model in rats to test for a loss of diffuse noxious inhibitory controls (DNIC) induced by morphine priming. The rostral ventromedial medulla (RVM) would prevent the loss of DNIC induced by morphine priming in the central nucleus of the amygdala (CeA), but not in other regions of the RVM. Additionally, we hypothesized that blockade of KOR signaling following systemic nor-BNI, a KOR antagonist, would be prevented by blockade of KOR signaling in morphine-primed male rats. In contrast, Nor-BNI administered into the left CeA or bilaterally to the RVM did not restore the DNIC response.

Results: We found that nor-BNI administered subcutaneously or into the right CeA prevented the loss of DNIC in morphine-primed male rats. In contrast, Nor-BNI administered into the left CeA or bilaterally to the RVM did not restore the DNIC response.

Conclusion: The CeA receives inputs from stress circuits and has outputs to descending pain modulatory centers highlighting the possibility of KOR-mediated enhanced descending facilitation as an amplifier of stress-induced hyperalgesia relevant to migraine pain. KOR receptors in the RVM are found on OFF (i.e., pain inhibitory) and neutral cells, but not on ON (pain facilitatory) cells suggesting that the loss of DNIC following morphine priming is unlikely to result from loss of descending inhibition. Thus, functional pain disorders may reflect net enhanced facilitation that may result from KOR signaling in the CeA.

Disclosure of Interest: None Declared

Headache Pathophysiology - Basic Science

EP-02-043

Changes in the Contralateral Cerebral Hemisphere in Response to Cortical Spreading Depression

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Objectives: It is often assumed that cortical spreading depression (CSD) is a unilateral event, affecting only the hemisphere in which it is evoked. The objectives of this study were to examine the neural and vascular changes in the hemisphere contralateral to spreading depression in mice in vivo.

Methods: Vascular and parenchymal responses to CSD in mice were recorded using optical intrinsic signal (OIS) and field potential recording techniques. Two thinned skull windows were prepared to visualize both hemispheres. Burrholes were made on each side. An electrode for measurement of local field potential (LFP) was placed on the contralateral side to the burrhole for KCl injection. In some experiments, an additional burrhole was placed for bilateral recording of LFP. Single or repetitive CSD events were evoked with transient or continuous application of 1M KCl. In control animals, saline was injected instead of...
KCl. In other experiments, CSD was evoked by light stimulation in an optogenetic model.

**Results:** A multiphasic deflection in local field potential was consistently observed in the contralateral hemisphere with a delay of 60–120 seconds following initiation of CSD. This was accompanied by a transient change in parenchymal OIS and vascular caliber. Sustained changes (30–60 minutes) in cortical bursting activity and associated vascular responses were also observed in the hemisphere contralateral to CSD initiation in some experiments. Similar changes on the contralateral hemisphere were observed with light-evoked CSD in an optogenetic model, indicating that these changes were not the result of KCl injection. Saline injections evoked no CSD or change in local field potential or OIS on either the ipsilateral or contralateral side.

**Conclusion:** The contralateral cerebral hemisphere can be affected in response to CSD with both rapid and sustained electrophysiological and vascular changes.

**Disclosure of Interest:** None Declared

**Headache Pathophysiology - Basic Science**

**EP-02-044**

**NON-MIGRAINE RELATED PAIN BEHAVIOIRS IN A TRANSGENIC “MIGRAINE MOUSE” WITH CIRCADIAN DISRUPTION**

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**Objectives:** Mice harbouring the human mutation responsible for familial advanced sleep phase syndrome (FASPS), a mutation in the circadian clock regulator gene casein kinase 1δ (CK1δ-T44A), have previously been shown to exhibit some aspects of migraine-related pain, akin to the human condition. Given the established circadian impact on pain more generally, we sought to confirm if CK1δ “migraine mice” demonstrated non-migraine-related pain phenotypes that could impact on migraine-related readouts, while also seeking to confirm aspects of the migraine phenotype previously described.

**Methods:** CK1δ (N = 28) and WT (N = 26) littermates underwent behavioural assessment of hind paw withdrawal thresholds, as well as spontaneous and neuropathic pain behaviours. Mechanical and thermal withdrawal thresholds were assessed using the von-Frey assay and hot-plate test, the formalin test to assess spontaneous pain behaviour, and the partial nerve ligation model to assess neuropathic pain. Migraine-related cortical spreading depression (CSD) threshold, induced with 1M potassium chloride, was determined.

**Results:** Overall, between CK1δ transgenic mice and WT littermates, there was no significant difference in hind paw mechano-sensitivity (t₁₅ = −0.303, p = 0.764), thermosensitivity (t₁₅ = −0.156, p = 0.878), formalin response (AUC t₁₅ = 0.560, p = 0.584), and mechano-sensitivity after peripheral nerve injury to induce neuropathic pain (F₁₈,72 = 1.295, p = 0.217). Regarding migraine-related CSDs, CK1δ showed a significant increase in the number of events over 1 hour compared to WT (CK1δ = 10.78 and WT = 7.63; t₁₅ = 3.574, p = ≤ 0.01), which is in agreement with the literature.

**Conclusion:** We have demonstrated that CK1δ-T44A transgenic mice experience no overt general pain phenotype that could impact on migraine-related pain readouts while confirming the presence of a migraine-specific phenotype in a model of cortical spreading depression. This work is supported by the Medical Research Council (MR/P006264/1) and PhD funding from The Migraine Trust.

**Disclosure of Interest:** None Declared

**Headache Pathophysiology - Basic Science**

**EP-02-045**

**Inhibitory effects of the histone deacetylase inhibitor, Vorinostat, on early life stress-induced increases in CSD susceptibility and anxiety-like behavior in male rats**

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**Objectives:** Childhood maltreatment, a form of early life stress (ELS), is associated with migraine as well as with psychiatric conditions comorbid with migraine, such as anxiety. Using a rodent model of ELS, we previously found that adult male rats exposed to maternal separation (MS), exhibited increased susceptibility to cortical spreading depression (CSD), the putative mechanism of migraine aura. In addition, we found a correlation between CSD susceptibility and anxiety-like behaviors. Studies on MS and its long-lasting effects on anxiety-like behavior suggest epigenetic processes as a potential mechanism. Thus, we investigated whether treatment of adult rats with Vorinostat, a histone deacetylase (HDAC) inhibitor, would reverse MS-induced effects on CSD susceptibility and anxiety-like behaviors.

**Methods:** Male and female Sprague-Dawley rat pups were exposed to MS for 3 hours daily or to a standard-reared (SR) control group for postnatal days (PND) 1–14. Pups were weaned on PND22 and on PND60-70 pups were treated.
with Vorinostat (10 mg/kg) or saline (1 mL/kg), which consisted of single daily peritoneal injections for 5 consecutive days. On the day following the last treatment (males) or during the earliest diestrous phase (females), we determined anxiety-like behavior using an open-field (OF) apparatus by measuring total grid crossings, center field entries and rearing behaviors. Four days following OF testing (males) or during subsequent diestrous phase, we measured the threshold electrical stimuli needed to evoke CSD from the occipital cortex. Two-way Anova analysis with Bonferroni posttests was performed on results from OF and CSD experiments. Image:

**Results:** We found a significant main effect of MS on lowering CSD threshold in the combined male and female cohort (p = .04, n = 20–22 per group), and in males alone (p = .03, n = 10–11 per group), but not in females (p = .36, n = 10–11 per group). This corroborates our earlier findings. The CSD thresholds in saline-treated MS combined sex and male groups were significantly lower than 1) saline-treated SR combined sex (55.9 V vs 69.0 V, p = .02) and male groups (54.5 V vs 74.0 V, p = .02) and in 2) Vorinostat-treated MS combined sex (55.9 V vs 68.6 V, p = .01) and male groups (54.5 V vs 71.8 V, p = .01). There was also a significant main effect of MS on increased anxiety-like behavior in males but not females, as indicated by reduced total grid crossings (p = .04) and center entries (p = .03). Saline treated MS males crossed fewer total grids (50.9) and entered the center area less frequently (.72) than saline-treated SR males (grids 50.9 vs 98.9, p = .003; center .72 vs 2.6, p = .002) or Vorinostat-treated MS males (grids 50.9 vs 94.0, p = .002; center .72 vs 2.4 p = .005).

**Conclusion:** The current experiments found that treatment with the HDAC inhibitor, Vorinostat, appears to reverse increased CSD susceptibility and anxiety-like behaviors found in adult MS male rats. These findings suggest that the effects of MS on CSD threshold and anxiety-like behavior may be mediated by epigenetic processes involving histone acetylation.

**Disclosure of Interest:** None Declared

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**Headache Pathophysiology - Basic Science**

**EP-02-046**

**P2X7 receptor regulates CSD and CSD-induced TNF-α induction**

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**Objectives:** Cortical spreading depression (CSD) is the substrate of migraine with aura. The ATP-gated P2X7 receptor (P2X7R) may participate in the pathogenesis of migraine, yet little is known about the role of cortical P2X7R in CSD. This study aimed to 1) examine the role of P2X7R in CSD elicitation by investigating how an anti-P2X7R antibody mediates on CSD in rats; 2) whether P2X7R contributes to the induction of IL-1β and TNF-α induced by CSD.

**Methods:** CSD was induced by K⁺-medium in the right cortex of rats and recorded by electrophysiology. Quantitative PCR was used for gene expression analysis of IL-1β and TNF-α.

**Results:** Pretreatment of the anti-P2X7R antibody into the left i.c.v. significantly suppressed CSD with a marked reduction of CSD number and propagation rate as well as a significant prolongation of CSD latency in rats. Induction of gene expression of IL-1β (12.7-fold) and TNF-α (5-fold) was observed post-CSD. Interestingly, this induction of TNF-α, but not IL-1β, was markedly reduced by the anti-P2X7R antibody.

**Conclusion:** This study demonstrates that P2X7R not only mediates cortex susceptibility to CSD but also contributes to subsequent induction of inflammatory factor TNF-α post CSD, indicating a therapeutic potential of blockade of P2X7R in migraine prophylaxis and treatment.

**Disclosure of Interest:** None Declared

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Enhanced susceptibility to cortical spreading depression and different degree in two-types of Na\textsuperscript{+},K\textsuperscript{+}-ATPase alpha2 subunit-deficient mice as a model of familial hemiplegic migraine 2

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**Objectives:** Patients with familial hemiplegic migraine type 2 (FHM2) have a mutated \textit{Na\textsuperscript{+},K\textsuperscript{+}-ATPase alpha2 subunit, mainly expressed in astrocytes} and show prolonged migraine aura. Cortical spreading depression (CSD), which involves mass depolarization of neurons and astrocytes that propagates slowly through the gray matter, is profoundly related to aura. In this study, we examined sensitivity and responsiveness to CSD in two types of \textit{Atp1a2}-defective mice, \textit{Atp1a2\textsuperscript{2m1Kwk}} (C-KO) and \textit{Atp1a2\textsuperscript{2m2Kwk}} (N-KO), compared with wild-type mice, in order to elucidate the mechanisms involved in the pathogenesis of FHM2.

**Methods:** Mutant and wild-type mice were examined under urethane anesthesia with mechanical ventilation (n = 45 in total). Sensitivity to CSD was evaluated as the minimum concentration of KCl required to elicit CSD by application of a 5 \textmu l aliquot of 0.025 M KCl solution, followed by further aliquots with concentrations increasing successively by 0.025 M. Propagation velocity of CSD wave was calculated from the time-lag and distance between the proximal and distal electrodes for DC potential. Full width at half maximum (FWHM) was determined from the DC potential curves recorded at the distal electrode. The change of root-mean-square values of electroencephalogram (EEG) was evaluated as an electrophysiological effect. A high dose of KCl (0.3 M) was administered to elicit repeated CSD and the duration of CSD (until the final occurrence) was evaluated. Regional cerebral blood flow (rCBF) was simultaneously recorded by laser-Doppler flowmetry.

**Results:** Heterozygotes of N-KO exhibited a low threshold KCl concentration for induction of CSD (0.12 \pm 0.04 vs 0.15 \pm 0.04 M, p < 0.05), faster propagation velocity (4.2 \pm 1.0 vs 3.4 \pm 0.5 mm/min, p < 0.05), slower recovery from DC deflection (FWHM; 52.0 \pm 14.2 vs 41.0 \pm 8.6 s, p < 0.05), and profound suppression of the EEG (43.1 \pm 14.7 vs 31.9 \pm 12.7 %, p < 0.05), compared to wild-type mice. A high dose of KCl elicited repeated CSDs for a longer period (95.7 \pm 22.7 vs 80.7 \pm 14.5 min, p < 0.05), with a tendency for a greater frequency of CSD occurrence (16.8 \pm 3.5 vs 15.9 \pm 3.6 times). The difference of every endpoint was slightly greater in N-KO than in C-KO. Change of rCBF in response to CSD showed no significant difference between the heterozygotes and wild-type mice.

**Conclusion:** Heterozygotes of \textit{Atp1a2}-defective mice, considered to be a model of FHM2, exhibited high susceptibility to CSD rather than cortical vasoreactivity. The precise effects may differ depending upon the knockout strategy for gene disruption. These results indicated that \textit{Atp1a2}-defective mice simulated FHM2, and suggest that patients with FHM2 may exhibit high susceptibility to migraine.

**Disclosure of Interest:** None Declared
Results: Nociceptive dural-evoked neuronal firing in the TCC was significantly reduced by orexin A ($F_{9,63} = 2.646$, $p = 0.011$) and by the α2-adrenoceptor agonist clonidine in a concentration-dependent manner ($F_{11,99} = 10.482$, $p < 0.01$). Glutamate also induced a significant transient inhibition of the nociceptive evoked firing in the TCC ($F_{11,55} = 7.428$, $p < 0.01$) that was completely blocked with α2-adrenoceptor antagonist pretreatment ($t_{(10)} = -3.158$, $p = 0.01$), that had no effect when given alone ($F_{11,44} = 0.926$, $p = 0.525$).

Conclusion: The results demonstrate a role for the LC in the modulation of trigeminal nociceptive processing that may provide a potential mechanistic link between sleep-wake disruption and migraine. This work was funded by MRC grant (MR/P006264/1) and Welcome Trust (Synaptopathies).


Headache Pathophysiology - Basic Science

EP-02-049

Chronic and Intermittent administration of systemic nitroglycerin in the rat induces an increase in the expression of c-Fos and CGRP mRNA in areas involved in migraine pain

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Objectives: Calcitonin gene related peptide (CGRP) is a key neuropeptide involved in the activation of the trigemino-vascular nociceptive system and it is likely implicated in migraine chronicization. In the present study we investigated the role of CGRP in migraine chronicization in an animal model that mimics the condition of chronic migraine.

Methods: The animal model was based on chronic and intermittent administration of nitroglycerin (NTG). Male Sprague-Dawley rats were injected with NTG (5 mg/kg, i.p.) or vehicle, every two days over a 10-day period (5 injections total). A group of animals was injected with Topiramate (30 mg/kg, i.p.) or vehicle every day for 10 days. Twenty-four hours after the last administration of NTG or vehicle, animals underwent a tail flick test for the evaluation of nociceptive threshold and a Von Frey test, for the evaluation of orofacial mechanical allodynia. Rats were subsequently sacrificed and their medulla-pons region, cervical spinal cord (C1-C2) and trigeminal ganglia were immediately chopped into parts for the evaluation of c-Fos and CGRP gene expression by real-time polymerase chain reaction (RT-PCR).

Results: Chronic and intermittent NTG administration caused a condition of hyperalgesia and orofacial allodynia, detected respectively as a reduction in the latency of the tail flick test and as a reduction in the threshold of mechanical sensitivity when compared either to baseline values or to control groups. NTG administration also induced a significant increase in the expression of c-Fos and CGRP mRNA in the medulla-pons region, cervical spinal cord and trigeminal ganglia. Topiramate treatment prevented the development of NTG-induced pain hyper-sensitivity, allodynia and gene expression in the above areas.

Conclusion: These findings describe the occurrence of neuronal activation and CGRP synthesis in the trigeminal ganglia and in specific areas of the CNS that are relevant for trigeminal pain processing in an animal model of chronic migraine. The inhibitory effect of topiramate, whose mechanisms of action involve blockade of voltage-dependent sodium channels, potentiation of GABAergic transmission and inhibition of glutamatergic transmission, points to an important role for these mechanisms in CGRP-mediated processes underlying pain chronication. From a translational clinic of view, these findings underline the possibility and opportunity to pharmacologically intercept and prevent migraine chronication.

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Disclosure of Interest: None Declared
**Headache Pathophysiology - Basic Science**

**EP-02-050**

**A novel mouse model for familial hemiplegic migraine type 3 reveals increased susceptibility for cortical spreading depression**

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**Objectives:** Familial hemiplegic migraine (FHM) is a rare and severe monogenic subtype of migraine, characterized by some degree of hemiparesis during the aura phase. Mutations in three causative genes, encoding ion channels and transporters in the central nervous system, have been identified (FHM1 - FHM3).

The FHM3 gene SCN1A encodes the alpha subunit of the voltage-gated sodium channel Na\(^{+}\)1.1, which is expressed by inhibitory interneurons. Previous functional studies in heterologous systems revealed diverse functional effects for FHM3-causing SCN1A mutations. Here, we set out to gain further insight into the pathophysiological mechanisms underlying FHM3 by creating a novel transgenic mouse model.

**Methods:** By means of homologous recombination, we generated the first FHM3 knock-in mouse model, carrying human point mutation L1649Q in the mouse ortholog Scn1a gene. To study the functional effects of the mutation on different levels, we used a combination of in vitro and in vivo approaches.

**Results:** In a first step, we performed electrophysiological studies in acute slices from FHM3 mice. In these experiments, fast-spiking interneurons from both the cortex and the hippocampus of FHM3 mice were found to show a significantly higher frequency of action potential firing (i.e. gain-of-function). In line with these findings, pyramidal neurons in layer V were found to receive significantly higher inhibitory input.

Next, we moved to an in vivo setting to focus on experimentally induced cortical spreading depression (CSD), the correlate of migraine aura. Mutant mice were found to display a significantly increased CSD frequency. Likewise, the threshold for CSD induction was significantly lower in transgenic animals.

**Conclusion:** We here for the first time present functional data on a transgenic FHM3 knock-in mouse model. Our in vivo data provide unequivocal evidence that FHM3 is caused by an increased susceptibility to CSD, which is in line with previous observations in FHM1 and FHM2.

Interestingly, this effect is paralleled by an increased activity of inhibitory interneurons in transgenic animals as a potentially novel mechanism underlying CSD susceptibility. Future studies will have to shed light on the mechanistic link between enhanced interneuron function and increased cortical excitability.

**Disclosure of Interest:** E. Auffenberg: None Declared, U. Hedrich: None Declared, H. Lerche: None Declared, M. Dichgans: None Declared, N. Plesnila Conflict with: Deutsche Forschungsgemeinschaft, T. Freilinger Conflict with: Deutsche Forschungsgemeinschaft, University of Tuebingen (ZSE, AKF)

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**Headache Pathophysiology - Basic Science**

**EP-02-051**

**Neuronal circuits underlying light-aversive behavior in mice.**

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**Objectives:** Veterans returning from active duty are at an increased risk for post-traumatic headache (PTH) and migraine. Migraine alone affects 10% of men and 25% of women, with the lifetime risk increasing to 18% and 43% respectively. Sensory abnormalities are present in individuals with PTH and migraine including extreme light and sound sensitivity. Light sensitivity in patients with PTH or migraine can be debilitating and treatments are lacking.

One reason interventions and treatments continue to fall short is that there is a poor understanding of the relevant neuroanatomical correlates that underlie sensory changes in headache. Calcitonin gene-related peptide (CGRP) is a critical neuropeptide involved in pain signaling and has recently come to the forefront of migraine research where it contributes to headache and associated sensory abnormalities.

In this study we attempt to identify anatomical regions where CGRP could act to induce light-averse behavior in migraine and PTH. The posterior thalamus (Po) has been suggested to be a brain region that could integrate light and pain. In addition to the Po, the periaqueductal grey (PAG) and amygdala are areas that may contribute to light-aversive behaviors in migraine. We hypothesized that CGRP acts as a neuromodulator in the Po and/or the PAG/Amygdala to induce light aversive behavior.

**Methods:** To test this hypothesis, we used two targeted approaches to probe these areas. The first was direct
CGRP injection into the Po. The second was optogenetic stimulation using channelrhodopsin to stimulate the Po, PAG, or amygdala. To further understand the role of these brain regions in migraine-like phenotypes, we performed the mouse grimace assay and squint analysis to assess pain related behavior in these mice.

**Results:** We found that CGRP injection in the Po and optical stimulation of the Po induces significant light aversive behavior, without increased anxiety. In contrast to the Po, PAG stimulation led to both light aversion and light-independent anxiogenic behavior. These data suggest that the Po can induce light aversion associated with CGRP actions, while the PAG may trigger not only the Po, but also other brain regions involved in anxiogenic behaviors. Surprisingly, optical stimulation of the amygdala produced no light-aversive behavior or anxiety phenotype in open field. To further understand the role of these brain regions in migraine-like phenotypes, we performed the mouse grimace assay and squint analysis to assess pain related behavior in these mice.

**Conclusion:** These results may begin to shed light on the complex circuitry of light-aversive behaviors in mice.

**Disclosure of Interest:** None Declared

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**Headache Pathophysiology - Basic Science**

**EP-02-052**

**Selective inhibition of trigeminovascular neurons by fremanezumab**

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**Objectives:** A large body of evidence supports an important role for CGRP in migraine pathophysiology. This evidence gave rise to a global effort to develop a new generation of therapeutics that inhibit the interaction of CGRP with its receptor in migraineurs. Recently, a new class of such drugs, humanized monoclonal anti-CGRP antibodies (CGRP-mAb) were found to be effective in reducing the frequency of migraine. The purpose of this study was to better understand how the CGRP-mAb fremanezumab (TEV-48125) modulates meningeal sensory pathways.

**Methods:** To answer this question we used single-unit recording to determine the effects of fremanezumab (30 mg/kg IV) and its isotype-conAb on spontaneous and evoked activity in naïve and CSD-sensitized trigeminovascular neurons in the spinal trigeminal nucleus of anesthetized male and female rats.

**Results:** The study demonstrates that in both sexes fremanezumab inhibited naïve high-threshold (HT) but not wide-dynamic range trigeminovascular neurons, and that the inhibitory effects on the neurons were limited to their activation from the intracranial dura but not facial skin or cornea. Additionally, when given sufficient time, fremanezumab prevents activation and sensitization of HT neurons by cortical spreading depression.

**Conclusion:** Mechanistically, these findings suggest that HT neurons play a critical role in the initiation of the perception of headache and the development of cutaneous allodynia and central sensitization. Clinically, the findings may help explain why the therapeutic effects of CGRP-mAb may be selective to headaches of intracranial origin such as migraine and why this therapeutic approach may not be effective for every migraine patient.

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**Headache Pathophysiology - Basic Science**

**EP-02-053**

**Pain suppression by MeCF in mice and rats using various in vivo models**

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**Objectives:** Nature is highly enriched in therapeutic agents and researchers continuously investigate natural products for better therapeutic agents. Plant based compounds are used in broad spectrum therapeutics to treat variety of diseases. Pain is one of the most common symptoms associated with many of illnesses and the treatments, presently, available therapies are opioids and NSAIDs but they brought severe complications and toxicities. Thus, the need for safer and potent analgesic drug is still required. In this study we have test the effect of Cassia fistula in rodents for its analgesic potential.

**Methods:** Methanolic extract of C. fistula was prepared using simple extraction method. The extract was then subjected to various analgesic tests such as, acetic acid induced writhing, tail flick and tail immersion in mice or rats. Three different doses of MeCF were used however, diclofenac sodium and tramadol were used as standard analgesics. Phytochemical analysis was performed for the presence of various chemical constituents in the MeCF.
Data was analyzed using SPSS and values were represented as ± SEM.

Results: Phytochemical examination confirmed the presence of different phytochemicals components that include terpenes, flavonoids, sugar moieties and alkaloids. However, in-vivo pain induced models testing assured approximately 12% and 22% increased in responses than standard analgesic drugs i.e. diclofenac and tramadol, respectively. In the acetic acid induced writhing, tail flick and tail immersion tests MeCF at 125, 250 and 500 mg/kg significantly exhibited analgesic activity. The results were comparable to standard analgesic drugs i.e. diclofenac sodium (10 mg/kg) and tramadol (12.5 mg/kg) *p < 0.05.

Conclusion: The present findings suggest that MeCF possess effective phytochemical that is responsible for its analgesic action. That could be good candidate for various type of headache also. However, further evaluation for mechanism of action is required to precisely explore it at molecular level.

Disclosure of Interest: None Declared

Headache Pathophysiology - Basic Science

EP-02-054

Soluble guanylate cyclase is a critical regulator of migraine-associated pain

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Objectives: Migraine is an extraordinarily common brain disorder for which therapeutic options continue to be limited. The nitric oxide pathway has been heavily implicated in migraine, and the nitric oxide donor nitroglycerin (NTG) has been shown to reliably trigger migraine in humans. NTG stimulates soluble guanylate cyclase (sGC), the main NO receptor in the body, which increases production of cGMP. However, NTG is also a major source of reactive oxygen species, and this increased oxidative stress could also contribute to the induction of migraine. The aim of this study was to identify the precise role of sGC in acute and chronic migraine. Specifically, we determined if acute and chronic treatment with a novel sGC stimulator (VL-102) would induce migraine-associated pain. We also tested the effects of the sGC inhibitor, ODQ, within a NTG-based model of chronic migraine.

Methods: VL-102 (sGC stimulator), NTG, and ODQ (sGC inhibitor) were administered IP to male and female C57BL6/J mice every second day for 9 days. To determine if there was an upregulation of sGC activity in chronic migraine, ODQ was administered 24 h following the final -NTG treatment (day 10). On test days, basal and drug-evoked mechanical hypersensitivity was evaluated using von Frey hair stimulation.

Results: VL102-evoked acute and chronic mechanical hyperalgesia in a dose-dependent manner. This hyperalgesia was blocked by the migraine medications sumatriptan and topiramate. The sGC inhibitor ODQ inhibited acute and chronic hyperalgesia induced by NTG. Interestingly, ODQ also blocked hyperalgesia already established by chronic NTG treatment.

Conclusion: These results indicate that NTG causes migraine-related pain through activation of the sGC pathway, and that super-activation of sGC may be an important component of chronic migraine pain. Furthermore, this work indicates that sGC inhibitors would be promising new migraine therapies.

Disclosure of Interest: None Declared
Big Data

PO-02-001

Headache Version 2.0 Common Data Element (CDE) Recommendations: Updates to the National Institute of Neurological Disorders and Stroke (NINDS) Headache CDEs

Sarah Tanveer1,*, Sherita Ala'i1, Joy Esterlitz1, Katelyn Gay1 and Michael L Oshinsky 2; on behalf of Headache V2.0 CDE Working Group

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Objectives: The National Institute of Neurological Disorders and Stroke (NINDS) Headache Common Data Elements (CDE) project was initiated to specifically develop data standards for clinical research within the neurological community. The vision of this initiative is to create common data elements and definitions so that information is consistently captured and recorded across studies in order to: increase the efficiency and effectiveness of clinical research studies and clinical treatment, increase data quality, facilitate data sharing across studies, more effectively aggregate information into significant metadata results, significantly reduce study start-up time, and help educate new clinical investigators. Since the 2011 release of Version 1.0 (V1.0) of the Headache CDEs, the research community felt that updates were necessary to better serve the purpose of harmonizing data collection. In July 2017, the Headache Version 2.0 (V2.0) CDEs will be released; the intent of the revisions are to provide updated recommendations based on the current state of headache research.

Methods: In 2016, a Headache V2.0 working group (WG) was established to review the CDEs and associated recommendations from 2011. The updates to the headache CDEs are based on clinical advancements and developments in the field of headache research, as well as user feedback of existing CDEs. The Headache V2.0 WG, consisting of 42 worldwide experts, met monthly from August 2016 to May 2017 to review, revise and add to the headache-specific V1.0 CDEs. WG members selected and recommended instruments and assessments, and also refined and added to existing field-tested data elements from national registries and studies. Recommendations were revised and posted to the NINDS CDE website for public use.

Results: This second iteration of Headache CDE recommendations spans the following five domains: Biomarkers; Demographics; Imaging and Neurophysiology; Therapies and Intervention; and, Diagnostics and Characteristics. Headache V2.0 CDEs will be released to the NINDS CDE website in July 2017. The latest information provided at this meeting includes examples of how headache CDEs may be used by researchers, and how to navigate and select CDEs from the NINDS CDE website.

Conclusion: The NINDS CDEs are an evolving resource that is constantly being updated as research progresses. NINDS encourages use of CDEs by the clinical research community in order to standardize the collection of research data across studies. Through the development of the Headache V2.0 CDEs, the initiative strives to promote CDE standards designed to assist researchers in the various stages of design, implementation, and interpretation of their clinical study data.

Disclosure of Interest: S. Tanveer: None Declared, S. Ala’i: None Declared, J. Esterlitz: None Declared, K. Gay: None Declared, M. Oshinsky Conflict with: National Institute of Health

Big Data

PO-02-002

N = 1 statistical approaches to examine risk factor profiles of ICHD-3-beta classified headaches versus migraines within individuals

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Objectives: To what extent do migraines vs non-migraine headaches (distinguished by ICHD-3-beta criteria) differ in underlying pathophysiology? This study examines risk factors associated with the (a) incidence (onset) and (b) severity of both migraine vs non-migraine headaches. Because profiles of headache triggers vary greatly among patients, statistical analyses were conducted at the individual level and the individual-level results were then used to draw sample aggregate conclusions.
Methods: Participants were 750 individuals with migraine identified by clinician referral or via the internet and registered to use a novel digital platform (Curelator HeadacheTM). Participants completed baseline questionnaires and then entered daily data on headache occurrence and severity (level of pain), ICHD-3beta migraine criteria, and exposure to 70 migraine risk factors. Nearly 88% of the sample was female. Risk factors spanned emotions, sleep qualities, environmental and weather factors, lifestyle, diet, substance use, travel, and three additional triggers selected by each patient. Cox regression hazard ratios tested associations between occurrence of a migraine (binomial) and the triggers. A form of hierarchical linear modeling tailored for \( N = 1 \) analysis (termed mixed model trajectory analysis or MMTA) tested associations between triggers and pain severity of (non)migraine headaches. MMTA statistically controlled for patient-specific time-related trends in pain severity, autocorrelation, and used statistical tests that generate conservative estimates for \( N = 1 \) analyses. Severity of headache was rated by patients on a mild – moderate – severe scaling.

Results: Among the individual-level associations between a risk factor and severity of pain from a headache, 50% of risk factors were associated with both migraine and non-migraine headaches whereas the other half were unique to one form of headache or the other. The particular risk factors that were associated with either form of headache varied greatly among individual patients.

Conclusion: Results suggest that triggers of onset of migraine attacks both overlap and differ from the risk factors that are associated with the severity of migraine pain. Moreover, these associations differ between migraine and non-migraine headaches. These observations imply that etiological factors differ between types of headaches. They further suggest that treatment of migraine headaches could aim to not only prevent the incidence of attacks, but also reduce the pain (and thus impairment) that patients experience during a migraine headache.


Cluster Headache and Other Trigeminal Autonomic Cephalalgias

PO-02-003

Clinical profile of SUNCT/SUNA in Japan - a clinic-based study

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Objectives: Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) are rare primary headache syndromes, classified as trigeminal autonomic cephalalgias (TACs). Most studies of SUNCT/SUNA have focused on Caucasian populations, and thus, little is known about the characteristics of SUNCT/SUNA in patients from Asia. We characterized the clinical profile of SUNCT/SUNA in Japan by surveying patients with SUNCT/SUNA registered at a Japanese regional headache center.

Methods: The classification and clinical features of 20 consecutive patients with SUNCT (8 males, 3 females; mean age, 59.5 ± 20.5 years) and SUNA (5 males, 3 females; mean age, 51.3 ± 18.4 years) visiting a tertiary Headache center (Tominaga hospital) from February 2011 to January 2017 were analyzed. The diagnosis of headache was established in accordance with ICHD-2 or 3beta.

Results: Eight cases were previously diagnosed as cluster headache (CH), 7 as trigeminal neuralgia (TN), and 2 as migraine at clinics or hospitals. Only 2 cases were diagnosed as SUNCT previously. The attacks were left-sided in 7 cases and right-sided in 13; none of the patients had bilateral or side-shifting attacks. All patients reported either brief clusters of separate attacks or a saw-tooth pattern of attacks. An episodic disease course was evident in 19/20 (95.0%) cases, whereas 1/20 (5.0%) had a chronic course. Mean attack duration was 91.9 ± 87.9 s, being <30 s in 6/20 (30.0%) cases, approximately 60 s in 5/20 (25.0%), approximately 120 s in 3/20 (15.0%), and >120 s in 6/20 (30.0%). Besides ipsilateral conjunctival injection and lacrimation, ipsilateral rhinorrhea occurred in 9/20 (45.0%) and facial sweating in 1/20 (5.0%). Three out of 20 (15.0%) patients were smokers and 4/20 (20.0%) were alcohol consumers. A good or excellent response to...
lamotrigine was seen in 9/9 (100%), but toxic eruption was seen in 2/9 (22.2%). Pregabalin was effective in 3/10 (30.0%), gabapentin in 4/5 (80.0%), topiramate in 2/3 (66.7%), and carbamazepine in 2/4 (50.0%). An intravenous lidocaine proved completely effective for acute attacks of SUNCT in 5/6 (83.3%). Poor response was seen in a chronic SUNCT case. Indomethacin was ineffective in 6/7 (85.7%) cases; the good response to indomethacin in one patient may be because of the coexistence of SUNA and paroxysmal hemicranias in that patient. Computed tomography was used for investigation in one patient and magnetic resonance imaging (MRI) in the remaining patients. In 11 cases, the MRI revealed ipsilateral trigeminal neurovascular compression (NVC). Five cases were thought to have been transformed from TN. One SUNCT case with ipsilateral trigeminal NVC was treated with microvascular decompression, and the pain relieved postoperatively.

**Conclusion:** As in Caucasian patients, lamotrigine is effective in the majority of cases, and intravenous lidocaine is useful as an acute medication for severe recalcitrant attacks in Japanese patients with SUNCT/SUNA. However, patients in this study showed a relatively low prevalence of chronic SUNCT/SUNA (5%). Chronic CH is reported to show relatively low prevalence in Asia. Thus, chronic TACs may show relatively low prevalence in Asia. MRI revealed ipsilateral trigeminal NVC in 11 cases, and 5 cases were thought to have been transformed from TN. Therefore, despite being considered distinct conditions, emerging clinical and radiological evidence supports a broader nosological concept for SUNCT/SUNA and TN. Further evidence is required to shed light on this nosological issue, given its potential impact on clinical practice and future studies.

**Disclosure of Interest:** None Declared
Cluster Headache and Other Trigeminal Autonomic Cephalalgias

PO-02-005
Cluster Headache – Clinical pattern and a new severity scale in a Swedish cohort
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Objectives: Cluster headache (CH) patients exhibit a broad variance regarding disease burden. The objectives of this study were to investigate clinical features of the CH population in the central part of Sweden and to construct a new scale for grading severity.

Methods: Subjects were recruited from central Sweden and identified by screening medical journals for patients with the ICD 10 code G44.0, i.e. cluster headache. The study was designed as an observational survey and health records were read to confirm that the diagnosis fulfilled the International Headache Society criteria. All participating research subjects filled in a questionnaire including personal, demographic and medical aspects as well as questions designed to assess the CH pattern. We constructed a novel scale for grading severity of CH: the Cluster Headache Severity Scale (CHSS). The scale included three score items; number of attacks per day, attack duration and period duration. The lowest total score summarizing these score items was three and the highest 12. We used the CHSS to grade 500 subjects suffering from CH and further implemented the scale by defining and characterizing a CH maximum severity (CHMS) subgroup with a CHSS score ≥ 9.

Results: Our data show that chronic CH patients have a later mean age at onset compared to episodic patients and a majority (66.7%) of the patients reported that attacks appear at certain time intervals. In addition we report that CH patients who are current tobacco users or have a history of tobacco consumption had a later age of disease onset (31.7 years) compared to non-tobacco users (28.5 years). The CHSS was higher in the patient group reporting sporadic or no alcohol intake, than in the groups reporting an alcohol consumption of 3–4 standard units/week or more. A larger proportion of episodic patients had a regular alcohol intake compared to chronic patients and alcohol was identified to be the most common trigger factor for cluster attacks during a bout. In addition, a large male dominance (68%) was found in the whole study population, in contrast to the most severely affected subgroup (CHMS) where the distribution was less shifted, 56.9% men compared to 43.1% women. CHMS patients were further characterized by a higher age at disease onset, greater use of prophylactic medication, reduced hours of sleep, and lower alcohol consumption compared to the non-CHMS group.

Conclusion: There was a wide variation of severity grades among CH patients, with very marked impact on daily living for the most profoundly affected.

Disclosure of Interest: None Declared

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

PO-02-006
Illicit Drug use among Cluster Headache Patients compared to the Dutch Population
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Objectives: Many cluster headache patients believe that illicit drugs might be effective in treating and preventing attacks. We systematically determined the use and assessed the effects of illicit drugs in a cluster headache population in the Netherlands - where use of cannabis is tolerated.

Methods: This cross-sectional study was conducted as part of the Leiden University Cluster Headache neuro-analysis programme (LUCA). Persons with cluster headache (n = 756) received a questionnaire designed by the authors, involving lifetime use of illicit drugs (cannabis, cocaine, heroin, PSI, MDMA, LSD, amphetamine and GHB) and their effect on attacks. Results were compared with age-matched data from the Dutch general population (n = 30.000) from the ‘Dutch annual health survey’.

Results: The response rate was 85.1%. There were more illicit drug users among cluster headache patients than in the general population (all drugs 32% vs. 24% (P < 0.01); cannabis 30% vs. 23% (P < 0.01); cocaine 9% vs. 5% (P < 0.01); amphetamine 6% vs. 4% (P = 0.01), PSI 9% vs. 4% (P < 0.01); heroin 1% vs. 0.5% (P = 0.04). No difference in illicit drug use was found between episodic and chronic cluster headache (31% vs. 32%; P = 0.41). Among cluster headache patients and in the general population, males more often used illicit drugs (29% vs. 19%; P < 0.01 and 35% vs. 24%; P < 0.01). The age distribution of illicit drug use followed the same pattern among cluster headache patients as in the general population, with less use of illicit drugs in older age cohorts. A positive influence on attack frequency was reported in 56% of LSD users, while 18% of GHB users reported a negative influence. Decreased attack duration was reported in 50% of PSI and heroin.
users, while 4–11% of cocaine, GHB, cannabis and MDMA users reported a prolonged attack duration.

**Conclusion:** In a Dutch cluster headache population remarkably many patients use illicit drugs. This might either be due to an actual alleviatory effect on cluster headache attacks, or due to false believe among people desperately seeking relieve of their cluster headache.

**Disclosure of Interest:** None Declared

**Cluster Headache and Other Trigeminal Autonomic Cephalalgias**

**PO-02-007**

**The Psycho-Social impact of living with Cluster headaches: A scoping study**

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**Objectives:** ‘Cluster headache (CH) is commonly regarded as one of the most disabling headache conditions, and referred to as one of the most painful conditions known to humankind (Torkamani et al., 2015)’. There has been limited research exploring the severe impact of CH and the consequences this has on the more psychological and social aspects of life. The objective of this research is to identify the social and psychological issues faced by those living with a diagnosis of Cluster headache and begin to explore some resilience factors and opportunities to offer appropriate support and advice to those living with a CH diagnosis. The primary author is a Chronic CH/TAC sufferer as well as a Social worker & Health psychologist.

**Methods:** Initially an online survey was advertised through online CH support groups, this elicited 375 responses. Demographics were collected and a single open ended question was asked, asking participants to identify areas of their life affected by CH diagnosis. The responses were analysed using thematic analysis. Following this In depth interviews (n = 10) with a small sample of respondents were arranged to begin to explore the complexities of the themes. Finally 2 focus groups were arranged to allow individuals living bringing CH patients together. Themes identified in the first 2 stages were reviewed by the groups and they were asked what it was about CH that led to people having issues in these areas of their life. The participants shared their experiences of living with the issues identified by the themes presented. These participants were asked to discuss what has helped them cope and what they feel is missing in order for them to be able to cope.

**Results:** 375 (48.66% Male, 51.34% female) completed an online questionnaire. All respondents had a formal diagnosis of CH (56.8% episodic and 4.2% chronic) and were asked ‘aside from the medical and physical impact of your CH diagnosis what areas of your life have been most affected by your CH diagnosis?’ Only 3 respondents said that their diagnosis has no impact on their lives. 13 key themes were identified in the analysis of the responses. During further analysis these themes were grouped together under 3 headings; ‘Work & career’, ‘Relationships’ and ‘Physical & mental wellbeing’. Further stages of the research reinforced these themes and allowed us to identify some of the complexities behind each theme. It became apparent that the themes identified were rooted in common experiences of CH patients including; pain; isolation; lack of/misunderstanding of the condition by health professionals and lay persons alike.

**Conclusion:** Patients with CH identified several areas where their day to day life was affected significantly by their diagnosis. Aspects of the condition such as pain and lack of sleep were identified as having consequences for psychological and social wellbeing. This reinforced the need for better management and ongoing support for patients living with CH by both medical and allied health professionals. The findings also concluded that better management by medical professionals would facilitate better self-management of the condition by the patient, the benefits of which are explored in this paper. There are additional challenges for patient groups and appropriate professionals to raise awareness of not only the identified psychological and social impact of a CH diagnosis but also a general increased awareness of the condition as this lack of understanding has a significant impact on patient wellbeing.

**Disclosure of Interest:** None Declared

**Cluster Headache and Other Trigeminal Autonomic Cephalalgias**

**PO-02-008**

**Trigeminal Autonomic Cephalalgias in tertiary Multi-disciplinary Orofacial Pain clinic**

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**Objectives:** Patients with headache often present to different specialities and in particular Trigeminal Autonomic Cephalalgia (TACs) patients are often seen by dentists. Of patients with cluster headaches 45% have consulted a dentist prior diagnosis and many have had procedures performed for the pain.
To evaluate the final diagnosis made from patients seen at a tertiary Multi-disciplinary Orofacial Pain clinic.

**Methods:** A retrospective review of clinic letters of patients who have attended the Multidisciplinary Orofacial Pain clinic over a ten month period, from September 2015 till July 2016, looking specifically at the final diagnoses.

**Results:** Of patients \((n = 126)\) seen in clinic, 34 were follow up assessments and excluded. New patients \((n = 92)\) had an average age of 52 years, and most were female \((n = 63, 68\%).\) The most common diagnosis made in the Clinic was a TAC \((38\%)\), followed by migraine \((37\%)\) and post-traumatic trigeminal neuropathy \((10\%).\) The most common TAC diagnosis was possible hemicrania continua \((74\%),\) three were confirmed with indomethacin testing \((\text{two had oral indomethacin trials}), two were negative on placebo-controlled intramuscular indomethacin testing and two were inconclusive on placebo-controlled intramuscular indomethacin test, the rest are awaiting testing.

**Conclusion:** TACs are the most common diagnosis made by the Headache team in our Multidisciplinary Orofacial Pain clinic. We conclude the importance of a multidisciplinary team approach to these complex patients.

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**Cluster Headache and Other Trigeminal Autonomic Cephalalgias**

**PO-02-009**

**Availability of effective evidence-based symptomatic treatments for cluster headache in the EU countries. A survey of the European Headache Alliance**

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**Objectives:** Treating cluster headache can be tricky because the pain becomes extremely severe very quickly and only few evidence-based treatments can work. Recent data from IHS suggest that oxygen is not universally reimbursed or available for CH patients. The aim of this study was to assess the reimbursement option and accessibility of 4 effective medicines for CH (sumatriptan s.c, oxygen, sumatriptan spray and zolmitriptan spray) across EU

**Methods:** A brief survey investigating the availability of symptomatic treatments for CH was send on e-mail on January 2017 to at least one headache specialist for every single country of the EU. For a complimentary point of view in the countries where active CH patients’ associations exist the survey was completed by CH expert patients.

**Results:** The questionnaire was completed by 26 headache specialists \((93\%\) of the EU countries representing 99.75% of the European population) and 10 CH expert patients \((representing 72\% of the European population).\) The answers provided by the headache specialists and expert patients were coherent in every country. Availability of ETs was defined as: a) complete: both oxygen and sumatriptan vial fully reimbursable and accessible; b) restricted: partial reimbursement or inaccessibility of one between Oxy and Suma s.c; c) lacking: both oxygen and sumatriptan s.c not reimbursable and not accessible. Oxygen was reimbursable for 62.68% of the CH population. Oxygen device was reimbursable for 49% of the CH population. Sumatriptan s.c. was reimbursable for 65% and accessible without restrictions for 37.1% of the CH population. Sumatriptan spray was reimbursable for 64% and accessible without restrictions for 43.7% of the CH population. Zolmitriptan spray was reimbursable for 23.7% and accessible without restrictions for 30.9% of the CH population.

Availability of CH effective treatments resulted complete, restricted or lacking for 49%, 30% and 21% respectively of the CH European patients

**Conclusion:** Based on this survey only 50% of the EU population had an unrestricted access to CH effective treatments with unacceptable inequalities between eastern countries and the rest of Europe. Headache societies and patients’ associations should pressure European and national health authorities to improve the availability of effective symptomatic treatments for CH.

**Disclosure of Interest:** None Declared

**Cluster Headache and Other Trigeminal Autonomic Cephalalgias**

**PO-02-010**

**Pre-attack symptoms in cluster headache**

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**Objectives:** In contrast to the premonitory phase of migraine, only little is known about the pre-attack
(prodromal) phase of a cluster headache (CH). We aimed to describe the nature, prevalence and duration of pre-attack symptoms in CH.

Methods: Patients with episodic CH and chronic CH, according to ICHD III (beta), were invited to participate. To avoid unnecessary recall bias, only episodic patients in active cluster and chronic cluster headache patients were included in the study. Patients were divided with regards to gender and CH diagnosis for group comparisons. All patients underwent a semi-structured interview where they were asked about presence of 31 symptoms in relation to a typical CH attack. Symptoms included previously reported CH pre-attack symptoms, premonitory migraine symptoms and accompanying symptoms of migraine and CH. Symptoms were grouped into: local and painful, local and painless and general.

Results: Eighty patients, 29 (36.3%) episodic CH, and 49 (61.3%) men, were included in the study. Of these patients, 86.3% reported pre-attack symptoms. Local and painful symptoms, occurring on average 29 min before the attack was reported by 70% of patients, 43.8% patients reported local and painless symptoms on average 38 minutes before the attack and 62.5% reported general symptoms on average 42 minutes before an attack. Of the local and painless symptoms, reported by 32.5% of patients, lacrimation, nasal congestion and rhinorrhea occurred at a median time of 5 minutes before the subsequent attack. Patients experienced on average 4.25 (SD 3.9) pre-attack symptoms: local and painful: 1.06 (SD 0.9), local and painless: 1.03 (SD 1.6) and general: 2.16 (SD 2.5). Apart from a dull/aching sensation in the area of the subsequent attack being experienced significantly (p < 0.05) more among men and episodic patients, no differences in the prevalence of pre-attack symptoms were identified in between groups.

Conclusion: Pre-attack symptoms are frequent in CH. Since the origin of CH attacks is still unresolved, studies of pre-attack symptoms could contribute to the understanding of CH-pathophysiology. Furthermore identification and recognition of pre-attack symptoms could potentially allow earlier abortive treatment.

Disclosure of Interest: None Declared

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

PO-02-011

Treatment of resistant cluster headache by sphenopalatine ganglion pulse radiofrequency ablation

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Objectives: We report a case of a treatment-resistant-episodic cluster headache-patient who was treated with various combinations of drugs and interventional methods including great occipital nerve (GON), supraorbital nerve (SON) and sphenopalatine ganglion (SPG) block and had remission with SPG pulse radiofrequency ablation finally.

Methods: A 25-year-old man presented with right-sided, periocular, pulsating type headache accompanied with tearing, conjunctival injection, ptosis and nose stiffness ipsilaterally. His headache lasted 1–3 minutes with a frequency of 10–15 per day. He had headaches for five months occurring three times a week and then he had been asymptomatic for seven months. Next year he returned to our unit with the same type of headache with a longer duration (30–50 minutes) and a frequency of 3–5 times/day which lasted for six months. Following six years he had bouts of headache with the same characteristics starting November lasting till March. Regarding to changing headache characteristics he was diagnosed as paroxymal hemicrania evolving to episodic cluster headache. During six years of follow-up he had used verapamil, lithium, pregabalin for profilaxis. Because of having more severe headaches for the last three bouts, GON and SON blocks had also been tried. His remission periods were approximately five months but in his last bout he had extremely severe headaches, his remissions lasted for a month and the headaches re-occurred in spite of taking verapamil combined with methylprednisolone and pregabalin followed by GON and SPG block. The patient underwent SPG pulse radiofrequency ablation finally.

Results: Our patient had only six headaches in the last four months and the headaches’ severity decreased prominently. Conclusion: SPG pulse radiofrequency ablation may be done when medical and interventional treatments are not effective enough for the management of intractable cases.

Disclosure of Interest: None Declared
Cluster Headache and Other Trigeminal Autonomic Cephalalgias

PO-02-012

Characteristics of SUNCT and SUNA in a Headache Clinic of Hong Kong

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Objectives: To report the clinical characteristics and treatment responses in a case series of Chinese outpatients diagnosed with SUNCT or SUNA in Hong Kong.

Methods: A prospective study was conducted to characterize the clinical phenotypes and treatment responses in patients diagnosed with SUNCT/SUNA by headache specialist in a headache clinic of Hong Kong between 2012 and 2016. The diagnosis was made according to the International Headache Society (IHS) diagnostic criteria.

Results: Eleven patients were diagnosed SUNCT ($n=5$) or SUNA ($n=6$) with a female to male ratio of 1.75 and a median age of onset at 55 (range 38–76). The median number of years to diagnosis was 6 (range 1–16). Pain occurred in V1 distribution alone in 36%, both V1 and V2 in 46%, V2 alone in 9% and both V2 and V3 in 9%. For cranial autonomic symptoms, lacrimation was the commonest feature in 100% subjects, followed by rhinorrhea (64%) and conjunctival injection (46%). Others included ptosis (18%), facial flushing (18%), periorbital swelling (9%), facial sweating (9%), nasal congestion (9%) and aural fullness (9%). Chewing (91%) was the most common trigger, followed by washing face (82%), brushing teeth (64%), wind blowing (55%), rubbing eye (27%), talking (27%), shower (14%), sneezing (14%), laughing (7%), shaving (7%) and exercise (7%). Neurovascular compression was demonstrated radiologically in 2 subjects (18%). Lamotrigine was the most effective (77%) prophylaxis in drug trials. Carbamazepine (effective in 57%) and pregabalin (25%) were also useful in reducing the pain intensity or frequency in our cohort. Adverse drug effect was the commonest reason of switching drugs in treatment trial.

Conclusion: In our cohort, female preponderance in SUNCT/SUNA is observed. The location of pain distribution, cranial autonomic symptoms, triggers and response rate to Lamotrigine are similar to those reported in the literatures. Our study demonstrated that it can take quite a long time to diagnose both conditions despite seeking early medical attention. This reflects the importance of recognizing the conditions and initiating treatment as soon as possible because the pain is debilitating and effective treatment is available.

Disclosure of Interest: None Declared

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

PO-02-013

Trigeminal autonomic cephalgia-like headache syndromes following surgery: a case series

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Objectives: The trigeminal autonomic cephalgias (TACs) are primary headache disorders characterized by lateralized pain with associated cranial parasympathetic autonomic features. In a small number of patients, TAC-like headaches are a secondary headache syndrome. There are rare cases of new-onset TAC-like headaches following cranial surgeries. We report a case series of TAC-like headaches developing after surgery on extracranial structures innervated by the trigeminal nerve.

Methods: Case series

Results: Patient 1: A 42-year-old man presented with 3 years of episodic severe left eye pain. The first episode occurred 1–2 days after deviated septum repair and sinus drainage. Twice a month, he develops left orbital pressure building over 1–2 hours. He then experiences sharp, stabbing eye pains for 1–2 minutes 10–15 times per day for 3–15 days. Rarely, milder pain occurs in the right eye simultaneously. Interictal soreness remains until the episode resolves. Associated symptoms include nasal congestion and occasional bilateral conjunctival injection, as well as persistent photophobia and phonophobia. He lies down and places pressure over his eye until the pain passes. Trochlear blocks improve the acute attacks, and lamotrigine improved the frequency and severity of his pain episodes.

Patient 2: A 60-year-old man presented with 3 years of constant left eye pain that onset following left retinal detachment repair with intraocular gas bubble and gradually increased in severity. Subsequent epiretinal membrane removal, cataract extraction, intravitreal steroid injection, Seton tube shunt (for new intraocular hypertension), and corneal transplant did not help his vision or pain. He has constant left eye pain that gradually worsens throughout the day to a throbbing in the left supraorbital and temporal region. He also experiences multiple attacks of severe, stabbing pain like a “sharp poke in his eye” every day. Most attacks occur between 5:00 pm and 2:00 am. Each attack lasts a few seconds, with residual pain resolving after 15–30 minutes. During these attacks, he has photophobia, restlessness, and erythema and swelling of the left eyelid. Triggers include eye movement, bending over, lying flat, and stress. He did not respond to indomethacin, verapamil, carbamazepine, or lamotrigine.

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Sphenopalatine ganglion block and trochlear blocks temporarily improved the pain.

Patient 3: A 25-year-old man with a history of migraines and testicular cancer presented with 2 years of persistent headache after left macula biopsy for painless progressive vision loss suggestive of an autoimmune retinopathy. He has constant sharp left retrobulbar pain. Every two weeks, the pain acutely worsens with throbbing and electric-like jolts radiating to the back of his neck. He has tearing, ptosis, nausea, photophobia, dizziness, and irritability during the attacks, which last 4–10 hours. The severe pain may awaken him from sleep or be provoked by focusing. He did not improve on a low dose of indomethacin, but could not tolerate higher doses.

**Conclusion:** We describe three cases of TAC-like headaches following surgical procedures on trigeminally-innervated structures. The trigeminal nerve carries autonomic fibers, and direct injury, tissue swelling, or an inflammatory response may lead to dysregulation of the trigeminal-autonomic reflex. Without prompt recognition and treatment of the symptoms, uncontrolled pain may lead to long-term central sensitization reminiscent of the complex regional pain syndrome that can follow minor trauma to other parts of the body. Although acute post-surgical pain requires appropriate assessment, recognition and diagnosis of the headache syndrome based on its clinical features is key to preventing unnecessary surgical intervention that may further exacerbate the pain syndrome.

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**Cluster Headache and Other Trigeminal Autonomic Cephalalgias**

**PO-02-014**

**A Comparative Study of Cranial Autonomic Symptoms/signs (CAS) in Trigeminal Autonomic Cephalalgias**

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**Objectives:** Patients with trigeminal autonomic cephalalgias (TACs) characteristically have side locked headache in V1 distribution and ipsilateral prominent one or more cranial autonomic symptoms/signs (CAS). However, there may be differences in occurrence, frequency, laterality, severity and consistency during the attacks between the subgroups.

The aim of this study was to study and compare the CAS in the 4 subgroups of TACs namely cluster headache (CH), paroxysmal hemicrania (PH), hemicrania continua (HC) and short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)/Short lasting unilateral headache attacks with autonomic features (SUNA) as diagnosed by ICHD3b.

**Methods:** We analysed following 10 CAS features namely lacrimation, conjunctival injection, eyelid edema, nasal congestion, rhinorrhea, facial/forehead sweating, facial/forehead flushing, drooping of eyelid, aural fullness and miosis. We noted their occurrence, laterality, frequency, extent of involvement, severity and consistency during the attacks.

**Results:** 122 TACs patients were studied. Out of them, 44 patients had CH, 36 patients had PH, 16 had HC and 26 had SUNCT/SUNA. Analysis of CAS features and their comparison in individual TACs group is summarised in table 1.

**Conclusion:** Overall, presence of at least one of the CAS was seen in 96–100% of patients of TACs. Lacrimation was commonest CAS in all TACs group. Although CAS ipsilateral to headache is the defining features of TACs, few CAS were seen bilaterally in 39 to 59% patients. Commonest bilateral CAS was facial and forehead sweating and flushing. Bilateral CAS was more common CH and HC. Within the TACs subgroups, frequency of CAS per patient was more in CH and HC than in PH and SUNCT/SUNA (3.6 versus 2.8). While most of the TACs patient had 2 CAS, nearly half of CH had 4 or 5 CAS/attack. CAS was more severe in SUNCT/SUNA and CH. About 80% of SUNCT/SUNA and 64% of CH patients had CAS in all their attacks as
compared to 60% in PH and 50% in HC during exacerbations. Thus, spectrum of CAS differs in subgroups of TACs.

Disclosure of Interest: None Declared

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

PO-02-015

OCCIPITAL NERVE BLOCK: A MANDATORY TREATMENT IN CLUSTER HEADACHE

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Objectives: In recent years, occipital nerve block (ONB) has been proposed as a good option of treatment in cluster headache (CH) patients. It is a clean, cheap, quick and easy technique in general clinical practice. The objective of our study is to prospectively analyze its use in a recently established Headache Unit in order to manage CH patients.

Methods: Since 2014, our protocol in CH management included ONB as first line treatment as soon as possible (asap) when a cluster period begins. ONB is made with bupivacaine 4 cc + triamcinolone 1 cc ipsilateral to the headache and autonomic signs. We used it in any CH patient (either episodic (ECH) or chronic (CCH)) attending our headache clinic with an active period. ECH patients were advised to come asap when a cluster period begins. Outcome was measured as: Complete response (no need to use any other transitional or preventive medication and cluster aborted since ONB); Good response (>75% improvement in duration of CH period and rescue medication use); Partial response (25–75% improvement); and No response (<25% improvement).

Results: 35 patients, 29 ECH and 6 CCH (17'1%) were attended. 27 males and 8 females (3'4:1). Mean age 42'4 years (16–64). Outcome is analyzed separately in CCH and ECH patients.

CCH: one patient rejected ONB, the resting 5 were injected 41 times (3–15, median 8); No patient got Complete response, 2 (40%) got a Good response, other 2 (40%) Partial and 1 (20%) got No response.

Table: Analysis of Cranial Autonomic Symptoms/Signs in Trigeminal Autonomic Cephalalgias

<table>
<thead>
<tr>
<th>CAS features</th>
<th>Cluster Headache n = 44</th>
<th>Paroxysmal Hemicrania n = 36</th>
<th>Hemicrania Continua n = 16</th>
<th>SUNCT/SUNA n = 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurrence of CAS</td>
<td>44(100%)</td>
<td>35(97.2%)</td>
<td>16(100%)</td>
<td>25(96.2%)</td>
</tr>
<tr>
<td>Three most common CAS</td>
<td>Lacrimation: 37(84%)</td>
<td>Lacrimation: 22(61.7%)</td>
<td>Lacrimation: 11(68.7%)</td>
<td>Lacrimation 18(69.2%)</td>
</tr>
<tr>
<td></td>
<td>Conjunctival injection: 30 (68%)</td>
<td>Facial sweating: 17 (47%)</td>
<td>Conjunctival injection: 9 (56.3%)</td>
<td>Conjunctival injection: 16 (61.4%)</td>
</tr>
<tr>
<td></td>
<td>Facial sweating: 19 (43%)</td>
<td>Aural fullness: 17 (47%)</td>
<td>Eyelid edema/Aural fullness: 7(44%)</td>
<td>Facial sweating/Eyelid edema/Aural fullness: 9(34.6%)</td>
</tr>
<tr>
<td>Laterality: Ipsilateral to headache</td>
<td>18(41%)</td>
<td>19(54.3%)</td>
<td>8(50%)</td>
<td>16(61.5%)</td>
</tr>
<tr>
<td>Frequency: Average number of CAS in a patient ± SD</td>
<td>3.6 ± 1.5</td>
<td>2.8 ± 1.3</td>
<td>3.6 ± 1.8</td>
<td>2.8 ± 1.4</td>
</tr>
<tr>
<td>Maximum number of combinations of CAS</td>
<td>4/5 CAS in 10(23%) patients</td>
<td>2 CAS in 10(27.8%) patients</td>
<td>2 CAS in 8(50%) patients</td>
<td>2/3 CAS in 8(30.8%) patients</td>
</tr>
<tr>
<td>Severity of CAS</td>
<td>Mild</td>
<td>12(27%)</td>
<td>13(37%)</td>
<td>7(44%)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>32(73%)</td>
<td>22(63%)</td>
<td>9(56%)</td>
</tr>
<tr>
<td>Consistency of CAS/Attack (or exacerbations in HC)</td>
<td>100%</td>
<td>28(63.5%)</td>
<td>21(60%)</td>
<td>8(50%)</td>
</tr>
<tr>
<td></td>
<td>50–100%</td>
<td>12(27.5%)</td>
<td>9(25.7%)</td>
<td>4(25%)</td>
</tr>
<tr>
<td></td>
<td>&lt;50%</td>
<td>4(9%)</td>
<td>5(14.3%)</td>
<td>4(25%)</td>
</tr>
</tbody>
</table>
ECH: 11 patients out of 29 were not active at the moment of the visit, even all of them have been advised to return asap when a cluster period begins. In the resting 18 ECH patients ONB was made 48 times (1–8, median 2'7, just one time in 5 patients and two times in 7 patients); Complete response was achieved in 11 patients (61'1%), Good response in 6 patients (33'3%), Partial response in 1 patient (5'6%) and there was no patient with No response. The duration of the cluster period was dramatically reduced in this group from a mean of 73 days (based in previous history) to 7. In accordance, the use of rescue medication (usually sc sumatriptan or en zolmitriptan) and transitional (usually oral corticosteroids) or preventive (verapamil and others) medication was not necessary in the great majority of patients.

Conclusion: Even the short number of patients included in the study, it seems that ONB must be mandatory in the management of CH patients. It is somewhat useful to improve CCH patients poor quality of life, some of them feel this technique permits them a better management of the illness. In ECH, ONB has changed dramatically the natural history of the disease. It's not just the numbers, which are stunning; it's the patient perception of the spectacular outcome that ONB permits and the self-confidence it deserves to them compared to previous experiences. ONB must be included as a first line treatment in the management of ECH patients. Used asap when the cluster period begins, as in our experience, cuts-off the headache in almost two-thirds of patients and shortens the duration of the cluster, reduces the use of rescue medication and oral preventive treatment in the rest.

Disclosure of Interest: None Declared

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

PO-02-016

Visual Images – an additional tool for the screening of cluster headache

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3Hull York Medical School, Hull, United Kingdom

Objectives: The project aims to determine if images could be used as part of a screening tool to diagnose patients with cluster headache. The project is a questionnaire based study that aims to test visual images depicting different pain levels on healthy subjects (subjects without a history of headache).

Methods: Six images were commissioned, drawn on the basis of real life pictures. Each image represents a different pain severity. In order to avoid bias, the images were subsequently drawn using the same artistic style, chromatic range and colour saturation. Three images picture women and three men. The six images were tested on 150 healthy people to test whether there is consensus for the pain severity (mild, moderate, severe or excruciating) depicted by each image.

Results: Two images were rated as showing excruciating pain, one image as severe pain, two images as moderate pain and one image as mild pain. The selected images depicted a range of pain severity from mild to excruciating.

Conclusion: The six images will be tested on patients with cluster headache and migraine in a subsequent study. Our hypothesis is that the images will differentiate between the severities of pain experienced by patients suffering from cluster headache and migraine.

Disclosure of Interest: A. Buture: None Declared, L. Dikomitis: None Declared, J. Boland: None Declared, F. Ahmed Conflict with: Allergan, Eneura, Electrocore, Novartis as Advisory Board member paid to British Association for the Study of Headache and the Migraine Trust, Conflict with: Educational Officer for British Association for the Study of Headache, Trustee of Migraine Trust, IHS Board Member

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

PO-02-017

Effectiveness and tolerability of greater occipital nerve blocks for the prophylactic treatment of cluster headache – A retrospective study

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Objectives: Greater occipital nerve(GON)-blocks have shown to be an effective prophylactic treatment for cluster headache in placebo controlled and observational studies. However, further evidence on its effectiveness is needed and consensus on its position within the treatment of cluster headache is lacking, i.e. add-on versus monotherapy. The aim of this observational study is to assess the effectiveness and safety of GON-blocks in our center.

Methods: All patients recieving GON-blocks for cluster headache in our center from January 1st 2014 to December 31th 2016 were identified. Medication used was 3 ml 2% lidocaine and 80 mg methylprednisolone. Patient histories were taken right before and six weeks after treatment as part of standard clinical care. Data on the type of cluster headache (eg. episodic vs chronic),
response to previous therapy, headache severity and frequency and occurrence of adverse events were recorded.

**Results:** We identified 89 injections in 57 patients with cluster headache (67 injections in patients with chronic cluster headache, 19 in patients with episodic cluster headache and 3 in patients with an unspecified type of cluster headache). The majority of patients had not responded to standard (noninvasive) therapy. Complete remission was reported in 25% (n = 22), partial decrease in headache severity or frequency in 36% (n = 32), no response in 24% (n = 21) and an increase in headache severity or frequency in 3% (n = 3) of injections. Results were similar for episodic and chronic cluster headache. No effect data was documented for 12% (n = 11) of injections. Mild to moderate side effects, such as local pain and an increase of headache complaints, were reported after 28% (n = 25) of treatments. No serious adverse events were observed.

**Conclusion:** This observational study showed beneficial effects in 61% of GON-blocks in our patients with cluster headache and forms a base for prospective and placebo-controlled studies. In additional analyses, outcome will be correlated to response to previous treatments.

**Disclosure of Interest:** T. Balvers Conflict with: Novartis, P. Doesborg; None Declared, R. Mielof: None Declared, E. Bartels: None Declared, M. Ferrari: None Declared, R. Fronczek: None Declared

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**Cluster Headache and Other Trigeminal Autonomic Cephalalgias**

**PO-02-018**

Forehead and facial flushing and sensation of fullness in the ear in cluster headache

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13Department of Neurology, Seoul Medical center, Seoul
14Department of Neurology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong, Korea, Republic Of

**Objectives:** In the international classification of headache disorder-3 beta (ICHD-3β), ipsilateral forehead/facial flushing and ipsilateral sensation of fullness in the ear were added to the cluster headache(CH) diagnostic criteria. We analyzed the diagnostic value of the two additional criteria and their association with existing autonomic symptoms.

**Methods:** Consecutive patients with cluster headache based on ICHD-3β were prospectively recruited from 4 headache clinics in South Korea from Oct. 2016. Questionnaire surveys with patients and interviews with headache specialists were conducted to analyze the distribution and association of eight associated symptoms including a sense of restlessness or agitation symptoms.

**Results:** A total of 22 patients of CH were enrolled (mean age, 36 ± 9.1 years; 90.9% male): 21 episodic CH, 1 chronic CH, 18 definite CH, and probable CH 4. Among them, 19 patients were in the cluster period. Associated trigeminal autonomic symptoms were conjunctival injection and/or lacrimation in 19(82.6%), nasal congestion and/or rhinorrhea in 14(60.9%), eyelid edema in 6(23.1%), forehead and facial sweating in 5(26.1%), miosis and/or ptosis in 6(26.1%), and a sense of restlessness or agitation in 11(47.8%) of patients. At least 1 autonomic symptom was present in 22(95.7%) of patients, and restlessness or agitation without autonomic symptoms was present in 1(4.3%) of patients. Forehead and facial flushing was present in 3 (13%) of the patients and no patient showed the sensation of fullness in the ear. All the three patients with forehead and facial flushing also had conjunctival injection and/or lacrimation.

**Conclusion:** The diagnostic usefulness of the additional two associated symptoms is low and forehead and facial flushing mainly appears in relation to conjunctival injection and/or lacrimation.

**Disclosure of Interest:** None Declared
Cluster Headache and Other Trigeminal Autonomic Cephalalgias

PO-02-019
Greater occipital nerve injections of methylprednisolone alone or in combination with lidocaine in episodic and chronic cluster headache

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Objectives: Many series suggested an effect of greater occipital nerve (GON) injections for cluster headache (CH). Steroids alone or in combination with anesthetics can be used. The substance or combination that is most effective and the optimal technique still remain controversy [1]. The aim of our study was to evaluate the effect of GON injections of methylprednisolone alone or in combination with lidocaine as treatment in CH patients.

Methods: Patients suffering from active chronic (CCH) and episodic (ECH) CH were prospectively recruited. During active bouts, patients received three repeated GON injections every other day of methylprednisolone (A) or a single injection of 80 mg of methylprednisolone mixed with 2 mL of 2% lidocaine (B). Responders were classified as having a total remission for at least one month. A or B injections could be repeated either because of failure of the first treatment or recurrence of headaches.

Results: A total of 71 patients (48 ECH and 23 CCH) were enrolled in this study. Out of these, 59 patients (45 ECH and 14 CCH) received treatment A and 20 (12 ECH and 8 CCH) treatment B. 8 patients (5 ECH and 3 CCH) received both treatments. No serious adverse event were reported. Responders were 49/59 (83%) in A e 12/20 (60%) in B. Comparing ECH and CCH, A was effective in 87% vs 71% and B in 83% vs 25%. Among patients that received both treatments, 6 of 8 achieved the same effect either with A or B. Remission lasted between 2 months and 30 months in both A and B.

Conclusion: Our data suggest that GON injections of methylprednisolone alone or in combination with lidocaine are both effective in treating cluster headache, with long term effect. Moreover, GON injections of steroids are superior to steroids in combination to anesthetics in treatment of chronic CH.

Disclosure of Interest: None Declared

References

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

PO-02-020
Diagnostic delays and mismanagement in cluster headache

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Objectives: Despite being considered the most excruciating primary headache syndrome, cluster headache (CH) is internationally reported to be often misdiagnosed, undertreated or mistreated. The objective of our study was to draw capture under-management, under-treatment and mis-treatment often encountered in clinical practice and hence improve recognition and successful treatment of cluster patients by Greek neurologists and other physicians.

Methods: Data on consecutive CH patients (n = 302) were prospectively recorded from February 2007 until June 2015. Patients came from all geographical regions of Greece, mainly through self-referral (84.7%). All patients were examined by the same headache specialist (MV).

Results: In the majority of our patients (175/302) a diagnosis of CH had not been previously made and was established during consultation at our center for the first time. The median time from disease onset to diagnosis in our cohort was 5 years (range 0–45, mean 7.2 years). Overall, time to diagnosis significantly improved with decade of onset, for the current decade being just one year (median), compared to 5 years for the 2000s, 12 years for the 1990s and 20 years for onset before 1990. The median number of physicians seen prior to diagnosis was 3 (range 0–15, mean 3.5) and significantly improved with decade of onset, from a median of 7 doctors seen prior to diagnosis for onset before 1989 to a median of 5, 3 and 1 for onset between 1990–1999, 2000–2009 and after 2009, respectively (p = 0.001 for all comparisons).

Factors identified as significantly correlated with greater number of years lapsed to diagnosis included earlier decade of onset, presence of side shift between bouts, pain location in the jaw, cheek, lower teeth or ear area, presence of photophobia, forehead and facial sweating, pain aggravation by physical activity and absence of typical
Cluster headache autonomic features. In addition, factors associated with a greater number of physicians prior to diagnosis included presence of CCH, earlier decade of onset, pain location in upper teeth, cheek, lower teeth, neck, nose, ear, shoulder or vertex, presence of eyelid oedema, miosis/ptosis and aggravation by physical activity. Among the total group, 188 patients (62.7%) had received pharmaceutical treatment of any type prior to CH diagnosis and 42 patients (14.0%) had undergone unnecessary procedures, mainly by dentists (10.2%) and ENT specialists (9.9%), most commonly tooth extractions, fillings, sinus washout or surgery for nasal septum deviation, in all cases without success. Among the 127 previously diagnosed patients, only a minority had been offered treatment with subcutaneous sumatriptan or high flow oxygen for acute attacks or verapamil, corticosteroids or lithium for prevention. In addition, a substantial proportion was offered treatment with carbamazepine, flunarizine, antidepressants or alternative treatments. Use of recommended treatments, such as sc sumatriptan, O2 inhalation, corticosteroids or verapamil did not seem to be much more common even among previously diagnosed patients who had been diagnosed by a neurologist.

**Conclusion:** CH patients in Greece may remain misdiagnosed or undiagnosed for rather lengthy periods of time, but time to diagnosis has improved recently. Even after diagnosis, treatment received is commonly suboptimal.

**Disclosure of Interest:** None Declared

**Cluster Headache and Other Trigeminal Autonomic Cephalalgias**

**PO-02-021**

**Baseline characteristics of medically intractable chronic cluster headache patients participating in a trial on occipital nerve stimulation**

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2Anaesthesiology, Erasmus University Medical Center, Rotterdam, Netherlands

**Objectives:** About 10% > 15% of chronic cluster headache patients are refractory or intolerant to standard prophylactics. Here we present the 3-month baseline observation characteristics of 116 patients with medically intractable chronic cluster headache participating in the ICON study assessing the prophylactic efficacy of occipital nerve stimulation.

**Methods:** Participants completed weekly headache diaries during a 3 month baseline-period. Data were prospectively collected and included several clinical characteristics including attack frequency, pain intensity, additional clinical characteristics, medication use, smoking habits, and alcohol consumption.

**Results:** Attack frequency was analysed in 108 patients (65.5% male). Complete diary data could not be retrieved in 6.9% (n = 8) of the patients. Mean attack frequency was 21 attacks per week +/- 17.8 SD (median 16.1, interquartile range 16.1). Median disease duration of cluster headache was 8 years (interquartile range 6.8) (n = 93) and median disease duration of chronic cluster headache was 4 years (interquartile range 4.5). Additional analyses still to conduct and to be presented at the meeting will include variability over the three month follow-up in attack frequency and intensity.

**Conclusion:** Clinical 3-month baseline observation characteristics of medically intractable chronic cluster headache patients participating in the ICON trial are presented.

**Disclosure of Interest:** None Declared

**Cluster Headache and Other Trigeminal Autonomic Cephalalgias**

**PO-02-022**

**Remission of Cluster Headache Periods with Topiramate in Developing Country: A Case Report**

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**Objectives:** Cluster headache is a primary headache with high morbidity related to its intensity of pain and almost 80% patients report some limitations in doing their activities daily living. Headache is one of the most common diseases in Neurology Outpatient Clinic Dr. Soetomo General Hospital Surabaya which is the main referral hospital in eastern Indonesia. Various options of treatments according to IHS recommendations have been used to treat cluster headache either as acute or preventive. Cluster headache treatments in patients with various comorbidities is difficult. Moreover, the availability of the drug is quite difficult in our healthcare facilities. We describe the case of successful treatments of cluster headache using topiramate.

**Methods:** Male 55-years old with severe right peri orbital pain that he never felt before. Pain was felt like a hard object pressed around his right eye radiated to the right temple, and followed by redness and lacrimation. The pain was almost daily in the last two months and lasted twice a day, especially at night with mean duration of attacks was 15–45 minutes followed by pain free between attacks. He
had chronic gastritis and hypertension since couple years ago. There was no history of alcohol consumption and has stopped smoking since three years ago. Physical and neurological examination were normal. Numeric Rating Scale (NRS) was 10 during acute attacks. Head MRI and MRA with contrast were performed to rule out intracranial abnormalities, because the first onset of headache was quite old. He was referred from primary healthcare service and ever treated with paracetamol, ibuprofen and valproic acid but no reduction either in intensity or frequency of pain. Then he was given a combination of paracetamol with tramadol, and topiramate in our hospital.

**Results:** Patients had remission of cluster headache period within 14 days of treatment with combinations of paracetamol with tramadol as abortive treatments, and topiramate 50 mg once daily as a preventive treatment. There was no cluster attacks anymore. NRS reduces until zero. Topiramate has various mechanisms of actions include inhibition glutaminergic transmissions, inhibition of voltage-gated calcium channels and voltage gated sodium channel. Topiramate enhances the activity of GABA, inhibits carbonic anhydrase and also has inhibitory effects on the nociceptive trigeminovascular system on animal experiment. Therapeutic use of paracetamol and opioid in this case was due to limited availability of specific drugs for abortive treatments of cluster headache in our healthcare facilities. Using opioid for cluster headache must be considered carefully due to the possibility of medication overuse headache and should be combined with specific preventive drugs. Topiramate was selected as a preventive drug due to patient’s comorbidities. Prednisone, as the first line preventive drug, was not used because history of chronic gastritis. Verapamil has a beneficial effect in this case due to hypertensive comorbidity but the drug availability is rare and uncommon.

**Conclusion:** Despite patient’s comorbidities and limited availability of specific abortive treatment in our healthcare facilities which is the main referral hospital in eastern Indonesia, a combination treatments of weak opioid (tramadol) and paracetamol for abortive treatment with topiramate 50 mg once daily as a preventive drug could treat episodic cluster headache within 14 days.

**Disclosure of Interest:** None Declared

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**Cluster Headache and Other Trigeminal Autonomic Cephalalgias**

**PO-02-023**

**Refractory post-surgical SUNCT responsive to lacosamide**

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**Objectives:** To report a patient with post-surgical headache with Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) characteristics who improved dramatically after treatment with lacosamide.

**Methods:** Case report

**Results:** A 46 year-old woman developed severe headaches starting immediately after sinus surgery in 2012. She presented with stereotyped severe left-sided headaches lasting 1–2 minutes with severe ipsilateral lacrimation swelling, injection, rhinitis and ptosis without agitation. The pain is located around the left eye but radiates to the left temple and face. There is no refractory period between attacks, but no significant background pain between attacks. Her attacks occurred spontaneously with no apparent triggers. Over the next 6 years she experienced between 25–85 attacks per day, with an average of about 50. The patient tried many treatments for headache without significant improvement. Intravenous lidocaine was somewhat helpful in the hospital but her attacks persisted at a lower level after 5 days and did not significantly improve after discharge. She experienced little to no improvement with medications such as lithium, indomethacin, lamotrigine, verapamil, phencytoin, oxcarbazepine, carbamazepine, mexiletine, divalprox sodium, duloxetine, gabapentin, pregabaline, amantidine, nortriptyline, baclofen, amitriptyline, topiramate and zonisamide. She also had little relief with peripheral nerve blocks, onabotulinumtoxin injections, and repeated sphenopalatine ganglion blocks. Olanzapine and corticosteroids were modestly effective during exacerbations, and extended-release diclofenac and clonipramine citrate modestly improved pain severity. She underwent a microvascular decompression which did not reduce attack frequency over the next few months.

As an alternative treatment for SUNCT she began lacosamide, titrating to a dose of 200 mg twice daily. On the 400 mg/day dose, her attacks began to improve. In the first few weeks the attacks decreased to 33/day, then 18/day the next month, then 5/day after that. She remains in this pattern of 5 attacks/day for the last 4 months and both the pain and autonomic symptoms during attacks are much milder.
Conclusion: Lacosamide is an anticonvulsant which acts via voltage-gated sodium channels and modulation of collapsin response mediator protein 2. It does not affect or modulate other receptors or neurotransmitters important in pain such as GABA-A/GABA-B, serotonin, dopamine, norepinephrine, cannabinoids, and potassium or calcium currents. Although clinical trials using lacosamide for the treatment of migraine have not demonstrated significant benefit, it may be worth considering it as a treatment for SUNCT, especially in those with inadequate response or poor tolerability with sodium channel blockers such as lidocaine or mexiletine.

Disclosure of Interest: M. Marmura Conflict with: Teva, eNeura, Conflict with: Supernus. Teva, C. Lauritsen: None Declared

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

PO-02-024

Definition of Alldynia in TACs patients through Turkish Version of the Alldynia Checklist

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Objectives: Alldynia refers to central pain sensitization following normally non-painful stimulation. Cutaneous alldynia (CA) is also expression of central sensitization and commonly associated with migraine disease. Trigeminal autonomic cephalalgias (TACs) are a group of primary headache disorders characterized by unilateral pain at trigeminal distribution accompanied by ipsilateral cranial autonomic features. In this clinical study rare TACs including paroxysmal hemicrania (PH), short-lasting unilateral neuralgiform headache attacks (SUNCT) and hemicranial continua (HC) are considered. Alldynia is clinical expression of central sensitisation and associated with chronicity. It’s present up to 2/3 of migraine patients, however alldynia is not comprehensively studied in SUNCT, Paroxysmal Hemicrania and Hemicrania continua. In this prospective study we aimed to define if there is association with TACs by the first valid Turkish alldynia assessment questionnaire.

Methods: The study performed in Mersin University School of medicine and Istanbul Training and Research Hospital, Neurology Departments, Headache outpatient clinics. All patients evaluated by experienced neurologists. Diagnosis based to International Classification of Headache Disorders (ICHD)-3 beta version. SUNCT, SUNA, Hemicrania continua and Paroxysmal Hemicrania patients included to study. The first valid Turkish alldynia assessment questionnaire based on 12-item alldynia symptom checklist is translated from alldynia symptom checklist (ASC) according to our cultural adaptation by headache specialists.

Results: We used Turkish alldynia symptom checklist to evaluate 37 TACs patients including 14 (37.8%) SUNCT patients, 16 (43.2%) PH patients and 7 (18.9%) HC patients. The study group comprised 20 female (54.0%) and 17 male (46.0%), the mean age of subjects was 37.8±12.8 years, median of education was estimated 8 (4–9) years. Cut-off value for ASC-12 regarded as ≥3 points. Cutaneous Alldynia observed at 8 patients (21.6%). The most common alldynia subtype was mechanical alldynia. There was no association of alldynia with age, headache subtype, frequency of headache.

Conclusion: The trigeminal autonomic cephalalgias (TACs) are rare headache syndromes. Typically in TACs patients the pain is usually located retroorbital, temporal and most often in the ophthalmic distribution (V1). Atypically patients with TACs have pain in other cranial areas, including top, side or back of head, the nose, trigeminal V2 and V3 regions, the teeth, the neck and the ear. In our study despite of the neurologic examination is normal in patients with TACs, we found abnormal sensation and alldynia in trigeminal V1 or V2 distribution in the face at the pain located side. We observed that alldynia is common and a Turkish version of the alldynia symptom checklist was found to be convenient for the identification of alldynia in TACs patients. This study confirmed that CA is closely related to TACs patients. There is need to broad studies to reveal association of alldynia in TACs.

Disclosure of Interest: None Declared

Comorbidity of Primary Headaches

PO-02-025

Olfactory hallucination in association with migraine

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Objectives: Visual hallucinations and osmophobia are well known symptoms of migraine. Olfactory hallucinations are rarely reported in association with primary headache.

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Methods: We experienced 3 cases involving migraine patients with olfactory hallucinations.

Results: The first patient was a 28-year-old woman. She had experienced migraine without aura since she had been in junior high school. Her headaches were frontal pulsatile, associated with nausea and frequently occurred before and after her menstrual period. A neurological examination and brain MRI and MRA showed no abnormalities. Treatment with lomerizine and triptan was effective. She reported that she occasionally smelled smoke even though there were no smokers around her. This olfactory hallucination was not associated with her migraine attacks and was observed before the initiation of migraine therapy at our hospital. She experienced these olfactory hallucinations, which were not affected by migraine therapy, several times a year.

The second patient was a 45-year-old man. He had experienced migraine without aura with nausea and photo hypersensitivity for 10 years. Triptan was effective. The patient had undergone the surgical removal of a front-temporal atypical meningioma 7 years previously and had undergone surgery 3 years previously for recurrence. He reported experiencing olfactory hallucinations several times a year in which he perceived the smell of urine. His olfactory hallucination was not associated with his migraine attacks. This olfactory hallucination was not affected by treatment for meningioma or the administration of anticonvulsants.

The third patient was a 22-year-old woman. She had been diagnosed with thrombocytopenic purpura and was treated with prednisolone. She visited our hospital with severe frontal headache and vomiting. A neurological examination and brain CT showed no abnormalities. We diagnosed the patient with migraine without aura. Treatment with sumatriptan was effective. She reported experiencing olfactory hallucinations in which she perceived a sweet smell; however, her hypersensitivity was not remarkable.

Conclusion: Olfactory hypersensitivity, which typically presents as osmophobia or olfactophobia, is well known symptom of migraine. Olfactory or gustatory hallucinations, which are phantoms, differ from olfactory hypersensitivity and are observed in the patients with temporal lobe epilepsy, Parkinson’s disease and schizophrenia.

Although the olfactory hallucinations in patients with schizophrenia are not experienced as real smells, the olfactory hallucinations experienced by migraine patients are sensed as a real, unpleasant smell. In our 2 patients, the olfactory hallucinations were not associated with migraine attack; thus, they did not represent a symptom of aura. Although most olfactory hallucinations that are reported in association with migraine are associated with aura, olfactory hallucinations that not related to migraine attacks have been reported in some cases. Olfactory hallucinations have also been reported in association with cluster headache and hemicranias continua. Although the pathophysiology of these olfactory hallucinations is not clear, dysfunction and/or hypersensitivity of the temporal lobe or olfactory structures and the degeneration and/or dysmodulation of the dopaminergic, serotonergic and cholinergic systems are suspected to be involved. Olfactory hallucination has been included in the International Classification of Headache Disorders (ICHD) 2 appendix, but was deleted in ICHD 3b. Since some data supported the high specificity of olfactory hallucination in the diagnosis of migraine, it should be included in ICHD 3b.

Disclosure of Interest: None Declared

Comorbidity of Primary Headaches

PO-02-026

Visual Snow syndrome is associated with reduced amplitudes and lack of habituation of visual evoked potentials independent from comorbid migraine

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Objectives: Visual Snow syndrome is highly comorbid with migraine and typical migraine aura. Patients suffer from a continuous TV-snow-like visual disturbance and additional visual symptoms. Currently, there is no established treatment. Its pathophysiology is unknown, but might overlap with the mechanism of migraine or migraine aura. Functional brain imaging has shown hypermetabolism of the lingual gyrus suggesting a dysfunction of visual processing. Here, we tested the hypothesis that Visual Snow is associated with altered cortical excitability by assessing visual evoked potential (VEP) habituation and magnetic suppression of perceptual accuracy (MSPA).

Methods: Patients with Visual Snow were compared to age- and migraine-matched controls. For pattern-reversal VEPs, N75–P100 and P100-N145 amplitudes were measured over six consecutive blocks of 75 VEPs each. Block 1 amplitude, amplitude regression slopes (n = 18 per group) and block 6-to-1 ratios (n = 17 per group) were used to quantify VEP habituation. Visual accuracy (n = 17 per group) was assessed by letter recognition with prior transcranial magnetic stimulation delivered to the occipital cortex at intervals of 40, 100 and 190 ms. After confirmation of normal distribution using Kolmogorov-Smirnov-test, two-sample t-test was used to assess group differences between patients and controls. The study was approved by the University of Munich ethics committee.
Results: VEP block 1 amplitudes were reduced in Visual Snow patients (N75-P100 amplitude: 7.4 μV vs 11.8 μV, p = 0.004; trend for P100-N145 amplitude: 8.1 μV vs 11.7 μV, p = 0.07). Further, VEP habituation of P100-N145 amplitudes was significantly reduced in Visual Snow patients compared to controls (amplitude regression slope: −0.02 vs −0.36, p = 0.048). There was no difference for N75-P100 habituation (slope: −0.15 vs −0.17, p = 0.88), block 6-to-1 ratios (N75-P100: 100.5 vs 96.8, p = 0.73; P100-N145: 108.9 vs 99.7, p = 0.52) and MSPA (40 ms: 70.7% vs 70.9%; 100 ms: 52.5% vs 48.4%; 190 ms: 74.9% vs 77.5%).

Conclusion: This study demonstrates differences in visual cortical processing in patients with Visual Snow syndrome when compared to migraine-matched controls. This supports the view that Visual Snow syndrome is - though highly comorbid with - distinct from migraine. Patients’ main symptom is a TV-noise-like visual disturbance of continuously flickering black and white dots in the entire visual field. Additional visual symptoms include poor night-vision, which could be explained by noise reducing the contrast during low light conditions. The substantial reduction of VEP block 1 amplitude in our study is consistent with such decrease of contrast in pattern-reversal VEP. This might be the first objective electrophysiological correlate of the patients’ subjective symptoms reinforcing that Visual Snow syndrome is not a psychogenic problem. Further, VEP amplitude could represent a useful parameter for monitoring treatment progress in prospective studies. The reduced VEP habituation might be a correlate of the subjective visual overload experienced by our patients. The source of the P100-N145 component of the VEP is thought to be in the extrastriate cortex, which would be in accordance with previous functional imaging showing hypermetabolism of the visual association cortex in Visual Snow syndrome. This suggests that the pathophysiology of the disorder is associated with dysfunctional visual processing. Understanding the mechanism of the cortical dysfunction demonstrated here might offer insights into how to treat this disabling condition.


Comorbidity of Primary Headaches

PO-02-027

The Relationship Between Sleep Disorders and Migraine: Results from the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study

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2Elliot Hospital, Center for Sleep Evaluation, Manchester
3Albert Einstein College of Medicine, Bronx
4Vedanta Research, Chapel Hill
5Allergan plc, Irvine, United States

Objectives: This cross-sectional analysis from the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study compared the rates of sleep disturbances and sleep apnea (SA) among men vs women with migraine.

Methods: CaMEO participants were recruited from an online US panel using quota sampling and completed baseline and follow-up surveys every 3 months over 1 year. Participants were aged ≥18 years and met ICHD-3-beta criteria for migraine. The Comorbidities/Endophenotypes cross-sectional survey module assessed the risk of SA using the Berlin Scale for Sleep Apnea and obtained self-reported physician diagnosis of SA. Sleep disturbances and habits were measured using the Medical Outcomes Study (MOS) Sleep Scale. Participants were also asked to report what time of day their headache usually began. Results were stratified by episodic migraine (EM), chronic migraine (CM), body mass index (BMI), and sex and tested for significance using chi-square.

Image:

Table. Migraine Respondents at High Risk for Sleep Apnea Stratified by Sex, Migraine Diagnosis, Body Mass Index and Headache Timing

<table>
<thead>
<tr>
<th></th>
<th>High Risk (n=4,739)</th>
<th>Chi-square</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1,431 (44.6)</td>
<td>624.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women</td>
<td>2,296 (45.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EM</td>
<td>4,164 (35.9)</td>
<td>113.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CM</td>
<td>575 (41.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Mass Index Category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>50 (1.0)</td>
<td>3,626.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normal</td>
<td>292 (14.4)</td>
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<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>1,054 (25.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>2,943 (74.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache Typically Begins</td>
<td></td>
<td>6.12</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Before/After Walking or Morning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>536 (20.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1,977 (22.8)</td>
<td></td>
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</tr>
</tbody>
</table>

Results: Of 16,763 (99.8%) CaMEO Study respondents who received Comorbidities/Endophenotypes survey invitations, 12,810 (76.4%) provided valid data including 3,220 men and 9,590 women. Based on the Berlin Scale, 4,739 (37.0%) respondents were “at high risk” for SA. SA rates...
were significantly higher for men than women, for those with high BMI and in persons with CM vs EM (all P < 0.001; Table). Self-reported SA rates were higher in men (n = 580, 18.0%) than in women (n = 713, 7.4%: P < 0.001). Among those reporting SA, 75.7% also self-reported a physician diagnosis: men (n = 440, 75.9% [13.7% of total]); women (n = 539, 75.6% [5.6% of total]). The mean ± SD MOS Sleep Index II (long form) was 41.3 ± 17.6 (men, 38.7 ± 17.2; women, 42.2 ± 17.7: P < 0.001), with higher scores for the overall index and the subscales indicating worse sleep problems, unless otherwise noted. Commonly endorsed MOS sleep subscales with significant gender differences were Snoring (men, 39.2 ± 33.5; women, 29.1 ± 31.4: P < 0.001), Shortness of Breath (men, 15.0 ± 21.2; women, 17.7 ± 22.5: P < 0.001), Sleep Adequacy (men, 39.7 ± 22.6; women, 38.4 ± 22.2: P < 0.01, lower scores indicate worse sleep problems), and the average number of hours slept per night (men, 6.6 ± 1.4; women, 6.8 ± 1.4: P < 0.001, lower scores indicate less sleep). There was a significant difference in temporal headache patterns between men and women, with a lower proportion of men than women reporting their most severe headache typically started before or during waking or immediately after waking/getting up (n = 349 [12.2%] vs n = 1,446 [16.6%]: chi-square, 31.5: P < 0.001). Similarly a smaller proportion of men than women reported their most severe headache starts before or during waking, immediately after waking/getting up, or in the morning (n = 585 [20.4%] vs n = 1,977 [22.6%]: chi-square, 6.1: P < 0.05).

Conclusion: Compared with reported population prevalence rates of 35.1% of men and 21.0% of women at risk for SA, data from the CaMEO Study revealed an increased risk and potential underdiagnosis of sleep apnea and sleep disturbances among people with migraine. This phenomenon was often significantly more prominent in men compared with women and in those with CM compared with EM.

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**Comorbidity of Primary Headaches**

**PO-02-028**

**Effects of OnabotulinumtoxinA Treatment on Chronic Migraine Comorbidities of Depression and Anxiety**

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5Jefferson Headache Center, Philadelphia, United States

**Objectives:** Chronic migraine (CM) is associated with comorbidities that may exacerbate the condition. This subanalysis of COMPEL addresses the effects of onabotulinumtoxinA prophylaxis on comorbid psychiatric symptoms of anxiety and depression.

**Methods:** The 108-week, multicenter, open-label COMPEL Study enrolled adult patients with CM in Australia, Korea and the United States receiving onabotulinumtoxinA 155 U with/without concomitant prophylaxis. Primary outcome was the reduction in headache frequency per 28-day period at 108 weeks (9 treatments). Anxiety symptoms were assessed using the Generalized Anxiety Disorder Assessment (GAD-7) with a total score ranging from 0–21 (best to worst) distributed as 0–4 (minimal), 5–9 (mild), 10–14 (moderate), and 15–21 (severe); a score ≥10 indicates probable GAD. Depression symptoms were determined using the Patient Health Questionnaire (PHQ-9) with a total score ranging from 0–27 (best to worst) distributed as 0–4 (minimal), 5–9 (mild), 10–14 (moderate), 15–19 (moderately severe),
Results: Enrolled patients (N = 715) had a mean (range) age of 43 (18–73) years and were predominantly female (84.8%, 606/715). Headache day frequency at week 108 (primary endpoint) was significantly reduced from a baseline mean (standard deviation, SD) of 22 (±4.8) to 11.3 (±7.4) days (P < 0.0001). Patient baseline mean (SD) GAD-7 score was 6.3 (±5.3). OnabotulinumtoxinA treatment significantly reduced (improved) mean GAD-7 scores by −1.4 at week 12, −1.9 at week 24, −2.0 at week 48, −2.8 at week 72, and −2.8 at week 108 (all P < 0.0001; Figure A). Similarly, 379/715 (53.0%) patients at baseline reported potential symptoms of anxiety (GAD-7 score ≥5), which decreased at week 12 (n = 263/641 [41.0%]), 24 (n = 203/578 [35.1%]), 48 (n = 173/497 [34.8%]), 72 (n = 124/443 [28.0%]), and 108 (n = 98/373 [26.3%]). Baseline mean PHQ-9 score of 9.2 (±5.6) significantly decreased (improved) by −2.5 at week 12, −3.4 at week 24, −4.2 at week 48, and −4.5 at week 108 (all P < 0.0001; Figure B). 522/715 (73.0%) patients at baseline reported symptoms of depression (PHQ-9 score ≥5), which decreased at week 12 (n = 371/642 [57.8%]), 24 (n = 287/579 [49.6%]), 48 (n = 252/500 [50.4%]), 72 (n = 178/443 [40.2%]), and 108 (n = 123/373 [33.0%]). Most AEs were mild or moderate in nature. Rates of treatment-related AEs were low; the most common (occurring in ≥2% of the population) were neck pain (4.1%), eyelid ptosis (2.5%), musculoskeletal stiffness (2.4%), and injection site pain (2.0%).

Conclusion: COMPEL Study results support the established effectiveness and safety profile of onabotulinumtoxinA treatment for reducing headache frequency in CM. Less established is our understanding of how effective preventive treatment can affect common comorbidities of CM. These findings demonstrate that onabotulinumtoxinA treatment improved the comorbid symptoms of anxiety and depression for up to 108 weeks (9 treatment cycles) in patients with CM.

Disclosure of Interest: A. Blumenfeld Conflict with: Allergan, Perrx, Teva, Avanir, Depomed, and Supernus, Conflict with: Received funding for travel, speaking, and/or royalty payments from Allergan, S. Tepper Conflict with: Alder, Allergan, Amgen, ATi, Avanir, ElectroCore, eNeura, Teva, Zosano, Conflict with: Acorda, Alder, Allergan, Amgen, ATI, Avanir, BioVision, ElectroCore, eNeura, Kimberly-Clark, Perrx, Pfizer, Teva and Zosano, Conflict with: Dartmouth-Hitchcock Medical Center, American Headache Society (AHS), Conflict with: Stock options, ATI, Conflict with: Received salary as Editor-in-Chief of Headache Currents from AHS and royalties for books published by Springer, L. Robbins Conflict with: Speaker for Avanir, Perrx, and Merck, A. Manack Adams Conflict with: Allergan, Conflict with: Allergan, S. Silberstein Conflict with: His employer receives research support from Allergan, Inc.; Amgen; Cumberland Pharmaceuticals, Inc.; ElectroCore Medical, Inc.; Labrys Biologics; Eli Lilly and Company; Merz Pharmaceuticals; and Troy Healthcare, Conflict with: Alder Biopharmaceuticals; Allergan, Inc.; Amgen; Avanir Pharmaceuticals, Inc.; eNeura; ElectroCore Medical, LLC; Labrys Biologics; Medscape, LLC; Medtronic, Inc.; Neuralieve; NINDS; Pfizer, Inc.; and Teva Pharmaceuticals

Comorbidity of Primary Headaches

PO-02-029

Headache and migraine in Parkinson’s disease: a multicenter cross-sectional study

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8Neurology, Saitama Medical University, Saitama, Japan

Objectives: The prevalence of headache and migraine and their impact on disease course in patients with Parkinson’s disease (PD) remain unclear.

Methods: We analyzed prevalence of headache and migraine and their clinical correlates in 436 PD patients and 401 age- and sex-matched controls from the cross-
sectional, multicenter study. Migraine was diagnosed by questionnaire made according to the International Classification of Headache Disorders-second version. Epworth sleepiness scale, PD sleep scale (PDSS)-2 and Pittsburgh Sleep Quality Index (PSQI) were administered to all the participants.

**Results:** Between patients with PD and controls, the prevalence of headache during the lifetime (38.5% vs. 38.9%, p = 0.91) and headache during the past year (26.1% vs. 26.2%, p = 0.99) did not differ. However, PD patients had a lower prevalence of migraine during the past year compared with controls (6.7% vs. 11.0%, p = 0.027). Also, we found a significant number of PD patients with headache and migraine reported improvement of intensity and frequency of their headache and migraine after the onset of PD. PD patients with migraine showed a higher rate of depression and higher score of PSQI and PDSS-2 than those without headache.

**Conclusion:** We found improved overall headache severity after the onset of PD and the association of migraine with sleep disturbances and depression in PD patients.

**Disclosure of Interest:** None Declared

**Comorbidity of Primary Headaches**

**PO-02-030**

**Poor sleep quality among individuals with probable migraine: a population-based study**

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**Objectives:** It has been reported that sleep or sleep-related problems were common among migraineurs. Both sleep quality and sleep quantity are related to health and well-being. Sleep studies among migraineurs have reported that sleep duration did not differ from that of non-migraineurs. Therefore, difference in sleep quality may cause for higher sleep disturbance among migraineurs than non-migraineurs. Probable migraine (PM) is a subtype of migraine which fulfilled all but one criterion of migraine. However, there is little knowledge of the association between sleep quality and PM. This study is to investigate the association of poor sleep quality among individuals with PM in comparison with those with migraine.

**Methods:** We used the data of Korean Headache-Sleep Study (KHSS) in the present study. The KHSS is nationwide population-based survey regarding headache and sleep for adults aged 16–69 years. We defined poor sleep quality as Pittsburgh Sleep Quality Index (PSQI) score > 5.

**Results:** Of 2,695 respondents, 143 (5.3 %), 379 (14.1%) and 715 (26.5 %) were classified as having migraine, PM and poor sleep quality, respectively. Individuals with PM (35.4%, p < 0.001) and migraine (47.6%, p < 0.001) had higher prevalence of poor sleep quality compared to individuals without headache (21.0%). The prevalence of poor sleep quality was significantly lower among individual with PM compared to that of migraineurs (35.4% vs. 47.6%, p = 0.011). Among components of PSQI, individuals with PM had lower sleep latency (p = 0.040) and sleep disturbance (p = 0.020) scores compared to those of migraineurs. Among individuals with PM, headache frequency per month (3.8 ± 6.7 vs. 2.2 ± 4.8, p = 0.009) and Visual Analogue Scale (VAS) score for headache intensity (median and interquartile range [IQR], 6.0 [4.0–7.0] vs. 6.0 [5.0–7.0]) was significantly lower compared to individuals without headache (21.0%). The prevalence of poor sleep quality was significantly lower among individual with PM compared to that of migraineurs (35.4% vs. 47.6%, p = 0.011). Among components of PSQI, individuals with PM had lower sleep latency (p = 0.040) and sleep disturbance (p = 0.020) scores compared to those of migraineurs. Among individuals with PM, headache frequency per month (3.8 ± 6.7 vs. 2.2 ± 4.8, p = 0.009) and Visual Analogue Scale (VAS) score for headache intensity (median and interquartile range [IQR], 6.0 [4.0–7.0] vs. 6.0 [5.0–7.0]) was significantly lower compared to individuals without headache (21.0%). The prevalence of poor sleep quality was significantly lower among individual with PM compared to that of migraineurs (35.4% vs. 47.6%, p = 0.011). Among components of PSQI, individuals with PM had lower sleep latency (p = 0.040) and sleep disturbance (p = 0.020) scores compared to those of migraineurs. Among individuals with PM, headache frequency per month (3.8 ± 6.7 vs. 2.2 ± 4.8, p = 0.009) and Visual Analogue Scale (VAS) score for headache intensity (median and interquartile range [IQR], 6.0 [4.0–7.0] vs. 6.0 [5.0–7.0]) was significantly lower compared to individuals without headache (21.0%). The prevalence of poor sleep quality was significantly lower among individual with PM compared to that of migraineurs (35.4% vs. 47.6%, p = 0.011). Among components of PSQI, individuals with PM had lower sleep latency (p = 0.040) and sleep disturbance (p = 0.020) scores compared to those of migraineurs. Among individuals with PM, headache frequency per month (3.8 ± 6.7 vs. 2.2 ± 4.8, p = 0.009) and Visual Analogue Scale (VAS) score for headache intensity (median and interquartile range [IQR], 6.0 [4.0–7.0] vs. 6.0 [5.0–7.0]) was significantly lower compared to individuals without headache (21.0%).

**Table:** Headache frequency and headache intensity according to the presence of poor sleep quality among individuals with migraine and probable migraine.

<table>
<thead>
<tr>
<th></th>
<th>Migraine</th>
<th></th>
<th>Probable migraine</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With poor</td>
<td>Without poor</td>
<td>p-value</td>
<td>With poor</td>
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<tr>
<td></td>
<td>sleep quality</td>
<td>sleep quality</td>
<td></td>
<td>sleep quality</td>
</tr>
<tr>
<td>Headache frequency per month</td>
<td>5.1 ± 7.9*</td>
<td>2.7 ± 4.1*</td>
<td>0.018</td>
<td>3.8 ± 6.7*</td>
</tr>
<tr>
<td>Visual Analogue Scale for headache intensity</td>
<td>7.0 [5.00–8.0]#</td>
<td>6.0 [5.0–7.0]#</td>
<td>0.247</td>
<td>6.0 [4.0–7.0]#</td>
</tr>
</tbody>
</table>

*Mean ± standard deviation, #median and 25% > 75% interquartile range
Disclosure of Interest: M. K. Chu Conflict with: Hallym University Research Fund, Conflict with: Advisory board for Teva, Conflict with: Allergan Korean and Yuyu Pharm, B. Choi Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict 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Comorbidity of Primary Headaches

PO-02-032

The prevalence of right to left shunts in Japanese patients with migraine: a single center study

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Objectives: An increased prevalence of right-to-left shunt (RLs) in migraine patients, particularly those with aura has been reported. However, the prevalence of RLs and its clinical correlation in Japanese patients with migraine remain unclear. In this study, we conducted a single center study to investigate the prevalence of RLs in Japanese patients with migraine.

Methods: A total of 112 consecutive patients with migraine were recruited from our headache outpatient clinic. Migraine with aura (MA) and migraine without aura (MWOA) were diagnosed according to the International Classification of Headache Disorders, 3rd edition (beta-edition). Contrast transcranial Doppler ultrasound was used to detect RLs, including patent foramen ovale (PFO). The associations between RLs and clinical background factors of patients MA and MWOA were assessed.

Results: MA patients were younger (p = 0.013) and had early onset age (p = 0.013) and increased prevalence of photophobia (p = 0.008) compared with MWOA patients. The overall prevalence of RLs and PFO in migraine patients was 54.5% and 43.8%, respectively. A significant increased prevalence of RLs and PFO in the MA groups was observed compared with MWOA groups (RLs, 62.9% vs. 44.0%, p = 0.046; PFO, 54.8% vs. 30.0%, p = 0.008).

Conclusion: In our study, over half of the Japanese patients with migraine showed RLs. Also, our study results suggest a possible association between RLs and MA.

Disclosure of Interest: None Declared

Comorbidity of Primary Headaches

PO-02-033

TREATMENT EFFECT IN VISUAL SNOW

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Objectives: Patients with Visual Snow suffer a pan-field, dynamic visual disturbance. Proposed diagnostic criteria require at least two additional visual symptoms from: palinopsia, entoptic phenomena, photophobia and nystagmus (1). Little is known regarding useful pharmacological treatments for patients. The aim of this study was to gain knowledge on the effect of a number of commonly used medications on Visual Snow.

Methods: A questionnaire was prepared in collaboration with the patient group Eye-on-Vision and sent to subjects who had expressed an interest in research. It asked the participant to select from a list of drugs, including antiepileptics, antidepressants and benzodiazepines, the ones that had been used at least once since symptom onset. Participants were then asked to mark the effect of these treatments on their Visual Snow, particularly if there had been an improvement or a worsening. The questionnaire also enquired on the use of recreational drugs, including cannabis, and their effect on Visual Snow. The study was approved by KCL Research Ethics Panel.

Results: Two hundred and four patients returned the questionnaire, with the effect of one-hundred and twelve drugs recorded in 611 reports. Less than half of the subjects (n = 92) showed any response to medication, either in the form of an improvement or a worsening. Antidepressants and antiepileptics were the most commonly used medications; they showed no effect on Visual Snow in 55% and 57% of reports, respectively. When benzodiazepines had been used in the past, an improvement of Visual Snow symptoms was reported in 29% of cases. Recreational drug use, always subsequent to symptom onset, was reported 117 times and caused a transient worsening in symptoms in 32% of cases, although in the majority of cases (61%) no effect was reported.

Conclusion: Visual Snow is a highly disabling syndrome, for which there is no widely accepted treatment. Most of the commonly used medications available show little or no effect on symptoms. In the future more effort needs to be made in understanding the pathophysiology and biological basis of this disorder, in order to allow focused treatment strategies for patients.

Disclosure of Interest: F. Puledda: None Declared, T. Lau: None Declared, C. Schankin: None Declared, P. Goadsby Conflict with: Dr. Goadsby reports grants and personal fees from Allergan, Amgen, and Eli-Lilly and Company; and personal fees from Akia Biomedical, Alder Biopharmaceuticals, Autonomic Technologies Inc, Avanir Pharma, Cipla Ltd, Colucid Pharmaceuticals, Ltd, Dr Reddy’s Laboratories, eNeura, Electrocore LLC, Novartis, Pfizer Inc, Promius Pharma, Quest Diagnostics, Scion, Teva Pharmaceuticals.

References


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Comorbidity of Primary Headaches

PO-02-034

Clinical Implications between Headache and Gastrointestinal Disorders: The Study using Hallym Smart Clinical Data Warehouse

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Objectives: The brain and gastrointestinal (GI) tract are strongly connected via neural, endocrine, and immune pathways. Previous studies suggest that headache, especially migraine may be associated with various GI disorders, including gastroparesis, irritable bowel syndrome, peptic ulcer, and celiac disease. But upper GI endoscopy in migraineurs have shown a low prevalence of abnormal findings. Also, most studies have not demonstrated any association between Helicobacter pylori (HP) infection in migraineurs and migraine, although a pathogenic role for HP infection in migraine has been suggested. Further knowledge about headache and GI disorders is important: it may affect therapeutic consequence. Thus, we sought to investigate possible associations between GI disorders and primary headache such as migraine and tension-type headache (TTH) using the Smart Clinical Data Warehouse (CDW) during 10 years.

Methods: We retrospectively investigated clinical information using a clinical data analytic solution called Smart CDW at Chuncheon Sacred Heart Hospital from January 2006 to August 2016. In patients with migraine and TTH, diagnosis of GI disorders visiting at gastroenterology center, upper GI endoscopy findings and results of HP infection collected and compared to clinical data in patients with controls (subjects who had medical check-up without headache). The time interval between diagnosing headache at neurology and underwent examination at gastroenterology center not exceed maximum of one year.

Results: We identified total 387 eligible case subjects in patients with migraine (mean age 41.39, 80.8 % female) and TTH (mean age 52.83, 61.4% female) respectively. Among the diagnosis of GI disorders by gastroenterologist, gastroesophageal reflux disorder is more prevalent in migraine than in TTH groups, whereas gastritis and gastric ulcer are more common in TTH than in migraine group (p < 0.001). In Endoscopic findings, high numbers of reflux esophagitis showed in migraine group, whereas gastric ulcer was significantly higher in patients with TTH compared with controls (p < 0.05). But, no differences were observed the prevalence of HP infection between the groups.

Conclusion: The observed association may suggest that primary headache suffers such as migraine and TTH are predisposed to GI disorders and this may have clinical implications. Further research about etiology of association of headache and GI disorders is needed.

Disclosure of Interest: None Declared

Comorbidity of Primary Headaches

PO-02-035

Risk factors for syncope in a migraine cohort

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Objectives: The co-occurrence of migraine and syncope is high. Studies have reported prevalence of between 5.3% and 46.0% for syncope in patients with migraine. Few studies have reported the risk factors for syncope. The present study aimed to estimate the comorbidity of syncope and investigate its clinical correlates in patients with migraine.

Methods: Patients who were newly diagnosed with migraine by neurologists in the headache clinic in the Taipei Veterans General Hospital between January 2015 and December 2016 were recruited into the study. Information on demographics, lifestyle, and comorbid health conditions was collected through questionnaires, and detailed anamnesis of migraine, aura symptoms, allosthenia, allodynia, anxiety, depression, and syncope were conducted. The associations between these personal and clinical factors and syncope were conducted using a case-control design, with the cases consisting of migraine patients with syncope, and the controls of migraine patients without syncope. Relative risks (RRs) were calculated using unconditional logistic regression. Statistical significance was defined as two-tailed p < 0.05.

Results: A total of 829 patients with migraine (219 cases and 610 controls) were recruited into this study. 26.4% of patients with migraine had syncope. The majority of these patients reported having first syncope after having first headache, with the events a median of 8.0 (interquartile range, 4.0 – 16.0) years apart. In multivariate analyses, being female and having migraine with aura were associated with a significantly increased risk of syncope, with adjusted RRs
of 2.07 (95% CI 1.26–3.40) and 1.87 (95% CI 1.16–3.01), respectively. Age, smoking, drinking, body mass index, level of education, age at first headache, frequency of headaches, and headache intensity were not significantly associated with the risk of syncope. Among the 10 comorbid health conditions that were studied, suicidal ideation was associated with a significantly increased risk of syncope (adjusted RR 1.68, 95% CI 1.17–2.41), even after correcting for multiple testing. Worse scores for the Migraine Disability Assessment (p_trend = 0.032), Hospital Anxiety and Depression Scale for anxiety (p_trend < 0.011), Depression Inventory (BDI) score (p_trend < 0.001), and higher number of sites of allodynia during migraine attack (p_trend = 0.049) were associated with an increased risk of syncope. Having two or more of the following factors: being female, migraine with aura, and suicidal ideations (or BDI score ≥ 19) was associated with higher risk of syncope when compared with having none of them.

Conclusion: The prevalence of syncope is 26.4% in our cohort of migraine patients. Being female, having migraine with aura, suicidal ideations, greater disability caused by migraine and having more anxiety and depression symptoms are significant risk factors for syncope in migraine patients.

Disclosure of Interest: None Declared

Comorbidity of Primary Headaches

PO-02-036

Clinical relevance of salivary cortisol in patients with fibromyalgia

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Objectives: Chronic pain is associated with altered hypothalamic-pituitary-adrenal axis function. Some studies have linked fibromyalgia (FM) to hypocortisolism. However, the clinical relevance of cortisol remains undetermined in patients with FM.

Methods: Consecutive patients with FM aged 20–69 and fulfilling the Modified 2010 ACR Criteria were enrolled from Taipei Veterans General Hospital. At first visit, all patients completed a questionnaire assessment on fibromyalgia symptoms [Widespread Pain Index (WPI) and Symptom Severity (SS) scale], functional status [Revised Fibromyalgia Impact Questionnaire (FIQR)], mood [Hospital Anxiety and Depression Scale (HADS)], sleep [Pittsburgh Sleep Quality Assessment (PSQI)], and stress [Perceived Stress Scale (PSS)] as well as an evaluation of tenderness (18 tender points). On a scheduled day (<1 week after first visit) while patients engaged in usual daily activities, salivary cortisol was collected at four time-points: awakening, 30 minutes after awakening, 3 pm, and 9 pm (at bedtime). Individual basal cortisol level was computed using the area under the curve (AUC) with respect to ground. Individual cortisol variability was also calculated as the difference between morning (30 minutes after awakening) and evening (bedtime) values. Appropriate power transformation was carried out for positively skewed variables before analysis.

Results: A total of 126 patients joined this study (107F/19M; mean age 43.6 ± 10.2). The cortisol levels at four time-points did not correlate with any clinical variables or tenderness. The basal cortisol level was associated with SS scale (r = 0.204, p = 0.022) but not with any other clinical variables. Cortisol variability was positively correlated with depression severity (r = 0.190, p = 0.034) and negatively correlated with tenderness (r = −0.195, p = 0.030) and global PSQI score (higher score indicating poor sleep quality; r = −0.198, p = 0.034). After adjustment of depression, all the above clinical correlations disappeared except for PSQI, as shown by a linear regression analysis that a lower cortisol variety was independently related with poor sleep quality (beta: −0.243, p = 0.008).

Conclusion: Salivary cortisol is associated with sleep quality and depression but not with pain or tenderness in patients with FM. Future longitudinal studies must investigate the temporal relationship of cortisol and fluctuating fibromyalgia-related symptoms.

Disclosure of Interest: None Declared

Comorbidity of Primary Headaches

PO-02-037

The Anxious Brain in Pain: Increased Levels of Anxiety, Depression and Stress Associated with Chronic Daily Headaches Patients Presenting to University-based Headache Clinic

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Objectives: The primary objective of this study was to survey patients referred to a university-based headache clinic with chronic daily headaches (CDH) regarding perceived stress, anxiety and depression. Patients referred to specialty headache clinics are more likely to have CDH, to be intractable, and have medication overuse. These
patients report increased rates of mood, anxiety, and stress issues.

**Methods:** All new patients at a tertiary headache clinic complete a detailed patient intake questionnaire prior to their first visit. Of the 1826 completed patient intakes, 1150 reported CDH. Headache triggers, Perceived Stress Scale (PSS) scores, PHQ-4 assessments of anxiety and depression were assessed.

**Results:** Patients with CDH report stress as their most common trigger (603, 52.6%). CDH patients had elevated PSS scores with a mean of 17.5 compared with a normative value of 13.7. When stratified according to PSS scores, 55% (613) had moderate stress (PSS 14 to 27) and 12% (142) severe stress (PSS > 27). Patients had elevated scores on the PHQ4 measurement of depression and anxiety, with a 3.8 mean. When we examined those patients with a PHQ4 score of 5 or above, which is suggestive of a diagnosable mood or anxiety disorder, they represented 33.7% of the chronic headache patients, with very elevated PSS scores with a mean of 24.3

**Conclusion:** Patients with CDH referred to a tertiary university headache clinic were noted to have elevated stress levels on the PSS and identify stress as their most significant headache trigger. Significant fractions of the CDH group reported either extremely high stress scores or high depression and anxiety scores. Since it is not realistic or helpful to simply counsel these patients to “avoid stress” or “avoid nervousness”, headache providers must be able to address these behavioral issues in their clinics or through referrals.

**Disclosure of Interest:** None Declared

**Comorbidity of Primary Headaches**

**PO-02-038**

Sleepy Brain in Pain: Prevalence of Sleep Problems in a University-Based Headache Clinic

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**Objectives:** The primary objective was to study the nature and prevalence of sleep complaints with specific headache diagnoses in patients presenting to a university-based tertiary care headache clinic.

**Methods:** All new patients at a tertiary headache clinic complete a detailed patient intake questionnaire prior to their first visit. This questionnaire contains a section on sleep symptoms and previous sleep disorder diagnoses. Later the clinician makes a specific headache diagnosis using IHS beta 3, this is entered into the database as well.

**Results:** Of the 864 patients, 548 (63.5%) endorsed sleep problems. The most common sleep problems reported were trouble staying asleep (62.4%), waking up feeling not refreshed (61.3%), and insomnia (34.1%). When compared to the subpopulation of headache patients who did not report sleep problems, certain headache diagnoses were much more common, including: chronic migraine (71% vs 52%), medication overuse headache (48% vs 34%), and cervicogenic headache (10.6% vs 5.7%)

**Conclusion:** A majority of the patients presenting to the university-based headache clinic have significant comorbid sleep disorders, especially trouble staying asleep, waking up feeling not refreshed, and insomnia. It is important to pay attention to sleep comorbidities associated with headache, since sleep disorders have been identified as modifiable risk factors for migraine progression. These results suggest that sleep assessment and treatment should become an integral part of specialty headache care.

**Disclosure of Interest:** None Declared

**Comorbidity of Primary Headaches**

**PO-02-039**

The Association between Alexithymia, Depression, Anxiety and Migraine in Migraine patients

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**Objectives:** Alexithymia concerns difficulty or incapacity to express emotions through words. The co-existence of psychiatric comorbidities with migraine is well-known; however, few studies have yet addressed the relationship between migraine and alexithymia. To assess the relationships between migraine, depression, anxiety, alexithymia and migraine-related disability.

**Methods:** One hundred and forty five migraineurs (33.18 ± 8.6; 111 female, 34 males), and 50 control subjects (29.06 ± 7.6; 34 females, 16 males) were prospectively enrolled for the study. The participants completed a sociodemographic data form and a migraine disability assessment scale, Beck Depression Inventory (BDI), Beck Anxiety Inventory and Toronto Alexithymia Score-20 (TAS-20).

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Results: Depression and anxiety scores in episodic migraine patients were normal except for chronic ones, while all migraineurs were more depressive (p = 0.01) and anxious (p = 0.001) than healthy subjects. The TAS-20 scores of the migraineurs and control group did not indicate alexithymia. The migraine-related disability of all migraine patients was severe (27.84 ± 29.22).

Depression scores in the migraineurs were correlated with anxiety (r = 0.47, p = 0.001) and alexithymia (r = 0.48, p = 0.01) and all its subscales in turn: difficulty in identifying (r = 0.43, p = 0.001) (Factor 1) and describing feelings (r = 0.45, p = 0.001) (Factor 2), and externally oriented thinking (r = 0.3, p = 0.001) (Factor 3).

Presence of a positive correlation with difficulty in describing feelings, externally oriented thinking, TAS-20 and BDI scores, respectively: (r = 0.21, p = 0.01), (r = 0.33, p = 0.001). Headache frequency in past 3 months (MIDAS A scores) were positively correlated with difficulty in describing feelings, TAS-20 and BDI scores, in turn; (r = 0.47, p = 0.001), (r = 0.39, p = 0.001), (r = 0.22, p = 0.008), (r = 0.46, p = 0.001), (r = 0.47, p = 0.001). MIDAS total scores showed a positive correlation with difficulty in describing feelings, and BDI scores, respectively; (r = 0.21, p = 0.01), (r = 0.33, p = 0.001).

Conclusion: The present study demonstrates that alexithymia is mainly connected with psychiatric pathology, not with migraine. Moreover the severity and disability of migraine are linked to depression, alexithymia and difficulty in describing emotions. Our findings showed that alexithymia was not an associated risk factor on its own for migraine without comorbid depression and anxiety. The early identification and treatment of psychiatric comorbidities and negative affect may be beneficial in preventing the chronification of migraine and reducing the economic burden of its effects.

Disclosure of Interest: None Declared

Comorbidity of Primary Headaches

PO-02-041

Noonan syndrome associated with migraine and cluster headache

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Objectives: Noonan syndrome is a genetic congenital disorder with phenotypic neurological features such as mental retardation, intracranial aneurysm, cavernous angioma, and Moyamoya disease. Although, a positive association between Noonan syndrome and migraine exists, NS with migraine and concurrent cluster headache has never been reported.

Methods: We present a a clinical case of a 35-year-old Caucasian woman with Noonan syndrome and migraine that associates with cluster headache.

Results: Our patient was diagnosed with Noonan syndrome at the age of 9. When she was 20, complaints of mild (pain intensity VAS = 3) left-sided fronto-temporoparietal throbbing headache started. Each attack lasted around 5 hours, with frequency of 6 attacks per month.

At the age of 29, a headache with different characteristics appeared along with the usual one. The new headache was more severe (VAS = 10). Pain was localized in the left retroorbital region. It was stabbing in character, accompanied by ipsilateral autonomic signs (conjuctival injection, lacrimation and eyelid edema). Attacks’ duration was around 2 hours. Frequency was twice daily. The headache was more likely to start late in the evening or during the night. The new attacks appeared in spring and autumn and the attack periods lasted for 2 months.

Conclusion: The described case provides evidence of co-existing migraine and cluster headache in a patient with Noonan syndrome. Although, unilateral cranial autonomic features may occur in migraine patients with longer disease progression, the last type of headache attacks of our patient fulfill the ICHD criteria for cluster headache. Similar pathogenetic mechanisms may be suggested between the two primary headaches in our patient. As Noonan syndrome is caused by missense mutations in the PTPN11 gene on chromosome 12, and migraine is often a co-morbid disease, other migraine and cluster headache genes can be studied in the same chromosome.

Disclosure of Interest: None Declared

Comorbidity of Primary Headaches

PO-02-041

Characteristic of headache in lacunar strokes in Kyrgyzstan and influence on outcome: short-term longitudinal study

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Objectives: Lacunar infarcts or small subcortical infarcts result from occlusion of a single penetrating artery and account for one quarter of cerebral infarctions, developed mostly in arterial hypertension cohort. In literature review headache in lacunar stroke is unspecific and not fully described.
To characterise headache in lacunar strokes, and to find a correlation between headache type, intensivity and stroke outcome.

**Methods:** We studied a sample of 68 patients with acute lacunar infarction according TOAST criteria and with lacunar lesion on DWI scans of MRI, scored NIHSS scale at onset. Fazekas scale was used for leukoaroeosis estimation. All patients were tested on the presence of headache in the onset of stroke, its localisation and severity was estimated according to Visual Analogue Scale (VAS). In 10 days after stroke NIHSS and VAS were repeatedly measured and statistical correlation between them was searched.

**Results:** Headache was present in 90 % of observed patients at onset, strongly connected with arterial hypertension (p = 0.0001). Systolic blood pressure higher than 156 mm was associated with increasing headache in sample (p = 0.01). Headache was diffused and “pressure type” in 78% of all headache patients. Mean baseline NIHSS score in patients with headache was 8 (±1.8), what is minor stroke and mean VAS was 6 (±2). There was no significant correlation between intensity of baseline headache and baseline NIHSS, and lacunar infarct localisation and headache intensity, but strong association of dull headache and infarcts with leukoaroeosis in 3rd stage. In 64% headache significantly decreased to 10th day of stroke (VAS 3 ± 0.9).

**Conclusion:** In patients with lacunar infarction, headache tends to be moderate, diffuse and “pressure type”, not correlates with infarction site and NIHSS scale. 3rd stage of leukoaroeosis we found strongly associated with headache (p = 0.001).

**Disclosure of Interest:** None Declared

### Comorbidity of Primary Headaches

**PO-02-042**

**The Prevalence And Severity of Headache in Multiple Sclerosis Patients treated with Interferon Beta**

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2Pharmacy
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**Objectives:** Evaluation of the prevalence and severity of headache in patients under treatment with IFNβ

**Methods:** 52 patients with RRMS treated with IFNβ (group 3) for at least three months in the Service of Neurology, at UHC “Mother Theresa”, Tirana were compared with two control groups, respectively with 37 patients with MS not under treatment with IFNβ (group 2) and 208 healthy individuals (group 1). Data on the clinical features of MS and about therapy were collected. An oral interview on headache and the MIDAS test were performed to the three groups. The patients with MS were evaluated with the EDSS scale of Kurtzke.

**Results:** The data indicate that the difference between the average values of MIDAS in group 3 and 1 is statistically significant (p = 0.0000), and the difference between these values lies in the Confidence interval of 95%. MIDAS score in people with MS under treatment with IFNβ is 8 times greater than in the healthy population. While there are large differences in the values obtained from the MIDAS test (p = 0.000) and in the presence or absence of headache (p = 0.05) between the group of patients with MS under treatment with interferon beta and the group of patients with MS which are not under treatment with interferon beta.

**Conclusion:** The study conducted on the importance of headache in patients with multiple sclerosis under treatment with interferon beta found that the prevalence of headache in this group of patients was 68%, while the severity of headache belonged to the third degree of the MIDAS test corresponding to a moderate disability.

**Disclosure of Interest:** None Declared

### Comorbidity of Primary Headaches

**PO-02-043**

**The association of epilepsy, headache and migraine: a case-control study**

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**Objectives:** Epilepsy and headache are commonly observed to occur together and they are perhaps comorbid pathologies. However, because of divergences in findings of a comorbid association between epilepsy and headache or migraine, and because of lack of reports from places where epilepsy is more common, the question of whether epilepsy and headache or epilepsy and migraine are linked remains unsolved, and a possible comorbid relationship between both conditions remains not fully understood. In this study, we have tried to investigate the association of headache and epilepsy using two different approaches. First, we studied frequencies of common types of headaches in focal or generalized forms of epilepsy, comparing results with individuals without epilepsy, but evaluated by the same neurologists who evaluated headache in patients with epilepsy, using the same tools. Secondly, we explored similarities and differences among risk factors for common types of headaches in epilepsy in...
Methods: This is a case-control study. Two hundred and forty-four consecutive patients with epilepsy were included in this study. One hundred and seventy-one healthy controls, selected among the healthy companions of other patients who came to our outpatient epilepsy clinic were invited as controls. Patients with cognitive deficits severe enough for difficult subjective evaluations were excluded from the study. All individuals, patients with epilepsy and controls, were submitted to the same semi-structured interview with specific questions focusing on health problems, medications in use, familiar history of diseases (epilepsy, headache and migraine), and specific questions about epilepsy or headache. For analysis, epilepsy was divided in focal or generalized type. Focal epilepsies were further divided in temporal and extra-temporal focal epilepsies. Multinominal logistic regression was used to stablish independence of associations observed.

Results: The mean age was 43.9 (SD = 14.8) for patients and 44.1 (SD = 15.1) for controls. As expected, patients with epilepsy were more often retired or not working. One hundred and eighty-one (75.1%) patients and 67 (39.2%) controls reported at least one episode of headache during the last year. Migraine occurred in 92 (38.2%) patients with epilepsy and 32 (18.7%) controls, a significant difference (OR = 2.63; 95% CI = 1.65–4.18; p < 0.0001). Tension-type headache was also more observed in patients with epilepsy when compared with controls (OR = 2.10; 95% CI = 1.08–4.10; p = 0.018). Headache affected predominantly women. After multinominal logistic regression, female sex, familial history of headache or migraine, and focal or generalized epilepsy were all independently associated with tension-type headache, with migraine and with the other types of headache grouped together. Migraine was more strongly associated with epilepsy. Our data support that, while migraine is more generally comorbid in epilepsy, tension-type headache or other forms of headaches are also independently associated with focal or generalized epilepsies.

Conclusion: In this study, we observed that tension-type headache, migraine and other less common forms of headache were all independently associated with focal or generalized epilepsies. Migraine showed the strongest relationship. Despite of the independence of these associations, when data are taken together for interpretation, our results support the view that, while migraine might share a more broad and common comorbid mechanisms with epilepsy, the other forms of headache also share common mechanisms with epilepsies and are also significantly increased in patients with focal or generalized epilepsies. Acknowledgements: this study was fully supported by Brazilian governmental agencies CNPQ, FAPERGS, HCPA-FIPE and CAPES.

Disclosure of Interest: None Declared

Comorbidity of Primary Headaches

PO-02-044

Greater occipital nerve block in the treatment of triptan-overuse headache: A randomized comparative study

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Objectives: This study aims to investigate the efficiency of a single and repeated greater occipital nerve (GON) block using lidocaine in the treatment of triptan-overuse headache (TOH), whose importance has increased lately.

Methods: In the study, 105 consecutive subjects diagnosed with TOH were evaluated. The subjects were randomized into three groups. In Group 1 (n = 35), only triptan was abruptly withdrawn. In Group 2 (n = 35), triptan was abruptly withdrawn and single GON block was performed. In Group 3 (n = 35), triptan was abruptly withdrawn and three-stage GON block was performed. All patients were injected bilaterally with a total amount of 5 cc 1% lidocaine in each stage. During follow-up, the number of headache days per month, the severity of pain (VAS), the number of triptans used, and hsCRP and IL-6 levels were recorded three times; in the pretreatment period, in the second month post-treatment, and in the fourth month of post-treatment. They were then compared.

Results: There was a statistically significant difference in the post-treatment fourth month in comparison with the pretreatment period in Group 3 (p < 0.05). Compared to Group 1, the number of headache days, VAS, and decrease in triptan need in Group 3 was statistically significant compared to Group 2 (p < 0.05). Compared to pretreatment, in the fourth month post-treatment, both hsCRP and IL-6 levels were lower only in Group 3 (p < 0.05).

Conclusion: We are of the opinion that repeated GON block in addition to the discontinuation of medication has significant efficacy for TOH cases.

Disclosure of Interest: None Declared
Comorbidity of Primary Headaches

PO-02-045

Carotid intima-media thickness and aortic pulse wave velocity in perimenopausal women with migraine: a cross-sectional study

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Objectives: Migraine is associated with increased cardiovascular mortality. There is still an unexplained link between them. It is possible that both conditions share an underlying vascular dysfunction. The aim of this study is to evaluate the association between migraine and increased carotid intima-media thickness (cIMT) and between migraine and arterial stiffness (increased aortic pulse wave velocity - aPWV) in perimenopausal women.

Methods: We recruited 304 consecutive women with more than 60 days of menstrual irregularity, aged 45 to 65 years-old who were submitted to a strict protocol, including a semi-structured interview, physical examination, blood tests, portable sleep study, high-resolution carotid ultrasound, and aortic pulse wave tonometry. We also used the hospital anxiety and depression scale, the general cardiovascular risk profile from the Framingham Heart Study, and the 6-item Headache Impact Test. The presence of increased carotid intima-media thickness was indicative of subclinical atherosclerosis and increased aPWV was indicative of arterial stiffness. All patients had given their informed consent. The study was approved by the Research Ethics Committee of the Oswaldo Cruz University.

Results: We included 277 women in the final sample. The prevalence of migraine and migraine with aura (MA) were respectively 40.1% and 16.5%. Women with migraine with aura (MA) were younger (51 ± 3 vs. 55 ± 7 years, p = 0.04) and had more diagnosis of arterial hypertension (76.1% vs. 59.1%, p = 0.04), depression (71.7% vs. 37.6%, p < 0.001), and anxiety (82.6% vs. 57.6%, p < 0.001) than those without migraine. Apnea-hypopnea index, diagnosis of obstructive sleep apnea and aPWV were not different between migraine, MA, or migraine without aura (MO) groups and non-migraine group. Six women (2.2%) presented increased cIMT which was more prevalent in MA group (6.5% vs. 1.2%, p = 0.04) than non-migraine group. After adjustment for confounding factors we found that MA increases seven-fold the risk of increased cIMT (OR 7.12, 95% CI 1.05–48.49). We found no difference on overall median Framingham score between migraine subgroups and non-migraine group.

Conclusion: Migraine is associated with increased arterial stiffness. Migraine with aura is associated with increased carotid intima-media thickness in perimenopausal women. Therefore, it is important to consider that cIMT could be a marker of endothelial dysfunction in migraineurs.

Disclosure of Interest: None Declared

Comorbidity of Primary Headaches

PO-02-046

Misclassification on the diagnosis of overweight/obesity in migraineurs using the body mass index as compared to body adiposity

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Objectives: The prevalence of both episodic and chronic migraine is increased in obese individuals when compared to normal weight. Body mass index (BMI) is the diagnostic tool widely used to classify obesity, but this method underestimates its prevalence, defined as an increase in body fat percentage (BF%). We aimed to examine the potential misclassification regarding the diagnosis of overweight and obesity by using BMI as compared with the determination of BF% ( Bod Pod®) in migraineurs.

Methods: Fifty-nine patients (18–49 years-old), 46 with episodic migraine and 13 with chronic migraine, underwent BMI and Bod Pod® exams. Patients with known comorbidities such as severe or systemic diseases, pregnancy or breastfeeding, major psychiatric disorders, immunosuppression or morbid obesity, according to BMI were excluded from the study. Bod Pod® parameters and anthropometric data were analysed. We performed a descriptive analysis to assess misclassification on the diagnosis of obesity using BMI as compared with BF% and Cohen’s Kappa Coefficient Index to evaluate the quality of agreement.

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Results: We found that 1 (1.7%) patient was classified as underweight, 43 (72.9%) normal weight, 11 (18.6%) overweight and 4 (6.8%) obese according to BMI. Using BF% 2 (3.4%) patients were classified as underweight, 19 (32.2%) patients as normal weight, 13 (22.0%) as overweight and 25 (42.4%) as obese. Cohen’s Kappa Coefficient Index value was 0.220 which is no more than a fair degree of agreement.

Conclusion: Our findings suggest that a relevant number of migraine patients are misclassified according to BMI as compared with BF% because of the fair degree of agreement. Replications of present findings in wider population with different frequency of migraine are warranted.

Disclosure of Interest: None Declared

Comorbidity of Primary Headaches

PO-02-047

Demographic and clinical profile of chronic migraine in a low income population of Bogota, Colombia

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Objectives: Background: Chronic migraine has a severe impact in quality of life. Chronic migraine affects 1–2% of the general population, and about 8% of patients with migraine. Risk factors for chronic migraine include medication overuse, depression, stressful life events, age, female sex and low educational status among others.

Aim: To describe the demographic and clinical features of headache in a population with chronic migraine in a low income population of Bogotá-Colombia

Methods: We conducted an observational, descriptive, and cross-sectional study from June to December of 2016. The data for patients with headache, attending the specialized headache consultation at the Hospital Occidente de Kennedy in Bogotá-Colombia. Diagnosis of headache was according to the International classification of headache disorders (ICHD-III).

Results: A total of 277 patients consulted for headache for first time at the headache unit. 40% (n:110) of patients meet criteria for chronic migraine. 83.6 % are women. The middle age was 47.7 (±13.9), most are single (63.3%), 26.4% did not have any type of education, 86.2% belongs to risk social population and 10% are special populations victims of armed conflict and forced displacement. Osmophobia (70%), medication overuse (51.4%), allodynia (47.7%), aura (46.4%), emesis (31.8%), depression (28.8%) and vertigo (28.4%) were more prevalent in the group of patients with chronic migraine (p < 0.05).

Conclusion: Our patients are part of a special group of vulnerable population, and at social risk. The presence of a high percentage of patients with osmophobia could be related with a central sensitization process. Also we have a significant prevalence of medical overuse related with free analgesic sale in our country. Aura, allodynia, emesis and vertigo were an important find in this population.

Key Words: Headache, low income population, chronic migraine, osmophobia

Disclosure of Interest: None Declared

Comorbidity of Primary Headaches

PO-02-048

Significance of fatigue in patients with migraine

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Objectives: Fatigue is often stated as a headache trigger or migraine-specific symptom. We investigated predictors of fatigue and its impact on quality of life (QOL) in patients with migraine.

Methods: Patients with migraine were recruited from a headache clinic and completed psychosomatic instruments, including the 12-item Allodynia Symptom Checklist (ASC-12), the Migraine Disability Assessment Scale (MIDAS), the Patients Health Questionnaire-9 (PHQ-9), the Generalized Anxiety Disorder-7 (GAD-7), the Epworth Sleepiness Scale (ESS), the Insomnia Severity Index (ISI), the Fatigue Severity Scale (FSS), and Migraine-Specific Quality of Life Questionnaire (MSQ).

Results: Two hundreds twenty-six patients with migraine were eligible for the study. Pathologic fatigue was manifested in 133 patients (58.8%). The FSS score was significantly associated with age, age at onset, the Visual Analog Scale (VAS) depicting headache intensity, photophobia, phonophobia, and the scores of the ASC-12, the MIDAS, the ESS, the ISI, the PHQ-9 and the GAD-7. The strongest predictor for the FSS was the PHQ-9 (β = 0.432, p = 0.001), followed by age (β = −0.169, p = 0.002), the ISI (β = 0.151, p = 0.016), and the VAS (β = 0.139, p = 0.018). There was an inverse correlation between the FSS score and three dimensional scores of the MSQ (p < 0.001).

Conclusion: Appropriate interventions for depression, insomnia, and headache intensity are likely to lessen fatigue and improve QOL.

Disclosure of Interest: None Declared
**PO-02-049**

**Association of headache impact test with chronotypes, sleep quality index, anxiety and depression in migraine without aura patients**

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**Objectives:** To evaluate the role of chronotypes, sleep quality, anxiety, and depression in migraine without aura patients.

**Methods:** Twenty-eight female patients (mean age ± S.D. 38.1 ± 11.9 years; range 22–59 years) were enrolled at the General Hospital of Mexico City. Diagnostic of migraine without aura were established following the criteria of the International Headache Society (IHS). Depression and anxiety, chronotypes and sleep quality were evaluated using the Hospital Anxiety Depression Scale (HADS), Morningness-eveningness Questionnaire (MEQ), and the Pittsburgh Sleep Quality Index (PSQI) respectively. Impact of headache pain was evaluated using the Headache Impact Test (HIT-6). Logistic regression modeling were used to analyse these data.

**Results:** Results: Poor sleep quality (PSQI ≥ 5) was 82.1%, and global score of PSQI was 8.78 (S.D. ± 4.02). Anxiety and depression (HADS) was 50% and 37.1%, (mean 9.7, S.D. ± 2.27; mean 8.6 S.D. ± 2.77) respectively. Chronotypes were moderate (50%) and morning types (50%), mean score 58.1 ± S.D.7.13. Headache Impact test scores were severe in 18 patients (68.4%) and the total score was 60.28 (S.D. ± 8.05). Best predictors for severity of HIT-6 were anxiety (2.755) depression (1.875) while chronotype predicted negatively (−0.603) and sleep quality predicted positively (0.657), constant (0.370).

**Conclusion:** Impact of headache in daily activities are more influenced by anxiety and depression than chronotypes and sleep quality. Among stressors of migraine sufferers anxiety and depression comorbidity play a major role in migraine without aura probably associated to chronic pain rather than circadian rhythms

**Disclosure of Interest:** None Declared

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**PO-02-050**

**INvolvement of the migraine SNP rs1835740 in cluster headache**

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**Objectives:** The pathophysiology and symptoms of cluster headache presents certain common features with other headache disorders such as migraine. For example, the activation of the trigeminal vascular system, inflammation and vasodilation of the large arteries of the brain. Genetic factors have been implicated in both migraine and cluster headache. In this study we chose to screen cluster headache patients for two genetic variants known to increase the risk for migraine in Sweden: rs2651899 in the PRDM16 (PR/SET domain 16) gene and rs1835740 closely located to MTDH (metadherin), in order to investigate whether these two disorders also share genetic factors of predisposition. Furthermore, we have studied the mRNA expression patterns of these two candidate genes in rodent tissue to achieve a better understanding of how they might affect headache pathophysiology.

**Methods:** We screened a Swedish cluster-headache case-control study population consisting of 541 cluster headache patients and 571 control subjects for two genetic variants, rs1835740 and rs2651899. Genotyping was performed with TaqMan real-time PCR on a 7500 Fast instrument, results for rs1835740 were further confirmed with pyrosequencing on a PSQ 96 System. Fisher’s test and Chi-square test were used in the statistical analysis. mRNA expression patterns were investigated using radioactive in situ hybridization in cryosections of fresh frozen rat tissue.

**Results:** We found that rs1835740, an intergenic SNP that is known to affect MTDH activity, was associated with increased risk for cluster headache in Sweden (p = 0.043). The association was stronger in patients suffering from both cluster headache and migraine (p = 0.031). rs2651899 in PRDM16, was not associated with cluster headache in Sweden. Preliminary data from the gene expression analysis shows that MTDH has a widespread expression in rats, covering the central nervous system and several peripheral tissues. Rat PRDM16 mRNA was absent in most peripheral and nervous tissues analysed, with the exception of the lateral septal nucleus, the stomach and the small intestine.

**Conclusion:** rs1835740 is associated to cluster headache. This variant was more common in patients with both migraine and cluster headache and might therefore
constitute a marker for severe headache in general. rs2651899 on the contrary is specifically related to migraine in Sweden.

Disclosure of Interest: None Declared

Genetics and Biomarkers of Headache Disorders

PO-02-051

Genetic pleiotropy between migraine and motion sickness

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Objectives: Motion sickness is associated with migraine. In fact, two-thirds of migraine sufferers are prone to motion sickness. Furthermore, migraine sufferers are more susceptible to symptoms evoked by visual simulation of movement, implying that migraine is associated with abnormal central integration of visual and vestibular cues. Given genetic factors may underlie the tendency to motion sickness and the neurotological symptoms of migraine, we examined whether the same genes are involved in both conditions.


Results: SNP rs7518255 on chromosome 1p36.32 shows genome-wide significant association ($P = 5 \times 10^{-8}$) with motion sickness and is significantly associated with migraine. Also, two additional SNPs significantly associated with motion sickness, rs705165 on 10q26.13 and rs11696973 on 20q13.2, show genome-wide suggestive association ($P < 1 \times 10^{-5}$) with migraine. For all three SNPs, the same allele is associated with an increased risk for both traits. Of the 182 independent SNPs showing genome-wide suggestive association with motion sickness, 28 (15.38%) show nominal association ($P < 0.05$) with migraine—more than the empirically derived null expectation of 6.89%, producing significant evidence for genetic overlap (pleiotropy) ($P = 8.95 \times 10^{-5}$).

Conclusion: The observed comorbidity between motion sickness and migraine can be explained, in part, by shared underlying genetically determined mechanisms. We are currently extending these findings by performing additional SNP- and gene-based analyses utilising results from a larger migraine GWA study (30,465 migraine cases and 143,147 controls) [Gormley, et al. Nat Genet. 2016;48(8):856–66]. Preliminary analyses have identified three SNPs with novel genome-wide significant association, and suggest several genes and pathways to be involved in migraine and motion sickness etiology.

Disclosure of Interest: None Declared

Genetics and Biomarkers of Headache Disorders

PO-02-052

Value of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in migraineur

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Objectives: The mechanism of migraine is not yet fully understood but may involve in part cortical spreading depression and neurogenic inflammation. Previous studies have shown blood neutrophil-lymphotocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) to be simple biomarkers for acute phase of inflammation and to be associated with predictor or prognosis of various disease, such as ischemic heart disease, stroke, chronic kidney disease, and neoplastic disorders.

To analyze the role of inflammation in migraine, we evaluated blood NLR and PLR in migraineurs.

Methods: Twenty-eight patients suffering from migraine with aura (MA) (9 men, 19 women, mean age: 39.1 years), 125 with migraine without aura (MO) (24 men, 101 women, mean age: 41.6 years), and 26 tension-type headache (TH) (9 men, 17 women, mean age: 59.5 years) participated in this study. The diagnosis of headache was made according to the International Headache Society (IHS) criteria. The blood sample for NLR and PLR assessment was collected in each ambulatory care. Acute phase (AP) and intermittent phase (IP) cases were defined respectively as the day of migraine attack and the other days after migraine attack. Patients were classified the frequency of attacks; 0–8 headache days per month, 9–14 headache days per month and 15– headache days per month. Patients were also classified with or without medication overuse headache. Comparisons among groups were assessed by the analysis of multivariate statistics. The level of significance was set at $p < 0.05$.

Results: The mean NLR in MA, MO, and TH were 1.79, 2.00, and 2.26. The mean PLR in MA, MO, and TH were 136.0, 139.1, and 143.0. The mean NLR was significantly
increased in AP than IP, especially with MO, while the mean PLR was also significantly increased in AP, especially with TH. As the frequency of attacks, there was no certain tendency in the mean value of NLR and PLR. There was no significant difference in NLR and PLR between subjects having medication overuse or not.

**Conclusion:** NLR and PLR can be easily calculated from the differential WBC count in outpatient clinic. NLR and PLR have considered simple biomarkers for acute phase of inflammation. Our results support the conclusion that increased NLR/PLR is associated with a kind of inflammation in acute phase of headache pain.

**Disclosure of Interest:** None Declared

**Headache and Gender**

**PO-02-054**

Symptoms of premenstrual syndrome in women with and without menstrual migraine

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**Objectives:** Menstrual migraine (MM) and premenstrual syndrome (PMS) are two conditions linked to specific phases of the menstrual cycle. The exact pathophysiological mechanisms are not fully understood, but both conditions are hypothesized to be triggered by female sex hormones. Co-occurrence of MM and PMS is controversial. The objective of this population based study was to compare self-assessed symptoms of PMS in female migraineurs with and without MM.

**Methods:** A total of 237 women from the general population with self-reported migraine in at least half of their menstruations were interviewed and diagnosed by a neurologist according to the International Classification of Headache Disorders II (ICHD II). All women were asked to complete a self-administered form containing 11 questions about PMS-symptoms adapted from the Diagnostic and Statistical Manual of Mental Disorders. The number of PMS symptoms was compared among migraineurs with and without MM.

**Results:** A total of 193 women returned a complete PMS questionnaire, of which 67 women were subsequently excluded from the analyses due to current use of hormonal contraception (n = 61) or because they did not fulfill the ICHD-criteria for migraine (n = 6). Among the 126 migraineurs who were included in the analyses, 78 had...
MM and 48 non menstrually related migraine. PMS symptoms were equally frequent in migraineurs with and without MM (5.4 vs. 5.9, p = 0.37).

**Conclusion:** We did not find any difference in the number of self-reported PMS-symptoms between female migraineurs with and without MM.

**Disclosure of Interest:** None Declared

**Headache and Gender**

**PO-02-055**

Sex differences in prevalence, symptoms, impact and comorbidities in migraine and probable migraine: results from Korean Headache-Sleep Study

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**Objectives:** The significant higher prevalence of migraine and probable migraine (PM) among women compared to men has been documented around the world. However, only few data on sex differences in headache characteristics, accompanying symptoms, impact of headache and their common comorbidities of migraine and PM are available in Asian region, an area that includes more than half the world’s population. Prevalence and clinical characteristics of migraine and PM in Asian countries were somewhat different from those of Western countries. This study is to investigate sex difference in prevalence, clinical symptoms, impact of headache and comorbidities of migraine and PM using a Korean nation-wide population-based sample.

**Methods:** The Korean Headache-Sleep Study (KHSS) is a nation-wide population-based door-to-door survey regarding headache and sleep. We used the data of the KHSS in the present study.

**Results:** The prevalence of migraine (7.9% vs. 2.7%, p < 0.001) and PM (18.0% vs. 10.1%, p < 0.001) was significantly higher among women compared to that of men. Visual Analogue Scale (VAS) score for headache intensity (median and interquartile range [IQR], 5.00 [4.00–7.00] vs. 5.00 [3.00–6.00], p = 0.019) and impact of headache (Headache Impact Test-6 [HIT-6] score, 48.6 ± 8.3 vs. 46.6 ± 8.2, p = 0.024) were significantly higher among women with PM than men with PM. In contrast, VAS score for headache intensity (6.00 [5.00–8.00] vs. 6.00 [4.25–7.00], p = 0.281) and HIT-6 score (54.7 ± 8.8 vs. 53.1 ± 10.7, p = 0.385) did not significantly differ between women with migraine and men with migraine. Headache frequency per month was not significantly different between women and men among individuals with migraine (4.2 ± 6.5 vs. 2.9 ± 5.7, p = 0.310) and PM (2.9 ± 5.6 vs. 2.4 ± 5.6, p = 0.387) (Table). Among individuals with PM, nausea (90.5% vs. 76.5%, p < 0.001) and osmophobia (51.0% vs. 40.4%, p = 0.048) were more prevalent among women than men. Insomnia symptom was more prevalent among women with migraine compared to men with migraine (26.2% vs. 8.3%, p = 0.025). Prevalence of anxiety (29.9% vs. 30.6%, p = 0.941) and depression (16.8% vs. 16.7%, p = 0.983) was not significantly different between women with migraine and men with migraine. Prevalence of anxiety (18.1% vs. 16.9%, p = 0.770), depression (8.2%...
vs. 9.6%, p = 0.660) and insomnia symptom (16.9% vs. 14.0%, p = 0.458) did not significantly differ between women with PM and men with PM.

**Conclusion:** Migraine and PM were more common in women than men in a Korean general population sample. Women with PM experience more severe headache intensity and higher impact of headache than men with PM. Some headache features of women with PM were different from those with men with PM.

**Disclosure of Interest:** M. K. Chu Conflict with: None, Conflict with: Hallym University Research Fund 2016, Conflict with: Advisory board member for Teva, Conflict with: None, Conflict with: Honoraria from Allergan Korea and Yuyu Pharm., Conflict with: None, Conflict with: None, Conflict with: None, J. Kim Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, Conflict with: None, W.-J. 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only), entered headache/migraine occurrence, symptoms and variables potentially affecting migraine attacks daily. Data used included women's daily reports of migraine (yes/no, assessed by ICHD-3b criteria) and menstrual bleeding (yes/no). We defined a four-part menstruation timing window that is specific to each individual's monthly cycle: 1) Pre-menstruation (PRE): 2 days prior to bleeding, 2) Active Bleeding (AB): days actively bleeding, 3) Post-bleeding (POST): 3 days after the last day of bleeding; 4) Baseline (BL): days outside of the Pre, AB, and POST time periods. Two n = 1 methodologies were used to quantify and visualize between- and within-person risk for PMDs. Method 1 was a categorical time approach which directly contrasts the menstruation time periods (e.g., PRE vs. BL, AB vs. BL, and POST vs. BL). Method 2 was a continuous time approach that allowed each individual’s migraine risk to vary between and within the time periods. For example, women can differ in how much their migraine risk changes from day 1 to day 2 of PRE, through their AB days, and across their 3 POST days. Individual n = 1 logistic regression models were fitted using Method 1 and Method 2. Data visualizations were utilized to depict inter- and intra-individual differences in migraine risk related to menstruation.

Results: Our analysis sample consisted of n = 50 menstruating females (average age of 35.3 and 12% used contraceptives pills) reporting on a median of 200 days. Method 1, categorical time, showed substantial individual differences in migraine risk across the menstruation time periods: 20% of women had greater than two-fold odds of having a migraine on a PRE day vs. a BL day; 44% for AB vs. BL; and 26% for POST vs. BL. Further, the level of migraine risk associated with the different time periods varied considerably across women. Method 2, continuous time, extended Method 1 by showing that each woman’s migraine risk often varied not only across menstrual stages (BL vs. PRE vs. AB vs. POST) but also within specific stages. Individual n = 1 plots visually depicted the individual differences in migraine risk related to menstruation and contrasted the unique inferences drawn from Methods 1 and 2.

Conclusion: Two different n = 1 analytic approaches can successfully be applied to analyze the association between migraine and menstruation and reveal inter- and intra-individual differences in migraine risk. The n = 1 methods showed strengths and weaknesses associated with treating time as a categorical versus continuous variable. A limitation of the current study is that we only considered a single extended time window. Future studies should empirically evaluate other potential timing structures for menstruation and examine how they relate to migraine.


Headache Classification

PO-02-058

Clinical features and outcomes of benign paroxysmal vertigo in adults: a clinic longitudinal study of 84 patients

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Objectives: To explore the clinical features, treatment response, and prognosis as well as applicability of the International Classification of Headache Disorders, 3rd edition beta version (ICHD-3 beta version) of benign paroxysmal vertigo (BPV) in a Chinese cohort.

Methods: Consecutive patients with BPV were prospectively enrolled in a neurology clinic between June 2013 and December 2015. All patients underwent detailed clinical interview and neuro-otological examinations. Twenty-eight patients with cochlear symptoms were studied pure-tone audiometry (PTA). Follow-up was conducted through direct or semi-structured telephone interview after starting prophylactic treatment.

Results: Eighty-four patients (62 female/22 male, 52.1 ± 11.8 years old) were identified with BPV. The majority of patients (63%) continued to have recurrent vertigo after a median follow-up of 22 months (range 10–41 months). Vertigo days (a day on which vestibular symptoms of at least moderate intensity occurred, regardless of the duration and frequency) were markedly reduced in 71% of patients who received flunarizine. Nine patients had chronic course (vertigo days ≥15 days per month for >3 months) and six of them reported overuse of symptomatic medications (on ≥15 days per month for >3 months). After discontinuing the excessive use of symptomatic medications and receiving flunarizine, these
nine patients were noted a markedly improvement in vertigo days. Four patients developed migraine on follow-up, and all of them also fulfilled vestibular migraine in ICHD-3 beta version. Comorbid anxiety or depression predicted a poor outcome. Inconsistent with the ICHD-3 beta version, 10% of patients with BPV had abnormal vestibular functions between attacks.

**Conclusion:** The majority of patients still have recurrent vertigo in the long-term evolution of BPV. Withdrawal therapy plus preventive treatment may help reduce the vertigo days in patients with chronic course of BPV. The transformation of clinical characteristics between BPV and vestibular migraine suggests the similar migrainous mechanism.

**Disclosure of Interest:** None Declared

**Headache Classification**

**PO-02-059**

An auto-accumulating and matching database and a rule-based artificial intelligence expert system for the International Classification of Headache Disorders 3 Beta

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**Objectives:** The International Classification of Headache Disorders 3 Beta (ICHD-3b) includes all headache diagnoses. However, the association between each criterion and symptoms/treatments is still controversial for many diagnoses, especially those of secondary headaches. Thus, the accumulation of matching patterns using a very large number of patients is needed. Such a database requires the integration of inquiry, symptoms, and laboratory data with diagnosis, as well as accurate judgments from the headache specialists of the large diagnosis group ICHD-3b. However, the accumulation of this type of data is very difficult. This study aimed to create a system comprising an auto-accumulating and matching database of patient information and a rule-based artificial intelligence expert system that suggests a diagnosis derived from the database. We also evaluated the accuracy of the suggested diagnosis and the patient impressions of the usability of this system.

**Methods:** Quoting all items of ICHD-3b, we established a database system comprising a comprehensive headache questionnaire (CoQ), a clinicians’ judgment enrollment application (CJE), and a rule-based artificial intelligence expert system for ICHD-3b (HEx), which automatically suggests headache diagnosis candidates based on the datasets derived from CoQ and CJE. All components work on a PHP + JavaScript + MySQL system with WEB browsers. As a trial, the results of patients (23 females and three males) who tested the system were collated with diagnoses from a headache specialist. Simultaneously, the patients answered another questionnaire on their impressions of the number of questions (IN), their sense of sufficiency regarding the interview (SF; whether the CoQ could adequately identify their headache characteristics), and overall satisfaction (OS) of CoQ. They were also asked to answer the paper-based MIDAS and HIT-6 questionnaires. Finally, Spearman’s rank correlation coefficients (ρ) were calculated using the results of the trial.

**Results:** CoQ required 21.50 ± 6.86 (Mean ± SD) min as answering time (TM) for 134.92 ± 6.90 questions. HEx suggested 2.77 ± 1.48 candidate diagnoses, which included the same as the diagnosis provided by the headache specialist in all cases except one. OS correlated with SF (ρ = 0.7469; p < 0.0001) but not with TM and IN (ρ = 0.1465; p = 0.4751 and ρ = −0.0336; p = 0.8707, respectively). However, HIT-6 revealed an inverse correlation with OS (ρ = −0.4520; p = 0.0304).

**Conclusion:** CoQ can accumulate the properties of patients’ headaches and does not affect patient satisfaction. Moreover, HEx with CoQ and CJE can suggest accurate diagnoses and may be helpful for headache specialists in the diagnostic process. However, there is a possibility that the burden that the patients feel regarding CoQ worsens with the increase in their headache severity. Hence, it is important to reduce the number of questions in the questionnaire. For example, the Naive Bayes classifier or artificial intelligence with deep learning that can be used for all natural languages would be useful to reduce the burden that patients feel; however, they might have less accuracy than CoQ. To establish this type of machine learning, our current system can also provide a fundamental dataset of the properties and diagnoses of patients' headaches.

**Disclosure of Interest:** None Declared

**Headache Classification**

**PO-02-060**

Chronic and Primary Persistent Vestibular Migraine - Two New Subtypes of the Disorder

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1Department of Neurology, University of Duisburg-Essen, Essen, Germany

**Objectives:** Vestibular migraine (VM) is a common cause of vertigo affecting approximately 1% of the population. In collaboration Bárány-Society and the IHS developed
diagnostic criteria for vestibular migraine which were added as appendix criteria to ICHD3-beta. Chronification of migraine headaches is a well-known condition. Clinical experience has shown, that vestibular migraine can also take a chronic course of disease. However, scientific data regarding this topic are sparse.

**Methods:** We retrospectively analysed records of patients diagnosed with vestibular migraine in a tertiary vertigo centre (vertigo centre Essen) between January 2011 and December 2016. Only patients suffering typical migraine headaches, fulfilling ICHD3-beta criteria for VM, and had vertigo/dizziness on at least 15 days per month were included into the analysis. Patients with concurrent vertigo disorders or psychiatric comorbidities were excluded.

**Results:** Thirty three (24 female) patients with chronic courses of vestibular migraine could be certainly identified. Patients age ranged from 18–72 years (average 35.82 years). On average vertigo was reported to be first recognized 42.37 [3–360] month before consultation in the vertigo center. On average patients suffered vertigo on 26.39 [15–30] days per month. If not persistent the duration of vertigo attacks was reported between min. 578 [10–2880] to max. 980 [10–4320] minutes. Fifteen patients reported their vertigo to be continuously present. A subset of 7 patients (=21.2%, age 34.29 years [19–53], 3 female) reported the vertigo as primary persistent (PPVM).

Fifteen patients (=45%) reported to suffer typical visual auras at least occasionally. The frequencies of the reported vertigo-accompanying symptoms are summarized in the table.

**Conclusion:** We here for the first time present two new subgroups of patients suffering high frequent vertigo caused by vestibular migraine. These preliminary data stress the need to further study different courses of vestibular migraine, which here are proposed as chronic vestibular migraine and primary persistent vestibular migraine.

**Disclosure of Interest:** None Declared

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**Headache Classification**

**PO-02-060**

**Towards an improved diagnostic criterion for Menstrually Related Migraine (MRM)**

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2 Curelator Inc., Cambridge
3 Barts and the London SMD, London, United Kingdom

**Objectives:** The ICHD-III classifies MRM as a subtype of migraine without aura if migraine attacks occur on 2 out of 3 menstrual windows (defined as the five days centered on the first day of bleeding) in women who also have non-menstrual attacks; we refer to this as the 2/3 criterion. Concerns exist that MRM diagnoses set by the 2/3 criterion may lead to unacceptable type-I and type-II error rates: MRM may be missed in women with sparse migraine patterns while women with frequent migraine may fulfill the 2/3 criterion spuriously.

Previous research has shown that in women with MRM, menstrual attacks last longer than non-menstrual attacks. The objective of this study was to compare the ability of a novel statistical method to diagnose MRM using this criterion (sMRM) against the ICHD-III 2/3 criterion (2/3MRM).

**Methods:** Data: We analyzed a pooled data set from 106 women using a digital platform [Curelator Headache™] during 2015–7 and 123 women attending the City of London Migraine Clinic during 1997–8, whose data have previously been published. All women had logged migraine attacks during at least 3 consecutive natural menstrual cycles. MRM was diagnosed by the standard ICHD-III criterion (2/3).

**Statistical:** The diaries were processed using a diagnostic algorithm (based on the Fischer’s exact test – implemented

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**Abstract number: PO-02-060**

**Table: Vertigo-accompanying symptoms**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>all patients</th>
<th>cVM only</th>
<th>PPVM</th>
</tr>
</thead>
<tbody>
<tr>
<td>photophobia</td>
<td>22/33 = 66%</td>
<td>19/26 = 73.1%</td>
<td>3/7 = 42.9%</td>
</tr>
<tr>
<td>phonophobia</td>
<td>21/33 = 63.6%</td>
<td>17/26 = 65.4%</td>
<td>4/7 = 57.1%</td>
</tr>
<tr>
<td>sickness</td>
<td>23/33 = 69.7%</td>
<td>17/26 = 65.4%</td>
<td>6/7 = 85.7%</td>
</tr>
<tr>
<td>vomiting</td>
<td>11/33 = 33.3%</td>
<td>9/26 = 36.6%</td>
<td>2/7 = 28.6%</td>
</tr>
<tr>
<td>need for rest</td>
<td>20/33 = 60.6%</td>
<td>14/26 = 53.8%</td>
<td>6/7 = 85.7%</td>
</tr>
<tr>
<td>vertigo worsened by</td>
<td>16/33 = 48.5%</td>
<td>14/26 = 53.8%</td>
<td>2/7 = 28.6%</td>
</tr>
<tr>
<td>physical activity</td>
<td></td>
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</tr>
</tbody>
</table>

(PPVM = primary persistent vestibular migraine, cVM only = chronic vestibular migraine without subset of PPVM patients)
in R) building on previous work by Barra et al (2). The algorithm yields p-values for each diary, which can be interpreted as the degree of certainty that the woman’s menstrual attacks of migraine are not a chance association. We used \( p < 0.1 \) (deemed a reasonable balance between specificity and sensitivity) as the diagnostic criterion for sMRM. Subsequently, negative binomial (mixed effects) regression models were designed to investigate if either criterion was able to select women with prolonged menstrual attacks. One model explained attack length (unit days) by whether the attack was menstrual (beginning within a menstrual window), whether the women had 2/3MRM, and their interaction-term, and included random effects accounting for within-woman correlation. The second model was similarly specified, but used sMRM instead of 2/3MRM.

Image:

<table>
<thead>
<tr>
<th>Model 1 (ICHD-III 2/3)</th>
<th>Pred.</th>
<th>Coeff.</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA</td>
<td>.14</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>MRM</td>
<td>-.09</td>
<td>.20</td>
<td></td>
</tr>
<tr>
<td>Interaction</td>
<td>.10</td>
<td>.15</td>
<td></td>
</tr>
</tbody>
</table>

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<tr>
<th>Model 2 (sMRM)</th>
<th>Pred.</th>
<th>Coeff.</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>sMRM</td>
<td>-.03</td>
<td>.07</td>
<td></td>
</tr>
<tr>
<td>Interaction</td>
<td>.16</td>
<td>.03</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Model estimates and significances. Dependent variable = attack length; MA = menstrual attack.

Results: The 229 women were mean age 38 years (SD 9), and had logged 158 (SD 98) migraine days; the mean number of menstrual cycles was 5 (SD 3), mean number of attacks was 14 (SD 12). 95 (41%) women had an MRM diagnosis and 71 (31%) had an sMRM diagnosis; 55 (24%) had both MRM and sMRM. The regression model showed reasonable fit, though the skewed attack-length distribution was an issue for all models (Poisson and loglinear models were discarded). Table 1 gives the coefficients and the \( p \)-values for the main predictors.

The model coefficients indicate that sMRM selects women with prolonged menstrual attacks, while MRM was unable to isolate this trait in our data.

Conclusion: Both models suggest a cross-sample prolongation of menstrual vs. non-menstrual attack length regardless of MRM or sMRM diagnosis. However, the sMRM model had a significant (and positive) interaction term – an indication that sMRM might have better specificity. The sMRM allows sparse attack patterns while at the same time controlling the rate of spurious diagnoses. We think that the ICHD should consider incorporating statistical association into the diagnostic criterion of MRM, but further research of the merit of the method is needed.

Disclosure of Interest: M. Barra: None Declared, G. Boucher Conflict with: Curelator Inc., Conflict with: Curelator Inc., E. A. MacGregor: None Declared, K. Vetvik: None Declared

References


Headache Classification

PO-02-062

A statistical criterion for Menstrually Related Migraine (MRM) without an independence-of-attacks assumption

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2Barts and the London SMD, London, United Kingdom

Objectives: The ICHD-III beta classifies MRM as a subtype of migraine without aura if migraine attacks occur on 2 out of 3 menstrual windows (defined as the five days centered on the first day of bleeding) in women who also have non menstrual attacks. Concerns that MRM-diagnoses thus obtained may lead to unacceptable type-I and type-II error rates have instigated scientific exploration of alternative criteria. As the etiology of MRM is unknown, the inclusion of spuriously diagnosed patients could hamper the advancement of a better understanding of this sub-type of migraine.

A promising probability-based criterion proposed by Marcus et al.1 was subsequently revised by Barra et al.2 However, this criterion assumes independence-of-attacks (IoA): i.e. that the probability of experiencing a migraine attack is unconditional on the previous day. The aim of this study was twofold: 1. to investigate how restricting this assumption is; 2. to specify a statistical criterion for MRM that does not rely on IoA.

Methods: Simple Markov-chains for individual migraine-histories were tested, and data from 123 women attending the City of London Migraine Clinic during 1997–8, whose data have previously been published,3 was used for estimating conditional probabilities for recording migraine days.

The criterion from Barra et al. was redefined so as to be statistically sound also without the IoA-assumption.
Results: A clustering of migraines was observed and consistent with a simple 2-state Markov-chain with a baseline probability for a recorded migraine on a day after a migraine-free day, and an elevated for a recorded migraine on a day subsequent to a migraine-day. Setting and produced simulated data similar to the observed. A re-specified statistical criterion that can accurately capture significant association between migraine and menstrual pattern on the individual level was obtained by modifying the method from Barra et al. by focusing on the day of an attack start rather than counting attack days. More precisely, the criterion developed by Marcus et al. and Barra et al. employs the statistically very simple Fischer’s exact test (with mid-p correction) for obtaining a conservative p-value representing the strength of the association between the catamenial cycle and the patient’s migraine attacks. Our new method keeps track of attack starts only (see table 1.) This new accounting for attack starts retains the desirable properties developed by Barra et al. (exact and conservative) but avoids the IoA-assumption (which could increase Type-I errors when not satisfied.)

Conclusion: Our study show that the IoA is unrealistic, and that the criterion (sMRM) in Barra et al. may yield elevated type-I errors. An improved version, accommodating non-IoA, is presented here. To ensure minimizing diagnostic error the ICHD should consider integrating the improved sMRM in its future revisions.

Disclosure of Interest: None Declared

References

Headache Classification

PO-02-063

Discriminative Analysis of Migraine with Aura using Non-Linear SVM Classification

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2 Faculty of Applied Science and Technology, Sheridan College, Brampton
3 Cerebral Diagnostics Canada Inc, Toronto, Canada

Objectives: The objective of this work is to implement a technique of characterizing and extracting significant, robust and informative features from EEG signals which are representative of the non-pain migraine with aura (MwA) brain state. EEG signals are used because they contain critical spatial and temporal information about the neural bioelectricity.

Methods: The study was approved by the Ontario Institutional Review Board of Institutional Review Board Services. All subjects were recruited online and gave their informed consent prior to their inclusion in the study. The participants consisted of 24 MwA patients and 24 NC individuals with no history of migraines. Subjects with migraine symptoms were screened using the International Headache Society criteria before they were admitted into the study. Thirty-two Ag/AgCl electrodes were secured onto a nylon electrode cap according to the standard 10–20 electrode system. The EEG signals were average referenced, amplified, and digitally sampled at 1024 Hz using a TMSI Refa 32 amplifier. All subjects underwent baseline recordings of 2 minutes of eyes closed no light. In all conditions, subjects were told to relax but remain alert.

The EEG signals were filtered using a high pass filter at 0.1 Hz to remove the DC drift and then subsequently decimated to 64 Hz. Independent component analysis was then applied to remove artifacts (eye blinks, ECG, muscle twitches) and 60 Hz notch filter to eliminate electrical interference. Finally, by visual inspection from an EEG expert, 30 seconds of clean EEG signal was selected to be analyzed.

Three electrical characteristic groups or features were obtained to characterize the EEG patterns: alpha phase synchronization (PLV), wavelet scale, and autoregressive (AR) based frequency statistics. Alpha phase synchronization was used to characterize the network structures of the brain. Wavelet scale was used to describe the transient activity and finally AR frequency statistics were used to obtain valuable time-frequency information.

Feature selection and reduction techniques were performed on the sub-features of these three mutually

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independent features, to combat the over-fit problem as well as maximize generality of the support vector machine classifier. Furthermore, extracted features were used as inputs to a 10-fold cross validated non-linear support vector machine (SVM) classifier. Interpretation of the reduced features adhered to previous migraine studies.

Results: As seen in the table, our proposed method consistently outperforms the classification of the individual features on our dataset. It is also important to note that though combining different features increased the classification performance of the individual features, our method is still superior improving accuracy by 10% to 20% compared to other methods. To further illustrate the discrimination capabilities of our proposed algorithm we plotted the decision hyperplane onto the features space, whereby each axis is comprised of each feature (see Figure). The hyperplane is shown in gray and it can be clearly seen separating MwA and NC.

Conclusion: The most discriminative features tend to comply with current findings in migraine studies. Though further confirmatory data analysis is needed to validate our findings, these series of features were used to train a non-linear SVM classifier to perform discrimination. The performance of the SVM classifier showed a total accuracy of 92.9%. Because this study was performed during non-pain period, the features we obtained can be electrical markers for predisposition of MwA. Future work may also look into the modifiable nature of these features to explore different types of preventative measures such as behavioral biofeedback, pharmaceutical intervention, relaxation and meditation techniques.

Disclosure of Interest: M. Garingo: None Declared, F. Sahba: None Declared, M. Doidge Conflict with: CEO

Headache Classification

PO-02-064

Four phenotypically distinct headache disorders in the same patient over 12 years follow up

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Objectives: Although migrainous headache is considered the commonest form of primary headache disorder, there are uncommon primary headache disorders that often present in a tertiary headache clinic. Nonetheless, it is relatively rare for a patient to have more than two different forms of primary headache disorders. We describe a female patient who developed four distinct primary headache disorders over a period of 12 year follow up that were managed with appropriate treatment.

Methods: A 70 year old female presented with classical left sided (V2 V3) trigeminal neuralgia in 2001 that responded well to Carbamazepine. Her neuralgia was stable until she presented again in 2011 with recurrent episodes of stabbing left sided V1 pain at a frequency of six per hour each lasting 10–20 seconds with conjunctival injections and tearing. This was typical for SUNCT and responded well to lamotrigine 200 mg bd. Three months later she developed a new, episodic, excruciating pain in the left peri-orbital region 3–4 times each day, each episode lasting 20–45 minutes with restlessness and full set of autonomic features. A diagnosis of cluster headache was made and she responded dramatically to a short course of
steroids and was able to go in remission with topiramate 50 mg bd. She has continued to have 4 weeks of cluster period every 3–4 months managed with either oral steroid or greater occipital nerve block. Since 2012 she developed a continuous left sided dull facial ache with no other associated symptoms and was treated as atypical facial pain that partly responded to pregabalin following no response to amitriptyline, gabapentin, epilim or indomethacin.

**Results:** The case report describes four distinct primary headache disorders in the same patient sequentially over 12 years timeframe.

**Conclusion:** To our knowledge, this is the first description in the literature of a patient who is simultaneously treated for four phenomenically distinct and rare headache disorders. Our case demonstrates the complexity of headache disorders that are managed in a tertiary headache clinic setting, and illustrates the importance that combinations of medication therapies plays in the appropriate management of patients with complex headache disorders.

**Disclosure of Interest:** F. Cheng: None Declared, A. Buture: None Declared, A. Ghabeli: None Declared, F. Ahmed Conflict with: Allergan, Eneura, Electrocore, Novartis as Advisory Board member paid to British Association for the Study of Headache and the Migraine Trust, Conflict with: Educational Officer for British Association for the Study of Headache, Trustee of Migraine Trust, IHS Board Member

### Headache Classification

#### PO-02-065

**Crying Headache: Frequency and clinical features among medical students**

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**Objectives:** To describe the frequency an clinical features of crying headache among medical students

**Methods:** Observational, descriptive, cross-sectional study prospectively recording data from medical students in clinical practice at Hospital Occidente de Kennedy. A questionnaire was used for data collection which was then analyzed by statistical methods.

**Results:** A total of 105 students volunteered in the study (77 females and 28 males). Among the students, 79% complained of headache when they cry and 38% said that was the only type of headache they had suffered. About clinical features we found: Mean intensity 5.62 (SD 1.88), more common type of pain was pulsatile (37%) and in frontal localization (32%). More frequent associated symptoms were photophobia (32%), phonophobia (21%) and nausea (18%). Duration of each episode was less than 4 hours in all cases. Situations related with crying headache were angry (46.7%), stress (43.8%), sadness (41.9%) and physic pain (10.5%). None of the students has headache when they cry because of cooking (peel an onion). About treatment, 44.8% feel relive with rest, 41% use non-steroidal anti-inflammatoty drug (NSAID), 21.9% has spontaneous relive, in 12.4% pain disappear when they stop crying and 7.6% use cold water.

**Conclusion:** Among our population of medical students, crying headache has a higher prevalence compare with literature [Blau (1995) y Fragoso (2003)]. About clinical features, crying headache was a short lasting headache (less than 4 hours), pulsatile, with photophobia and phonophobia as principal associated symptoms. Negative emotions were the trigger of pain, suggesting a possible physiopathology in where cortical and diencephalic structures were involved with sphenopalatine ganglion as principal intermediary between central and peripheral structures. **Key Words:** Headache, crying, medical students

**Disclosure of Interest:** None Declared

### Headache Classification

#### PO-02-066

**Improving discrimination between migraine with aura and transient ischemic attacks using the ICHD-3 beta appendix criteria**

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2Department of Neurology, Rigshospitalet, Glostrup, Denmark

**Objectives:** Migraine with aura and transient ischemic attacks (TIAs) are two very different, hugely prevalent conditions encountering the neurologist in the emergency department on a daily basis. Distinguishing between the two is not always straightforward, however mistakes are very harmful: Misdiagnosing a migraine patient with a TIA renders him or her to an unnecessary expensive diagnostic work-up as well as lifelong antiplatelet and lipid-lowering therapy while misdiagnosing a TIA as a migraine with aura may result in an avoidable stroke. Monetary incentives, whereby the diagnosis of a TIA is reimbursed more than a migraine with aura, may also introduce conflicts of interest in the healthcare setting.

**Methods:** In this prospective study, 60 patients admitted to the Department of Neurology, University Hospital Lübeck, Germany with a suspected TIA were interviewed about their symptoms leading to admission. In a second step, both the main body and appendix criteria of ICHD-3 were applied to these patients.
Results: Our interim analysis shows that the appendix criteria in ICHD-3 beta had a significantly lower rate of false positive diagnoses (and thus higher specificity) than the main body criteria.

Conclusion: ICHD-3 appendix criteria for migraine with aura and migraine with typical aura are superior to the corresponding main body criteria in distinguishing between a migraine and a TIA. They serve as a robust tool both for the clinician as well as the researcher, and should be used to reduce rates of misdiagnosis.

Disclosure of Interest: None Declared

Headache Disorders in Children and Adolescents

PO-02-067

Prevalence of infantile colic and relationship to parental migraine in a Japanese population

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2Pediatrics, Teikyo University School of Medicine, Tokyo, Japan

Objectives: Infantile colic is classified as a subgroup of migraine in the International Classification of Headache Disorders, 3rd Edition, beta version (ICHD-3 beta) (appendix), and is described in the Comments section as affecting approximately one out of five babies worldwide. The likelihood of having an infant with colic is 2.5 times higher for fathers with (vs. without) migraine, and 2 times higher for fathers with (vs. without) migraine. We examined the prevalence of infantile colic, and its relationship to parental migraine, in a Japanese population.

Methods: From June 2015 to February 2017, we interviewed all parents who brought healthy babies ≥5 months old to the Hikita Pediatric Clinic for vaccinations, using a standard questionnaire. Questions covered the following points: does baby have (or previously had) colic; [if so,] duration of colic (min); frequency of colic (times/wk); ages at which colic symptoms began and ended; parental migraine history. Possible disorders other than colic causing similar symptoms were ruled out. Questionnaire responses were analyzed to make diagnoses of infantile colic and parental migraine according to ICHD-3 beta criteria.

Results: The study included 105 babies (61 female, 44 male), with age range 150–281 days. Of the 105 babies, 67 (63.8%) showed no colic symptoms, and 38 (36.2%) (23 female, 15 male) showed some colic symptoms (irritability, fussing/crying episodes). Among the 38 babies with colic symptoms, median crying time was 30 min (range 0–300), median age at which colic symptoms began was 0 months (range 0–4), median colic frequency was 2 times/wk (range 0–7), and colic duration >3 wk was reported in 7 cases (range 3–84 wk). Among the 38 babies with some colic symptoms, 3 (2.9% of the 105 in the study) (all female) were diagnosed with infantile colic according to all three of the ICHD-3 beta criteria; i.e., crying time >3 hr/day; colic frequency >3 times/wk; colic duration >3 wk. The remaining 35 babies, who met two or fewer of the criteria, were broken down into the following groups: (i) crying time <3 hr/day; colic frequency >3 times/wk; colic duration >3 wk: n = 3. (ii) crying time >3 hr/day; colic frequency >3 times/wk; colic duration <3 wk: n = 1. (iii) crying time >3 hr/day; colic frequency <3 times/wk; colic duration >3 wk: n = 1. (iv) crying time <3 hr/day; colic frequency <3 times/wk; colic duration <3 wk: n = 17.

Of the 105 mothers in the study, 32 (30.5%) had a migraine history according to ICHD-3 beta criteria. These 32 cases consisted of 11 cases of migraine without aura, 17 of probable migraine without aura, 2 of migraine with aura, and 2 of probable migraine with aura. Of the 105 fathers in the study, 11 (10.5%) had a migraine history. These 11 cases consisted of 6 cases of migraine without aura, 3 of probable migraine without aura, and 2 of probable migraine with aura. For the 3 babies diagnosed with infantile colic (see above), neither parent had a migraine history.

Conclusion: Infantile colic is much less common in Japan (2.9% prevalence in our study population) than in most other countries. Among our study population (n = 105), 30.5% of the mothers and 10.5% of the fathers had a migraine history; however, these did not include either parent of the 3 babies diagnosed with infantile colic. Thus, we observed no relationship between infantile colic and parental migraine.

Disclosure of Interest: None Declared

Headache Disorders in Children and Adolescents

PO-02-068

Paroxysmal Headache as the only presenting feature of extensive Brain and spinal cord demyelination in an adolescent boy

Shantanu Shubham1,*; on behalf of Dr Hrishikesh Kumar, Dr , Supriyo Chaudhuru, Banashree Mondal, Koustav Chatterjee, Hrishikesh Kumar1, Supriyo Choudhury1, Banashree Mondal1, Koustav Chatterjee1 and Rebecca Banerjee1

1Neurology, Institute of Neurosciences, Kolkata, India

Objectives: Childhood demyelinating disorders usually present with encephalopathy, brainstem signs, long tract involvement or polysymptomatic presentations. We report clinical, laboratory and radiological features of a
15 year old boy with extensive demyelination involving supratentorial region, brainstem and longitudinally extensive cervical and dorsal cord involvement presenting only with paroxysmal holocranial headache.

**Methods:** A detailed history was taken and thorough neurological examination was performed. He was evaluated extensively with MRI, blood investigations and a lumbar puncture

**Results:** Our patient presented with a 6 months history of paroxysmal, holocranial episodic headache of moderate to severe intensity lasting for 30 minutes to 4 hours without any autonomic symptoms, nasal congestion, vomiting, photophobia or phonophobia. There was no history of febrile illness or vaccination prior to onset of symptoms. There was no history suggestive of encephalopathy, seizures or visual disturbances.

Systemic examination was normal. Fundus examination was normal. Visual acuity was normal. Power and deep tendon reflexes was normal. Cerebellar signs were absent. Sensory examination was normal.

**Radiology:** MRI showed bilateral T2/FLAIR hyperintense signal changes in subcortical frontal, bilateral anterior temporal white matter and pons. Longitudinally extensive T2 hypointense signal from C2 to D6 region was present. No contrast enhancement of the lesions was visualized. No microbleeds on GRE sequences was seen. MR Angiogram and DSA was not suggestive of any vasculitic features.

**Laboratory:** L.Lactate: Normal. ANA profile including all vasculitis markers: Negative. Anti aquaporin antibody was negative. CSF: 1 lymphocyte, 32 proteins. Oligoclonal bands: Negative. CSF for HSV/VZV/CMV and TB PCR was negative. CSF cytospin did not reveal any atypical cells Serum Angiotensin convertase enzyme level was normal. Antibodies for Lymes, Brucella: Negative. Paraneoplastic antibody profile: Negative. CT Thorax and abdomen not suggestive of lymphadenopathy or any mass lesion. Notch 3 gene test: negative. EEG: Normal. Vitamin B12 levels: Normal. Peripheral smear and bone marrow aspiration: Normal

**Conclusion:** Only paroxysmal headache as the initial presentation of extensive brain and cord demyelination without any focal neurological deficits, encephalopathy or long tract signs is extremely rare. Although headache as a presenting feature has been reported in pediatric multiple sclerosis, our patient was unique due to the glaring clinico-radiological dissociation, paroxysmal symptoms, extensive spinal cord involvement and total absence of objective neurological signs. This case expands the spectrum of demyelinating disease in adolescent age group. Paroxysmal headache not meeting criteria for primary headache categories in adolescent age group could be a harbinger of demyelinating disease and may provide an opportunity for earlier diagnosis and intervention before potentially debilitating neurological deficits appear.

**Disclosure of Interest:** None Declared
Headache Disorders in Children and Adolescents

PO-02-070

The Development and Well-Being Assessment (DAWBA) screening for psychiatric comorbidity in urban Siberian adolescents with tension-type headache and migraine

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¹Department of child's physical and mental health, Scientific Research Institute of medical problems of the North, Krasnoyarsk, Russian Federation

Objectives: The Development and Well-Being Assessment (DAWBA) diagnostic tool was developed by R. Goodman et al. [J Child Psychol Psychiatry. 2000; 41: 645–655] as comprehensive semistructured interview for the diagnosis of psychiatric disorders and has been found to been an effective diagnostic tool in clinical and epidemiological settings. Data regarding the DAWBA estimated psychiatric symptoms in Russian adolescents with different headache types are limited.

Methods: 224 urban Siberian (Krasnoyarsk, Russia) adolescents aged 12–18 attending a tertiary medical center for primary diagnosis of tension-type headache (n = 109, TTH, including the subtypes “frequent episodic TTH, chronic TTH”), migraine (n = 89), and mixed type (n = 26, TTH + migraine). All of them and 180 healthy matched controls completed computer-assisted DAWBA package of interviews. Each of psychiatric disorders was coded on a computer-generated 5-point probability scale. Data are shown as Mean (Mean–SE-Mean + SE) of computer-predicted probability. The Mann-Whitney U test is used to compare differences between groups.

Results: Significant positive associations were detected between all headache subgroups (TTH, migraine, and TTH + migraine) and posttraumatic stress disorder, generalized anxiety disorder, and depressive disorder probabilities (Table I). Specific and social phobias were more characteristic for adolescents with TTH (TTH and TTH + migraine groups), whereas obsessive-compulsive disorder was more typical for migrainers (migraine and TTH + migraine groups).

Conclusion: Urban Siberian headache adolescents referred to tertiary medical center have a significantly high prevalence of psychiatric comorbidity, predominantly anxiety and depressive disorders. Spectrum of psychiatric disorders may be different in headache types (TTH or migraine) that should be taken into account when evaluating the adolescent’s mental health status.

Reference:

Disclosure of Interest: None Declared
Headache Disorders in Children and Adolescents

PO-02-071

Treatment of chronic headache disorders with greater occipital nerve injections in a large population of childhood and adolescent patients

Francesca Puledda1*, Peter J Goadsby1 and Prab Prabhakar2

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2Department of Paediatric Neurology, Great Ormond Hospital for Children NHS Foundation Trust, London, United Kingdom

Objectives: Chronic headache disorders in children are common and highly disabling, with chronic migraine affecting between 0.8% and 1.7% of subjects in pediatric age groups (1). Management can be challenging, with a lack of rapid and sustained treatment options. The objective of this clinical audit was to determine the efficacy and safety of greater occipital nerve injections in a large population of paediatric headache sufferers.

Methods: We performed a retrospective review of our clinic letters from children and adolescents seen within the Specialist Headache Service at Great Ormond Street Hospital, who received a greater occipital nerve injection between 2009 and 2016. We included first time and repeat injections. Infiltrations were always unilateral and consisted of 30 mg 1% lidocaine and 40 mg methylprednisolone acetate. The primary outcome measure of ‘benefit’ from the injection was defined as either a significant (more than one third) decrease in headache frequency and intensity or by a documented headache improvement in the clinical notes, determined by a neurologist specialized in headache.

Results: Two hundred and six patients received GONI injections (n = 841). Follow-up data was available for 145 patients (70%), who had 369 injections. Of the 145 patients, 117 (80%) had chronic migraine (migraine with aura, n = 21), 19 (13%) had New Daily Persistent Headache (NDPH), five (4%) had a chronic trigeminal autonomic cephalalgia, three (2%) had a form of secondary headache and one patient had chronic tension-type headache. Medication overuse was present in 37 (26%) subjects. The mean age was 15 ± 2 with a range between 8 and 18 years. Female to male ratio was 1.9:1. Mean number of headache years was 4 ± 3 and on average

Abstract number: PO-02-070

Table 1: Computer-predicted probability of psychiatric disorder, generated by the DAWBA, in adolescents with tension-type headache and migraine

<table>
<thead>
<tr>
<th>PSYCHIATRIC DISORDERS</th>
<th>No headache (n = 180)</th>
<th>TTH (n = 109)</th>
<th>Migraine (n = 89)</th>
<th>TTH + migraine (n = 26)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific phobia</td>
<td>0.28 (0.00–0.56)</td>
<td>1.51 (0.72–2.31)</td>
<td>0.00 (0.00–0.00)</td>
<td>0.60 (0.00–1.20)</td>
<td>P0–1 = 0.049</td>
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<td>P0–3 = 0.104</td>
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<td>P1–2 = 0.069</td>
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<td>P2–3 = 0.059</td>
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<tr>
<td>Social phobia</td>
<td>0.02 (0.00–0.04)</td>
<td>0.33 (0.13–0.53)</td>
<td>0.07 (0.02–0.11)</td>
<td>0.00 (0.00–0.00)</td>
<td>P0–1 = 0.049</td>
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<tr>
<td>Posttraumatic stress disorder</td>
<td>0.08 (0.00–0.16)</td>
<td>0.54 (0.08–1.00)</td>
<td>1.10 (0.47–1.73)</td>
<td>2.62 (0.63–4.60)</td>
<td>P0–1 = 0.050</td>
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<td>P0–2 = 0.008</td>
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<td>P0–3 &lt; 0.001</td>
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<td>P1–3 = 0.099</td>
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<tr>
<td>Obsessive-compulsive disorder</td>
<td>0.10 (0.02–0.18)</td>
<td>0.00 (0.00–0.00)</td>
<td>0.27 (0.09–0.45)</td>
<td>0.24 (0.07–0.41)</td>
<td>P0–2 = 0.079</td>
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<td>P0–3 = 0.021</td>
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<td>P1–2 = 0.026</td>
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<td>P1–3 = 0.003</td>
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<tr>
<td>Generalized anxiety disorder</td>
<td>0.10 (0.02–0.18)</td>
<td>0.95 (0.46–1.45)</td>
<td>1.07 (0.46–1.68)</td>
<td>2.48 (0.49–4.47)</td>
<td>P0–1 &lt; 0.001</td>
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<td>P1–3 &lt; 0.001</td>
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<tr>
<td>Depressive disorder</td>
<td>1.11 (0.55–1.67)</td>
<td>3.12 (2.06–4.18)</td>
<td>3.26 (2.09–4.43)</td>
<td>3.46 (2.20–4.73)</td>
<td>P0–1 = 0.004</td>
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<td>P0–2 = 0.002</td>
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<td>P0–3 &lt; 0.001</td>
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</table>

* For ease of exposition, only p values ≤ 0.1 are displayed.

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patients had tried at least two previous preventives with a range between 0 and 5.

A benefit was seen in 101 (69%) subjects. The mean duration of improvement was 9 ± 4 weeks. Benefit reached 70% in the chronic migraine population (n = 82) and was 63% in the NDPH subgroup. Four of the five patients with trigeminal autonomic cephalalgias benefitted from the injection. Side effects were reported in eleven patients: ten cases had a headache worsening and one case had soreness at the site of injection.

**Conclusion:** Greater occipital nerve injections are a safe, effective and useful strategy for chronic headache disorders in children. They appear more beneficial in the migraine and trigeminal autonomic cephalalgia subgroups. In the clinical approach to the treatment of chronic headache disorders in a paediatric setting, this strategy should be considered as first line management alongside the classic medications, which are often more side-effect prone.

**References**

**Disclosure of Interest:** None Declared.

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**PO-02-072**

**Mathematical predicting of risk of chronic tension-type headache in adolescents**

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**Objectives:** Despite the fact that tension-type headache is the most common form of primary cephalgia in the population, including adolescents, there is no clear understanding of the risk factors and approaches to prediction the development of tension-type headache and its transition to a chronic form.

**The aim:** To develop a method for predicting the occurrence of chronic tension-type headache in adolescents with infrequent episodic tension-type headache.

**Methods:** 2,342 adolescent boys and girls aged 13–17 in schools in Kharkiv were examined. We used questionnaire to identify the headache. A group of adolescents with tension-type headache - 947 people (infrequent episodic tension-type headache - 854 people and chronic tension-type headache - 93 people) was selected. The control group included 246 healthy adolescents. Possible risk factors in the formation of tension-type headaches were divided into 4 groups: genetic, biomedical, psychosocial and welfare. Mathematical predicting of risk of tension-type headache in adolescents was performed using the method of normalization of E.N. Shigana intensive indicators, based on probabilistic Bayesian method. The result is presented in the form of prognostic coefficients.

**Results:** The most informative risk factors for developing tension-type headache were the pathology of the fetus and newborn, overweight, the presence of headache and autonomic disorders in the family history, traumatic brain injury, extragenital pathology of the mother before birth, stress. Diagnostic scale has been developed to predict the risk of tension-type headaches. It includes 22 prognostic factors with their grading and meaning of integrated measures of risk, depending on the strength of the effect of a single factor.

The risk of tension-type headaches ranged from 35.79 to 67.5 predictive coefficient values (low probability (35.79–46.37), the average probability (46.37–56.95) and high probability (56.95–67.53)).

**Conclusion:** The study of risk factors of chronic tension-type headaches, which were obtained by using an assessment and prognostic tables show the importance of overweight, diseases of the fetus and newborn, trauma of the head, stress, family history of headache and autonomic dysfunction in the development of chronic tension-type headache.

**Disclosure of Interest:** None Declared.

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**PO-02-073**

**Cerebrospinal Fluid Leak in Children and Adolescents**

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**Objectives:** Reports of CSF (cerebrospinal fluid) leak in children were rare. CSF hypovolemia due to CSF leak occasionally causes longstanding disability in school life.
The aim of this study was to clarify the cause, symptoms, radiological study and outcome.

**Methods:** 70 children and adolescents (35 male, 35 female) were studied by brain and spinal MRI, RI cisternography and CT myelography. All patients with CSF leak were treated with epidural bloodpatch.

**Results:** Causes of CSF leak were sports 35%, traffic accident 20%, fall 20% and unknown 25%. Main symptoms were headache (66 cases), fatigue (59 cases), dizziness (40 cases), neck pain (30 cases), insomnia (29 cases) and loss of concentration (27 cases). Rate of neuroradiological positive findings were 45% in brain MRI, 71% in RI cisternography, 83% in CT myelography. Outcome after bloodpatch was cure 60%, good recovery 26%, recovery 10% and no change 0%.

**Conclusion:** This study revealed that CSF leak in children was not rare and bloodpatch was a very effective treatment. CSF leak is an important differential diagnosis in child headache.

**Disclosure of Interest:** None Declared

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**Headache Disorders in Children and Adolescents**

**PO-02-074**

The Effect of Baseline Preventive Medications on the Efficacy and Safety of Zolmitriptan Nasal Spray (ZNS) in Adolescent Migraine Patients

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1 Cincinnati Children’s Hospital Medical Center, Cincinnati
2 Raleigh Neurology Associates, Raleigh
3 Impax Laboratories, Inc., Hayward, United States
4 AstraZeneca, Molndal, Sweden

**Objectives:** To assess the use or non-use of baseline preventive migraine medications on the safety and efficacy of an acute migraine treatment (ZNS) in adolescent patients (aged 12 to 17 years) treated in the TEENZ study.

**Methods:** The TEENZ study was a global, multicenter, randomized, double-blind, parallel-group study of Zolmitriptan Nasal Spray (ZNS) compared with placebo (NCT01211145). Adolescents (12–17 years old) with an established diagnosis of migraine with or without aura by International Classification of Headache Disorders were enrolled. They were required to have at least 2 moderate to severe migraines per month for at least 1 year. Following a placebo challenge run-in period, non-responders were randomized to ZNS 5 mg, ZNS 2.5 mg, ZNS 0.5 mg, or placebo in a 5:3:3:5 ratio and given 10 weeks to treat a single migraine attack. After treatment of this migraine, patients completed a headache diary for 24 hours. The primary efficacy outcome measure was pain-free status at 2 hours post-treatment. In this post-hoc analysis, safety and efficacy (pain-free status and headache response at 2 hours) are evaluated across dosing groups based on the use or non-use of at least one baseline preventive migraine medication (divalproex/valproate, topiramate, metoprolol, propranolol, timolol, atenolol, nadolol, pindolol, amitriptyline, nortriptyline, venlafaxine, cyproheptadine, or verapamil).

**Results:** Of the 656 randomized patients (full safety analysis set), 84 (12.8%) were taking at least one preventive migraine medication on entry into the study. For the primary endpoint for randomized patients reporting use of preventive medications, the treatment group sample sizes were relatively small (approximately 30/group), making statistical conclusions challenging for this cohort. The two cohorts were fairly well matched in terms of demographics, except the cohort taking preventive medications had a relatively higher percentage of females (75.0% vs. 59.4%; p = 0.0062) and whites (98.8% vs. 92.1%; p = 0.0252). For the group not taking preventive medications (non-use), the primary endpoint is statistically significant in favor of ZNS 5 mg versus placebo. In the group taking preventive medications (use), this comparison (ZNS 5 mg vs. placebo) was not significant but the numbers were small (ZNS 5 mg, N = 27 and placebo, N = 32). A comparison of the 2-hour pain-free differences (active – placebo) in proportions (use: 10.3% vs. non-use: 13.2%) suggests little difference between the two cohorts. Similar statistical trends are observed for the ZNS 5 mg versus placebo 2-hour headache response, although, in this case, the cohort taking preventive medications showed a larger difference in proportions (use: 18.1% vs. non-use: 10.1%). The pattern of reported adverse events (AEs) was similar between the two cohorts. A higher percentage of placebo-treated subjects taking preventive medications reported at least 1 AE (31.3%) as compared with those placebo-treated subjects not taking preventive medications (13.1%).

**Conclusion:** Despite the migraine severity and frequency required by the study entry criteria, relatively few subjects reported use of migraine preventive medications and, consequently, this cohort was statistically challenging because of its small treatment group sample sizes. Notwithstanding, data from this post-hoc analysis suggests that the use or non-use of preventive migraine medications has little impact on the efficacy or safety of ZNS in adolescent migraineurs.

Benign intracranial hypertension in children can be due to hypoparathyroidism: a case-report

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Objectives: To present the rare case of a girl with idiopathic intracranial hypertension (IIH) secondary to hypoparathyroidism (HPTH).

Methods: Workup of a 9-year-old girl with IIH and HPTH, including physical examination, blood tests, diagnostic imaging, and lumbar puncture.

Results: We present a 9-year old female patient who was hospitalized for headache associated with nausea and vomiting for 3 weeks. She underwent ophthalmologic examination which showed papilledema. She had never had cramps, paraesthesias or tetany. Lumbar puncture (LP) revealed an opening pressure of 65 cm H2O. CSF analysis and brain CT scan were normal. The patient was started on acetazolamide 375 mg/die. However, a low serum calcium level (6.3 mg/dL) was found, thus leading us to suspect HPTH. Indeed, phosphorus was 10.2 mg/dL, parathormone was very low (3 pg/mL). Chvostek and Trousseau signs scored positive. Neck ultrasonography showed normal thyroid, while parathyroids were not viewable. Oral supplementation with calcitriol (0.50 mcg/day) and calcium (500 mg/day) was started.

Conclusion: IIH is defined as an elevated intracranial pressure (>25 cmH2O) without clinical, laboratory or radiological evidence of hydrocephalus, infection, tumor or vascular abnormality. Annual incidence is 1–2 per 100,000. Several hypotheses have been proposed for the IIH pathophysiology, but none of them has reached a general consensus. Rare cases of IIH secondary to HPTH have been described (Aragones and Alonso-Valdés, 2014). It is supposed that hypocalcemia causes a decrease in the CSF absorption at level of the arachnoidal granulations (Sambrook and Hill, 1977). Interestingly, our patient did not present with the typical neurological HPTH symptoms, such as tetany, cramps, paraesthesias, seizures, behavioral disorders, and intracranial calcifications. Only the serum calcium dosage led us to suspect this condition. Therefore, we recommend that possible HPTH should be always checked in children with clinical findings of benign intracranial hypertension.

Disclosure of Interest: None Declared

Validity of the ICHD-IIIb criteria in the diagnosis of migraine with aura in children and adolescents

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Objectives: Though common in pediatric age, migraine with aura (MA) has been scarcely studied in children. Our main aim was to test whether the International Classification of Headache Disorders criteria 3rd edition (ICHD-IIIb) are useful to diagnose MA in children and adolescents. Moreover, we aimed also at investigating: 1) the clinical characteristics of the aura in a cohort of MA children, and 2) the features of the headache associated with the aura.

Methods: The present study was based on data retrospectively collected from 164 MA children referred to our 3rd level Headache Centre.

Results: In our patients, aura mainly included visual symptoms, which were far more frequent (93%) than
somatosensory, motor, and speech disturbances. Aura preceded the headache onset in most cases (69.1%) and its duration ranged from 5 to 60 minutes. We divided our patients in 4 different age groups (less than 7 years, between 7 and 10 years, between 11 and 14 years, more than 14 years). No difference in the aura characteristics was found between the groups (Table). On the other hand, when the headache type was classified according to the ICHD-IIIb criteria, migraine was diagnosed only in 40.2% of patients and the diagnosis remained undetermined in 4.3% of children. However, if headache duration was not considered, the headache could be classified as migraine in 67% of patients and in no child the diagnosis was undetermined. **Conclusion:** Our pediatric population showed aura features that did not depend on the age and were similar to those of adult patients. Although the headache type was difficult to be classified if headache duration was considered, the new criteria reduce the importance of the headache type associated with the aura, thus allowing the diagnosis of MA also in children and adolescents.

**Disclosure of Interest:** None Declared

**Headache Disorders in Children and Adolescents**

**PO-02-077**

**School Nurses’s Management for Schoolchildren with Headache**

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**Objectives:** Recurrent headaches are common among Korean students, causing absences from school or learning impediments. However, most school nurses are unable to provide appropriate diagnosis and treatment as they lack accurate information about the clinical aspects or treatment of headaches. The aim of this study was to investigate school nurses’s clinical knowledge, assessment, and management of headache and educational needs in headache management.

**Methods:** This was a cross-sectional study targeting 250 school nurses who participated in the training lecture hosted by and were working at elementary, middle, and high schools. Surveys with insufficient data were excluded.

**Results:** Participants were 237 school nurses; 122 elementary school nurses, 62 middle school nurses, and 53 high school nurses, with an average age of 42.4 ± 8.8 years. In all, 58.2% of the school nurses responded that they had received headache education, 68.8% responded that they knew the classifications of a headache, and 38.4% responded that they knew a headache assessment method. Only, 29% had a protocol for headache treatment. The educational needs (0–7 points) of school nurses to manage students with headaches were 5.8 for headache knowledge education, 5.5 for acute pharmacotherapy, 5.0 for preventive pharmacotherapy, 6.0 for lifestyle modification, and 6.0 for complementary remedy.

**Conclusion:** School nurses had insufficient knowledge of headaches and high educational needs for headache management and had not a protocol for the headache management in the most cases. It suggests that headache knowledge education should be performed and the standardized headache management guideline should be developed to improve the performance of school nurses.

**Disclosure of Interest:** None Declared

**Headache Disorders in Children and Adolescents**

**PO-02-078**

**New Daily Persistent Headache in children: a clinic- based study in a specialist headache service**

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**Objectives:** As New Daily Persistent Headache (NDPH) is still poorly defined in the paediatric population, we conducted a clinic based review of our patients with NDPH, to understand better the clinical phenotype of this disorder.

**Methods:** This retrospective study was conducted as an audit in a tertiary paediatric headache centre. We identified the list of patients whose clinical features were consistent with NDPH by the International Classification of Headache Disorders 3rd edition (ICHD-3 beta) from 2004 until 2016. On reviewing the clinical notes, the relevant data was collated with a standardised data collection form.

**Results:** We identified 34 patients with NDPH, average age of NDPH onset 13 years old. The majority were female (n = 25, 74%). The median duration till diagnosis was 436 days, the interquartile range was 232–546 days, with the longest being 1960 days. Antecedent events were clearly identified by 26 patients, the most common being a preceding viral illness, such as upper respiratory tract
infection); physical exertion, and situational events, such as a clear recollection of attending a prolonged history lesson class, visiting a London museum, long car journey. The majority of patients were able to identify the time of onset of their symptoms ($n = 32, 94\%$). Migrainous symptoms were common with exacerbations: $71\%$ had movement sensitivity, $68\%$ had phonophobia, $65\%$ had nausea, $59\%$ had photophobia and $41\%$ had vertigo, of which $29\%$ could specify it was internal vertigo. Of the cohort, $18\%$ had medication overuse.

**Conclusion:** Paediatric patients with NDPH often have migraine symptoms. Overuse was not commonly implicated in our patients.


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**PO-02-079**

The chief complaints and exacerbating factors of migraine in children and adolescents

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**Objectives:** Migraine is common in children and adolescents, with the reported prevalence between 3.8\% and 13.5\%. Both children and adolescents are unable to describe their symptoms exactly, and their chief complaints are diverse. To our knowledge, little is known about how children describe their migraine symptoms. This study aims to reveal the migraine symptoms and exacerbating factors of migraine in Japanese children and adolescents.

**Methods:** We retrospectively reviewed the clinical records of children and adolescents (12–20 years old) with migraine according to the ICHD-3 beta who visited the department of neurology in a single center from January 2014 to December 2016. We analyze their migraine symptoms and the reason for the visit (chief complaint). We also clarify their exacerbating factors of migraine.

**Results:** 57 patients (18 boys, 39 girls) with the median age of 16 (range, 12 to 19) were included. 33 (58\%) patients presented with a complaint of ‘headache’. Other chief complaints were visual aura ($n = 11, 19\%$), nausea ($n = 7, 12\%$), dizziness ($n = 4, 7\%$), stomachache ($n = 1, 2\%$), and photophobia ($n = 1, 2\%$). Their exacerbating factors of migraine were regular examinations at schools ($n = 12, 21\%$), and lack of sleep ($n = 13, 23\%$). Twenty-nine (51\%) patients had ‘unilateral’ headaches.

**Conclusion:** This study suggests 42\% of children and adolescents with migraine presented with complaints other than ‘headache’. Stressful events such as examinations and lack of sleep are associated with the development of migraine in Japanese children and adolescents.

**Disclosure of Interest:** None Declared

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**PO-02-080**

United Kingdom NICE Quality Standards applied to a child and young person’s headache clinic: always room for improvement

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**Objectives:** The UK’s National Institute for Health and Care Excellence (NICE) published their evidence based headache guideline (CG150) and Quality Standard (QS42, see https://www.nice.org.uk/guidance/qs42) recently. We therefore decided to undertake a clinical audit of our tertiary headache clinic, as part of our Quality Improvement programme.

**Methods:** Cases attending a tertiary headache clinic for the first time in 2013 and 2014, with at least 2 year’s follow-up, were ascertained from the headache clinic lists and data extracted from the digital health record clinic letters, using a standard proforma. Simple descriptive statistics were used. The clinical audit was registered with the hospital Trust.

**Results:** So far 82 patients’ records (52 female) have been reviewed. The ages ranged from 1–16 years (mean 12) on the 1st visit. 38/82 (46\%) were referred by a paediatrician, 24/82 (29\%) by another specialist, 18/82 (22\%) by a Family Practitioner, and 2/82 were self-referred through an advertisement for a research project. For 71/82 (90\%), headache was the main presenting complaint, and in 66/71 (93\%) the headache diagnosis was documented within 6 months.

The headache diagnoses observed were: “migraine” 54/71 (76\%), “tension-type headache” 8/71 (11\%) including “new
daily persistent headache" 2/71 (3%), “paroxysmal hemicrania” 3/71 (4%), cluster headache 2/71 (3%). Secondary headache was diagnosed in 10/71 (14%), including “idiopathic intracranial hypertension” in 6/71 (8%), and “medication overuse headache” (MOH) in 1/71 (1%). Unclassified headache (not otherwise specified) was the diagnosis at last observation in 11/71 (15%). 14/71 (20%) were diagnosed with more than one type of headache.

Of the 60 with primary headache (migraine, tension, cluster, paroxysmal hemicrania) advice on preventing MOH was documented as in 34/60 (57%), and a head MRI or CT scan was only requested in 15/34 (44%) of those not already scanned before referral. Appropriate rescue treatment advice, i.e. a triptan together with a non-steroidal anti-inflammatory drug (NSAID) or paracetamol, was documented in 43/54 (83%) with migraine.

Conclusion: Migraine was the commonest diagnosis made in the headache clinic. More patients with primary headaches should have had advice on MOH documented, and fewer should have undergone brain imaging. However, appropriate rescue treatment advice for migraine was well documented.

Disclosure of Interest: None Declared

Headache Disorders in Children and Adolescents

PO-02-081

The relationship between adolescent and parental use of non-prescription analgesics for headache and somatic pain – a cross-sectional study

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Objectives: Concern has been expressed about adolescents’ possible liberal attitude towards - and increasing use of non-prescription analgesics. Headache is the most common reason for analgesics use by adolescents. A high consumption of analgesics may be unfortunate in the headache setting as it may lead to medication induced worsening of headache (medication-overuse headache) in addition to other side effects. Several studies show that adolescents have a high consumption of non-prescription analgesics, such as paracetamol and non-steroid anti-inflammatory drugs (NSAIDs), which are often available as over the counter (OTC) non-prescription medication and are often, as in Norway, also available outside pharmacies. In order to address this challenge, it is necessary to achieve more extensive knowledge about adolescent consumption and in order to assess also OTC medication, prescription registries are not sufficient as direct user data is necessary. In the case of children and young adolescents, this necessitates information from both the parents and the children. Parental use of, and attitudes to analgesics have been suggested to affect the medication-related behavior of their children. The aim of this study was, in a general population sample, to examine adolescent use of non-prescription analgesics for headache, as well as the association between parental and adolescent use of analgesics, also taking other somatic pain states into account.

Methods: The study is based on data from two cross-sectional population-based data sets collected in 2005 and 2012 in Norway, including 646 adolescents, each with an accompanying parent. By using sample weights to correct for possible population bias in the sampling, the final weighted sample used in the analysis was 1326. Data was collected through postal questionnaires to parents and adolescents as well as parental telephone interviews. Questionnaires included questions on different pain locations and the pain for each location was graded according to how troubling the pain was. Medication data on prescription and non-prescription analgesics was from telephone interviews and was quantified based on the pattern over the past 4 weeks. No clinical examination of participants was made, thus diagnostic data of pain states are based on self-reports. Multivariate logistic regression models and complex samples analyses were used.

Results: 20% of adolescents were reported as using non-prescription analgesics during the previous 4 weeks, more commonly girls than boys. Headache was the most common pain state and was reported more frequently among girls. Other somatic pain locations except back pain were also reported more commonly for girls, boys more frequently reported back pain. 34% of adolescents with headache used non-prescription analgesics versus 19% of adolescents with other somatic pain and 14% of adolescents not reporting pain. 9% of adolescents reporting headache used non-prescription analgesics daily or almost daily versus 3% and 2% among those reporting other somatic pain or no pain, respectively. Parental use of non-prescription analgesics was a strong independent predictor of adolescent use (adjusted OR 1.69 for boys, 1.54 for girls). This relationship was stronger when the adolescents were less bothered by headache themselves.

Conclusion: Headache is the dominant medication-driving pain for non-prescription analgesics among adolescents but parental medication use of non-prescription analgesics...
We enrolled 84 consecutive patients suffering from migraine without aura (female: 45, male: 39; age range 8–18 years; mean age 11.8 ± 2.4 years). Patients were divided into two groups according to frequency of the migraine episodes (high or low). Patients were divided into two groups according to headache attack frequency: (1) high frequency patients, having from weekly to daily episodes and (2) low frequency patients, showing ≤3 episodes per month. According to headache attack intensity, patients were classified into two groups: (1) mild pain, allowing the patient to continue his/her daily activities and (2) severe pain, leading to interruption of patient activities or forcing the child to go to bed. Children’s psychological profile was assessed by SAFA Anxiety, Depression and Somatization scales. Attachment style was measured by the semi-projective SAT test and children were divided in “secure” and “insecure” (“avoidant”, “ambivalent” and “disorganized/confused”) attachment patterns. We used ASQ and TAS-20 questionnaires to assess respectively the maternal attachment style and alexithymia levels.

Objectives: Migraine is a complex phenomenon where genetic, biological and environmental factors interact to each other. Attachment theory suggests that early interpersonal relationships may be important determinants of psychopathology and pain management. In a recent study, we found an association between ambivalent attachment style, migraine severity and psychological symptoms. Our findings supported the hypothesis that a dysfunctional parent-child interaction may be a common vulnerability factor for both pain severity and psychological symptoms, in young migraineurs. There is evidence that caregivers’ attachment styles and their way of management/ expression of emotions (alexithymia traits) can influence children’s psychological profile and pain expression. To date, data dealing with headache are scarce. Aims of our study were to investigate the role of maternal alexithymia and attachment style on: 1) their children headache features (intensity and frequency), 2) children’s psychological profile (anxiety, depression, somatization).

Methods: We enrolled 84 consecutive patients suffering from migraine without aura (female: 45, male: 39; age range 8–18 years; mean age 11.8 ± 2.4 years). Patients were divided into two groups according to frequency of the migraine episodes (high or low). Patients were divided into two groups according to headache attack frequency: (1) high frequency patients, having from weekly to daily episodes and (2) low frequency patients, showing ≤3 episodes per month. According to headache attack intensity, patients were classified into two groups: (1) mild pain,
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PO-02-084
Predictors of response to biofeedback therapy for persistent post-concussive headache in children
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Objectives: Post-traumatic headaches represent a common, often disabling, and potentially difficult to treat consequence of pediatric concussion or mild traumatic brain injury. Biofeedback therapy is currently being used in children for the management of post-traumatic headaches. However, while biofeedback has been established as an effective tool for migraine, its utility has not yet been examined in children and adolescents with post-concussive headaches. This retrospective cohort study both measured the response to biofeedback therapy and examined factors associated with response in order to determine potential predictors of positive response to biofeedback in pediatric post-concussive headache.

Methods: Subjects were those children ages 8–18 that had completed at least two biofeedback therapy sessions for post-concussive headache at Seattle Children’s Hospital from 2010–2016 and were identified through electronic medical record search. Additional data were collected via subsequent chart review. Response to biofeedback therapy was defined as either 50% reduction in headache frequency or at least 3-point drop in maximum Likert pain scale ratings between first and last biofeedback sessions. Variables identified in pediatric migraine and concussion populations as likely to be relevant to headache or biofeedback response were examined in the responder and nonresponder groups in order to identify associations between these factors and treatment response.

Results: The study group was 77% female, with average age 15.5 (standard deviation (SD) 1.8) and a median time from injury to evaluation of 5.7 months (interquartile interval 3.9–10.8 months). 66% of children reported headache 7 days per week at their initial visit. We found a 46% response rate to biofeedback therapy. Of all subjects, 35% had a 50% reduction in headache frequency, 23% described at least a three-point drop in headache severity, and 12% experienced both. Responders were significantly more likely to have stayed in school (chi-squared = 5.52, p = 0.02), and were also significantly less likely than nonresponders to be taking selective serotonin reuptake inhibitors or tricyclic antidepressants at the time of biofeedback therapy (chi-squared = 3.86, p = 0.05). The
response and nonresponse groups were not significantly different in age, sex, weight, BMI, therapist, personal or family headache history, depression or anxiety scales, number of headache days per week, or pain duration prior to biofeedback therapy.

**Conclusion:** This is one of the first studies to evaluate the efficacy of biofeedback therapy for the management of post-concussive headaches in a pediatric population. Initial data suggest that it may be effective for children and adolescents with persistent headaches secondary to mild traumatic brain injury. In addition, those children who responded to biofeedback were more likely to have remained in school and were less likely to be taking psychotropic medications at the time of therapy. We did not find an association between responder status and pain duration, indicating that positive response was unlikely to be related simply to the passage of time after concussion. These early data may help guide clinicians and institutions in identifying those children and adolescents who would be most likely to benefit from biofeedback. The implications of these findings may be widespread given that compared to pharmaceutical options, biofeedback therapy is safer, and skills learned can be used indefinitely for management of headaches over the lifespan.

**Disclosure of Interest:** None Declared

**Headache Disorders in Children and Adolescents**

**PO-02-085**

**Evaluation of patient satisfaction among adolescents who received infusion treatment for headache**

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**Objectives:** Currently, there is limited research data on infusion centers for pediatric headache. The objective of this study was to assess the satisfaction of adolescent patients who received infusion treatment for headache in an outpatient setting. Additional analyses examined differences between receiving infusion treatments in an outpatient setting versus in an emergency department (ED). Findings of this study may help gain a greater understanding of patient experiences during infusion treatments so that more effective and satisfactory care can be provided to patients acutely suffering from headache.

**Methods:** Institutional Review Board approval was obtained. Patients aged 12–17 years who received infusion treatment for headaches from September 9, 2015 to June 14, 2016 at Akron Children’s Hospital NeuroDevelopmental Science Center (NDSC) were eligible for inclusion in this study. After obtaining consent, patients were administered a patient satisfaction questionnaire. Patients were asked to rate their satisfaction with factors such as pain alleviation, noise level, and overall comfort with respect to their infusion visit experience. Patients previously treated in an ED were asked to rate their satisfaction with the infusion visit compared to their visit(s) in the ED. Medical information was also collected, including the following data points at the time of the patient’s infusion for which they completed the questionnaire: diagnosis, administered medications, number of ED infusions, and number of NDSC infusions. Data analyses were performed and results were compiled from both questionnaire responses and clinical data.

**Results:** A total of 43 patients (males = 7, females = 36) participated in the study. The average age of participants was 15.22 years (range = 12.30–17.70 years). Twenty-five (58%) patients received infusion for prolonged migraine/status migrainosus. Thirteen patients (30%) received infusion for post-traumatic headache; 4 patients (10%) for chronic daily headache and 1 patient (2%) for tension-type headache. The average baseline pain score prior to infusion was 6/10 and the average post-infusion pain score was 1/10. Twenty-four of the patients (56%) were headache-free after the infusion. Thirty-six of the patients (84%) experienced at least 50% reduction in their headache pain.

Based on the questionnaire responses, 91% reported significant pain relief with the infusion irrespective of pain score. The overall level of infusion experience satisfaction was an average of 8.86 [0 (least satisfied)-10 (most satisfied)]. Of those patients with a prior infusion history in an ED (n = 24), 17 (71%) reported greater success in pain alleviation in an outpatient infusion center than in an ED. Nearly 80% of patients (n = 19) reported greater overall comfort with the outpatient infusion center than with an ED infusion.

**Conclusion:** Our study shows that outpatient infusion treatment is viewed as a positive and beneficial therapy option for adolescents suffering from headache pain. It also suggests that headache infusion treatment in an outpatient center provides more pain relief and satisfaction when compared to headache treatment in the ED. The greater degree of pain relief and satisfaction may be due to a variety of factors, including medications given and the environment of the outpatient center, which tends to be quieter and more controlled than that of the ED. Our study is limited to patients treated at one hospital, thereby possibly limiting its generalizability. Future studies should consider including data from multiple outpatient infusion centers as well as other EDs.

**Disclosure of Interest:** None Declared
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PO-02-086
Non-invasive Vagus Nerve Stimulation (nVNS) for the Acute Treatment of Migraine Without Aura in Adolescents: Preliminary Clinical Experience
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Objectives: Study results and clinical experience have demonstrated the safety, tolerability, and efficacy of non-invasive vagus nerve stimulation (nVNS; gammaCore®) for the acute and prophylactic treatment of primary headache disorders including migraine and cluster headache. nVNS is easy to use and has a favorable adverse event profile, making this therapy an attractive option for sensitive patient populations. We explored the safety, tolerability, and efficacy of nVNS as an acute treatment of migraine without aura in adolescents.

Methods: Nine 13- to 18-year-old patients who had migraine without aura according to International Classification of Headache Disorders, 3rd edition (beta version) criteria (4 to 8 migraine days per month) were recruited into this single-arm open-label study. The patients and their parents participated in a 1-hour training session where they were instructed on how to acutely treat attacks with nVNS for a 4-week period (4 to 8 episodes). For each attack, patients administered one 120-second nVNS stimulation on the right side of the neck. Within 1 hour of the first treatment, a second stimulation was allowed as needed if the patient was not pain free. Patients recorded the pain intensity of the treated attack at several pre-specified time points between 30 minutes and 24 hours after treatment. Rescue medication was allowed after 2 hours post treatment if the patients did not perceive a meaningful reduction in pain. At the end of the study, patients and their parents completed a questionnaire to rate the effectiveness, safety, and ease of nVNS use on a scale from 0 to 5 (where 0 was the lowest score and 5 was the highest score).

Results: Forty-seven migraine attacks were treated. Of these, 22 (46.8%) did not require rescue medication and were deemed treatment successes. Nineteen (40.4%) of the treated attacks were pain free at 1 hour. In an additional 3 attacks (6.3%), patients experienced pain relief (pain intensity reduction to mild) at 2 hours. In the remaining 25 treated attacks, insufficient pain relief or a patient’s fear of migraine progression led to his or her choice to take rescue medication within 1 hour after treatment with nVNS. Patients did not report any device-related adverse events. All patients and parents completed the questionnaire and rated nVNS as having the highest safety and ease of use (score = 5). More than half of the patients (5/9) were highly satisfied with the overall effectiveness of nVNS (score = 5). The remaining 4 patients were not at all satisfied (score = 0).

Conclusion: This preliminary study suggests that the use of nVNS in adolescents is safe, well tolerated, and practical for the treatment of migraine without aura. Acute nVNS treatment was effective in approximately half of the treated migraine attacks, none of which required rescue medication. As reported in previous studies, initiation of nVNS treatment when pain is milder in intensity is more likely to result in a pain-free outcome. This finding is particularly relevant given the rapid onset and short duration of attacks that occur in adolescents. Results of this pilot study are comparable to open-label data from other sensitive patient populations and provide a rationale for larger studies of nVNS as an acute treatment option for adolescents with migraine.

Disclosure of Interest: L. Grazzi Conflict with: Consultancy and advisory fees from Allergan, Inc., and electroCore, LLC, G. Egeo: None Declared, E. Liebler Conflict with: Receives electroCore, LLC, stock ownership, Conflict with: Employee of electroCore, LLC, P. Barbanti Conflict with: Consultancy fees from Allergan, Inc., electroCore, LLC, Janssen Pharmaceuticals, Inc., and Lusofarmaco, Conflict with: Advisory fees from Abbott Laboratories and Merck & Co., Inc

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PO-02-087
An app to describe headache and pain in children: A proposal
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Objectives: Children under 8 y/o cannot describe pain accurately. The diagnosis of painful states relies on indirect data from the mother or teachers, or from direct observation and deduction by the physician. In any case, there is uncertainty about the pain quality or other characteristics. In the headache field this is particularly important. At the present times, tablets and other gadgets are available or almost omnipresent and children learn to manipulate them at early ages. We thought that his could be used to evaluate pain.
Methods: We designed an app to help children to describe their pain, based on cartoons with their own picture and different sketches that depict different pain descriptors.

Results: The app and preliminary results will be presented along with clinical examples.

Conclusion: We think this app will be useful in the evaluation of pain, specially headache. However, there could be cultural differences that deserve some variations. Clinical validation is currently under way.

Disclosure of Interest: None Declared

Headache Disorders in Children and Adolescents

PO-02-088

Accompanying migraineous features in pediatric migraine patients with restless leg syndrome

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2Neurology, Mersin University Medical Faculty, Istanbul
3Neurology, Suleyman Demirel University Medical Faculty, Isparta
4Child and Adolescent Psychiatry, Mersin University Medical School, Mersin, Turkey

Objectives: The aim of this study was to analyze the frequency of Restless legs syndrome (RLS) in pediatric patients with migraine and compare the results with those of tension-type headache (TTH) patients and healthy controls, and also compare migraineous accompanying symptoms, sleep characteristics, and serum ferritin levels between the pediatric migraine patients with RLS and those without RLS.

Methods: We included 85 consecutive patients with the diagnosis of migraine with or without aura (n = 65) and TTH (n = 20) and 97 headache-free children to our study. Demographics, clinical and laboratory data were recorded. The presence of primary headache was diagnosed using the ICHD-II criteria and RLS was determined with face-to-face interview by an experienced neurologist based on the revised International RLS Study Group criteria for pediatrics.

Results: The frequency of RLS in pediatric migraine patients and patients with TTH was significantly higher than in controls. (p = 0.0001, p = 0.025; respectively). The frequencies of allodynia, vertigo/dizziness and self-reported frequent arousals were significantly higher and serum ferritin levels were significantly lower in migraine patients with RLS compared to those without RLS (p = 0.05, p = 0.028, p = 0.02, p = 0.038; respectively).

Conclusion: Our study suggests that the frequency of RLS is higher in pediatric migraine and TTH patients compared to controls. Therefore, pediatric headache patients should be questioned about the presence of RLS, as this co-occurrence may lead to more frequent migraineous accompanying symptoms and sleep disturbances.

Disclosure of Interest: None Declared

Headache Disorders in Children and Adolescents

PO-02-089

Parental attitudes in children with primary headaches

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Objectives: To determine whether there is a relationship between migraine and tension-type headache, and depression, anxiety, and parents attitudes in the pre-adolescent pediatric population.

Methods: Participants included 195 children with headache and 43 healthy children ages between 10 and 15 years (mean 12.6 ± 1.1) and their parents who presented at a headache clinic. A detailed self report questionnaire for sociodemographic variables, Visual Analogue Scale (VAS), Social Anxiety Scale for Adolescent, and Children’s Depression Inventory were administered to the children. Parents were interviewed using validated Parents Attitude Scale which is an attitude measure specifically designed to evaluate psychological adjustment. The SPSS for Windows 23.0 program was used for analyses.

Results: According to the International Headache Classification (ICH-D-III beta version), 38% of the patients were episodic migraine and 11% were chronic migraine, 34% were tension-type headache. There was no significant difference among headache groups and healthy subjects in terms of depression, anxiety and fathers’ attitude scale scores. However mothers’ attitude scale scores of migraine group, particularly chronic migraine, was significantly higher than controls (p = 0.04). VAS and depression scores had positive correlation (p = 0.009) and there was a direct relationship between anxiety and mothers’ attitude scale scores among children with migraine (p = 0.016). Both headache groups and controls had a significant correlation between fathers’ and mothers’ attitude scale scores (p = 0.000). Age of children with episodic migraine was correlated negatively with parents’ attitude scale and depression scores, and mothers’ attitude scale scores.

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were correlated positively with children’s anxiety scores (p = 0.025).

**Conclusion:** Our findings support that mothers’ attitude has effects on migraine in children. Parental attitudes may elevate anxiety and depression symptoms and influence children’s perception of pain. In the management of treating childhood headaches, the association of psychiatric comorbidities should be considered.

**Disclosure of Interest:** None Declared

**Headache Education for Clinicians and Patients**

**PO-02-090**

**The Validation of a Self-Efficacy Scale for Chronic Headache: A methods study**

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**Objectives:** Chronic headaches affect approximately 4% of the adult population in the United States, and have a debilitating impact on daily activities and quality of life. Self-efficacy is a situation specific sense of self-confidence that one can perform needed actions to achieve desirable or avoid undesirable outcomes. Self-efficacy, or the ability to manage and control headaches, in patients with chronic headaches has been reported to be low. Defining the level and specific elements of self-efficacy in patients with chronic headaches may help to reduce the disability associated with chronic headaches. We have developed a patient self-reported outcome measure to assess and define the factors of daily activities and behaviors related to self-efficacy in patients with chronic headaches, called the Chronic Headache Self-Efficacy Scale (CHASE). The objective of this study is to assess the validity and reliability of the CHASE questionnaire in patients with chronic headaches.

**Methods:** The validity and reliability of CHASE will be examined in 100 patients with a diagnosis of chronic headache or chronic migraine. The patients will complete the CHASE, SF-12 (Short Form-12), HMSE (Headache Management Self-Efficacy Scale), HIT-6 (Headache Impact Test-6), GROC (Global Rating of Change), Patient Acceptable Symptom State (PASS), and questions related to history of treatment and frequency of headaches. Patients will complete the questionnaires at three time points: initial encounter, 24 to 72 hours after initial encounter, and 12 weeks after initial encounter. Statistical analyses will be performed to determine reliability, error estimates, validity, and responsiveness of the scale.

**Results:** To be completed after the study is completed.

**Conclusion:** Characterizing the reliability, error, and validity of this scale will provide practitioners with a means to assess the self-efficacy. Particularly, self-efficacy related to the ability to perform daily and lifestyle activities, as well as a variety of behaviors specific to the management of chronic headaches.

**Disclosure of Interest:** None Declared

**Headache Education for Clinicians and Patients**

**PO-02-091**

**Current gaps and challenges in migraine care in Canada: a multi-stakeholder perspective**

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3 The Shapero Markham Headache and Pain Treatment Centre, Markham
4 Department of Family and Community Medicine, University of Toronto, Toronto, Canada
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6 Department of Clinical Neurosciences, University of Calgary, Calgary, Canada

**Objectives:** Despite migraine being a common reason for medical consultation, patients remain sub-optimally treated and managed. Lack of sufficient training in medical school and lack of continuing education training around migraine has been mentioned as an underlying cause for sub-optimal migraine care (Gladstone 2010). A Canadian study was conducted to identify challenges, clinical practice gaps and potential educational needs of health care providers caring for patients suffering from migraine, with the goal to inform the design of future educational activities and programs.

**Methods:** This IRB-approved educational and behavioural research study uses a mixed-methods (qualitative and quantitative) methodology with a multi stakeholders approach in four (4) provinces of Canada: Alberta, British-Columbia, Ontario and Quebec. The initial qualitative phase included multiple data sources: 1) literature review, 2) input from an expert working group & 3) semi-structured telephone interviews with: Neurologists (NEU) and General Practitioners (GPs), Nurses with special expertise in migraine (NUs), Pharmacists (PHs), Clinic Administrators (CAs), Policy Influencers or Payers (PIs) & Patient Advocates (PAs). Data sources were triangulated to obtain a comprehensive understanding of factors undermining optimal migraine care. The quantitative phase (survey) will validate the extent to which the identified gaps are present in a larger sample of healthcare
professionals and will allow a comprehensive understanding of challenges and their causalities.

**Results:** 29 participants were enrolled in the qualitative phase; NEU (n = 8), GPs (n = 7), NUs (n = 2), PHs (n = 4), CAs (n = 3), Pls (n = 3) & PAs (n = 2). A majority of Health care provider participants worked in community setting (65%) and had over 20 years of experience (60%). Caseload of patients with migraine varied from 10 to 100% of overall caseload. Six (6) preliminary key findings and their underlying causalities were identified in the patient’s care pathway: (1) Challenges in differential diagnosis, (2) Challenges in selection of treatment (migraine specific vs. non-migraine specific), (3) Challenges in incorporating non-pharmacological therapy, (4) Challenges in monitoring treatment response, (5) Lack of availability of effective therapies and (6) Sub-optimal sharing or roles and responsibilities in migraine care. The underlying causalities identified for each challenge included specific knowledge and skills gaps, confidence and attitudinal issues, as well as system and contextual factors, all potentially contributing to impaired care. Results from the quantitative phase (survey), including validation of the aforementioned challenges and their causalities, will be integrated into the final findings and presented.

**Conclusion:** Six (6) preliminary key challenges and their causalities were identified in migraine care in 4 provinces of Canada. Findings from this study underline the need to examine how further support, resources and medical/health education interventions could be provided to health care providers involved in the care of patients suffering from migraine in Canada. A similar study is currently underway in US and Europe.

compared with regards to their perceived social status among residents.

**Conclusion:** The results are currently being analysed and will be presented at the meeting.

**Disclosure of Interest:** None Declared

**Headache Education for Clinicians and Patients**

**PO-02-093**

**Headache Medicine Knowledge Assessment Survey of Primary Care Providers**

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**Objectives:** The objective of this study was to develop a survey to assess knowledge gaps in primary care regarding headache medicine. This is the first step in a process to develop a headache education program for primary care providers in a University-based healthcare system.

**Methods:** A survey for primary care providers was developed by two providers in a university-based specialty headache clinic (one physician board certified in headache medicine and one doctorate prepared nurse practitioner) in collaboration with a doctoral family primary care nurse practitioner student. The survey included questions regarding diagnosis and treatment of headache disorders and was distributed by Catalyst survey to 132 primary care providers throughout 12 primary care clinics within the university-based healthcare system.

**Results:** A total of 51 participants completed the survey, a 40% response rate. Common areas of knowledge gaps were identified through data analysis. These areas included assessment and management of medication overuse headache, assessment of psychosocial co-morbidities, use of International Headache Society Beta 3 Diagnostic Criteria, acute pharmacological management, and non-pharmacological treatment of headache. Participants reported the highest confidence in diagnosing migraines, with nearly 50% of them reporting 4 or 5 on a confidence scale of 0–5 (0 being “not confident at all,” and 5 being “extremely confident”). They were the least confident in diagnosing cluster headache, chronic daily headache, and medication overuse headache. Participants were largely aware that NSAIDs, Tylenol, and opioids can cause medication overuse headache (MOH), but fewer than 60% of participants were aware that other medications can cause MOH, such as benzodiazepines, barbiturates, and ergotamines. Only 16% of the participants reported using the International Headache Society Beta 3 criteria when diagnosing headaches. Despite recommendations against prescribing opioids and barbiturates for headache relief, 24% of the participants would consider prescribing opioids, and 39% of them would consider prescribing barbiturates for acute headache management. Most participants actively assess for comorbid anxiety, depression and sleep disorders (85%, 98%, 93% respectively), however only a small number assess for comorbid elevated body mass index (39%). An overwhelming majority of primary care providers completing the survey (98%, n = 50) were interested in learning more about headache medicine through either online modules or in person training.

**Conclusion:** There are both significant learning opportunities and the desire to learn more about headache medicine among primary care providers in this university-based healthcare system. Primary topics for a headache training program are those which meet knowledge deficits and have the potential to significantly improve care, including medication overuse headache diagnostic criteria and treatment options, acute and preventive treatment options, use of International Headache Society Beta 3 Diagnostic Criteria for all headache diagnoses, and comorbid conditions important to assess and address in headache that may directly or indirectly impact treatment success.

**Disclosure of Interest:** None Declared

**Patients and Carers Education - Cumbria Headache Forum**

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**Objectives:** Headache disorders are often disabling conditions impacting on all aspects of normal living. It can lead to decreased performance at work or school, depression, disability and decreased quality of life. Cumbria Headache Forum (CHF), was established in 2013. It provides regular, three-monthly, large scale meetings regionally, open to all patients with headache and migraine as well as health professionals in Cumbria. CHF enables access to medical professionals with an expertise in the headache field from Cumbria as well as invited experts from the outside of Cumbria. This is an educational platform which aims to enable patients to take an active role in management of their often-debilitating condition.
Methods: The concept combines pharmacological and non-pharmacological approach, lifestyle advice, advice about stress management and diet. Invited speakers are headache experts, GPs with special interest, Headache Specialist Nurses, psychologist, physiotherapist and dietary nurse, nutritional therapist. CHF meetings are organised and chaired by Dr Vanderpol Consultant Neurologist with expertise in headache field who heads Headache Service in Cumbria. To establish benefit and gather qualitative data a survey was conducted with participants who attended headache forums between December 2014 and January 2016.

Results: In total 25 responded to the survey. 87.5% learned new information about headache or migraine which has helped them to better understand the condition. 83.33% have taken more active role in management since attending the forum. 96% participants would recommend to family or friend who suffers from headache or migraine to attend the forum.

Conclusion: This concept provides multidisciplinary approach enabling and supporting Self-Management. The aim was to create a comprehensive program to increase the likelihood of successfully managing headaches and provide support to patients who often felt left alone for many years with their condition. More than 3 years of experience of running CHF meetings and outcomes of the survey has shown very positive results. Positive feedback is provided after every meeting. The attendance of the meeting has been growing, many patients travel from neighboring regions far away, to get the needed help and support.

Disclosure of Interest: None Declared

Headache Education for Clinicians and Patients

PO-02-095

Progressive Multifocal Cerebral Infarction Due to Reversible Cerebral Vasconstriction Syndrome without Headache

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Objectives: Multiple attacks of thunderclap headache are cardinal features of reversible cerebral vascoconstriction syndrome (RCVS). However, few studies reported that RCVS could occur without typical thunderclap headache. Here, we report on an unusual clinical course of progressive multifocal cerebral infarction probably due to RCVS without headache.

Methods: Case report.

Results: A 46-year old woman visited our emergency department due to 1-day history of suddenly developed visual field defect. She had no history of conventional vascular risk factors, such as hypertension, diabetes, and dyslipidemia, as well as migraine and other headache disorders. Initial magnetic resonance imaging (MRI) and angiography (MRA) revealed acute cerebral infarct in the left middle cerebral artery (MCA) territory that was likely embolic in nature and diffuse multivascular stenoses involving bilateral the proximal and distal segments of the MCAs, the anterior cerebral arteries (ACAs), and the posterior cerebral arteries. She was started on aspirin and clopidogrel initially. At the 2nd day of her admission, she reported sudden-onset left lower limb weakness; and follow-up MRI showed new acute ischemic stroke in the right ACA territory. Cerebral angiography was performed to further evaluate the multivascular stenotic lesions. Laboratory studies provide no evidence of systemic vasculitis and other autoimmune disease. Although she had never complaint any headache at all, she was treated with oral calcium channel blocker (nimodipine 30 mg bid). There was no subsequent cerebral infarction. Three-month follow-up MRI and MRA showed complete recovery of the multivascular stenoses.

Conclusion: This is an uncommon case of progressive cerebral infarction probably due to RCVS, despite the absence of headache. The clinico-radiological findings of our case suggest that RCVS can be a potential cause for cerebral infarction even if headache does not exist at all during clinical course.

Disclosure of Interest: None Declared

Headache Education for Clinicians and Patients

PO-02-096

The Clinical Research Nurse: a 5-Year Experience in a 3rd Level Headache Centre

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Objectives: The role of the headache nurse within the activities of a headache centre is becoming increasingly important, even more so in those structures where care and research are institutional activities. I have been working as a clinical research nurse in such a structure for 5 years and I have dynamically adapted my supporting role within the research team with a multitude of tasks. The aim of this abstract is to illustrate my experience for the perusal of other centres and colleagues.

Disclosure of Interest: None Declared
Methods: I have retrospectively analysed the type of activities and the organizational adaptations that have been put in place in order to support and expedite activities within the research team, focusing the attention also on the initiatives taken to optimize the management and wellbeing of patients during the procedures, with the aim to improve their satisfaction.

Results: My activities initially consisted mainly in sample collection and planning of patients’ appointments. Over the years, they increased in number and type. Today they can be associated to several domains, with different levels of responsibilities: protocol development, organization of activities, spaces, supplies and documents, distribution/collection of informed consents, patient recruiting and scheduling, data collection and safety reporting, tissue and sample collection, processing and mailing, remote follow-up of patients, triage of complaints. All of these activities require accurate planning. In addition, most, if not all, studies foresee a variable overlapping of research and care activities. In this frame it is very important to reach and keep a good balance between the requirements of the research and the needs of patients.

Conclusion: Being a clinical research nurse entails a large amount of responsibilities in the outcome of studies and in the quality of care delivered to patients. To perform the role at best, the clinical research nurse requires a large repertoire of clinical expertise, organizational skill and capability to critically evaluate problems and dynamically search for the possible solutions. An expert and well-trained research nurse is pivotal for the conduction and completion of clinical studies in the field of headache and greatly contributes to patient’s satisfaction.

Disclosure of Interest: None Declared

Headache Education for Clinicians and Patients

PO-02-097
Barriers to Care among Indian Children with Recurrent Headache

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Objectives: Reasons which prevent headache patients from seeking healthcare are labelled Barriers to Care. There is little information on these in the context of pediatric headache. This study was done to identify various barriers to care among children with recurrent headache attending a general pediatric OPD.

Methods: After IEC clearance and informed consent, consecutive children attending our Pediatric department with either Migraine or Tension-type headache (as per ICHD-3) were enrolled between April, 2014 to February, 2015. Complete history and physical examination was done in all children. Barriers to care were explored during a one-to-one interview with the parents using a list of previously described factors categorized as Clinical, Social, and Others,¹ along with open-ended questions.

Results: Forty children (24 males) with mean (SD) age of 10.6 (1.7) year were enrolled. Migraine was diagnosed in 24. Majority of the headache patients (83.3% migraine, 100% TTH) had more than two barriers to care identified, and none was without an identified barrier. The major group was Clinical barriers, with ‘wrong diagnosis’ (90%) and ‘improper treatment’ (75%) being common. Delayed referral was significantly higher (P < 0.001) among TTH patients than migraine. The Social barriers were also frequent, with ‘Wrong expectations’ observed in all patients, and ‘Frequent change of doctors’ being more in those with TTH (P = 0.039).

Conclusion: Identification of barriers is a step towards appropriate strategies for addressing these, provided similar community-based data is generated. Clinical barriers are amenable to intervention by improving teaching during clinical training and by CME programs for clinicians, though Social barriers will require more sustained public health awareness campaigns.

Disclosure of Interest: None Declared

Headache Education for Clinicians and Patients

PO-02-098
Frequency of Vertigo in Pediatric Migraine

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Objectives: In its appendix section, the International Classification of Headache Disorders, 3rd edition, beta (ICHD IIIb) has identified a new diagnostic category of vestibular migraine[1], which has been validated in adult populations[2]. However, the utility of this diagnosis among pediatric patients with migraine is unclear. Vertigo is a commonly reported symptom in children with migraine and may be as common as photophobia or nausea. The current study sought to establish the frequency of vertigo in pediatric patients seeking care for migraine.

Methods: This study is a retrospective chart review that includes all patients less than 18 years old with migraine who were seen at the University of California, San Francisco (UCSF) Pediatric Headache Clinic in 2014. Notes from
patients’ initial encounters were reviewed, as all patients presenting to the clinic undergo a semi-structured interview that includes a specific query regarding the presence or absence of vertigo with their migraine attacks.

**Results:** Of 103 pediatric patients with migraine, the mean age was 13.4 years, 70% were girls, 21% had migraine with aura, 59% had chronic migraine, and the mean frequency of migraine days per month was 19. Among this population, 49 patients or 48% reported experiencing vertigo at least once in association with their migraine headaches.

**Conclusion:** The high percentage of pediatric migraine patients experiencing vertigo supports the hypothesis that vertigo is a common symptom in the pediatric migraine population. Of note, our sample was from a tertiary care center, and the majority of these patients had chronic migraine. Nevertheless, our finding should spur further research to determine whether a subset of migraine patients with vertigo would meet criteria for vestibular migraine and whether pediatric migraine patients with vertigo respond differently to acute and preventive treatments compared to those without vertigo.

**Disclosure of Interest:** K. Hamilton: None Declared, A. Gelfand Conflict with: from eNeura and Allergan, Conflict with: to Zosana and Eli Lilly, Conflict with: Travel expenses from Teva. Her spouse has received research support from Genentech, MedDay, and Quest Diagnostics and has received personal compensation for medical-legal consulting and consulting fees from Genentech.

**References**


**Headache Education for Clinicians and Patients**

**PO-02-099**

**Cycling Through Migraine Preventive Treatments: Implications to All-Cause Total Direct Costs**

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**Objectives:** Migraine is a common and disabling neurological condition associated with a substantial economic burden. Currently available preventive migraine medications (PMM) are marginally effective and induce side effects that can lead to multiple PMM switches or discontinuation. It is unknown if cost differences exist among migraine patients when PMM switches occur. The aim of this study is to understand the cost burden of patients who cycle through 1 (PMM1), 2 (PMM2), or ≥3 (PMM3) unique PMM drug classes over a 12-month period compared to patients who are persistent on their initial PMM class.

**Methods:** This retrospective observational study used the Truven MarketScan U.S. Commercial and Medicare Supplemental claims database to identify adult migraine patients initiating their first PMM class (antidepressants, antiepileptics, beta-blockers, or neurotoxins) from 2011–2013 (index = first PMM claim), with a 1 year pre-index clean period established for all PMMs. Patients were required to have at least 2 (1 if inpatient) migraine diagnosis codes (ICD9: 346.xx) from 1 year pre-index to 1 year post-index with at least 1 code occurring pre-index. The inclusion criteria also required 12 months of pre- and post-index continuous medical and prescription enrollment. Patients were excluded if, during the 12 months before the first claim for any PMM class (index or switched drug), they received an ICD9 code for a non-migraine comorbidity treated by that PMM class (epilepsy and antiepileptics, hypertension/congestive heart failure and beta-blockers, depression and antidepressants). Based on the 2014 medical consumer price index, all-cause total direct costs (outpatient, inpatient, emergency room, and prescriptions) were estimated for the 3 PMM cohorts vs. the persistent (remained on initial therapy) cohort in the 12 months post-index. Propensity score bin bootstrapping controlling for patient baseline characteristics was used to compare costs between each PMM and persistent cohort. Bootstrap simulations were performed, resulting in adjusted calculations of each subgroup’s mean total costs and standard deviation (SD).

**Results:** The study population included 61,232 patients who received a PMM and met all other study inclusion/exclusion criteria. Study patients were mainly female (85%) with a mean age of 38.6 yrs and mean Charlson comorbidity index of 0.34. Adjusted mean all-cause total direct costs ± prescription costs for the 4 cohorts are presented in the table above; statistically significant differences were observed between each PMM group and the persistent cohort.

**Conclusion:** All-cause total direct costs rose with increased number of PMM switches over the 1-year period, and were significantly higher than the persistent group with the exception of PMM1. PMM-persistent patients had the potential for higher pharmacy costs due to subgroup selection bias. When all-cause pharmacy costs were excluded, incremental increases for all groups were observed as expected. These data suggest increased cost burden for migraine patients who cycle through a higher number of PMMs vs those who continue to receive their initial medication. Additional analysis will be completed to investigate the relationship between cycling through
Objectives: To present baseline demographic and clinical characteristics, and patient-reported outcomes (PROs) of migraineurs initiating a preventive migraine medication and enrolled in a prospective observational study: Assessment of Tolerability and Effectiveness in Migraineurs using Preventive Treatment (ATTAIN).

Methods: Subjects with a clinical diagnosis of episodic (EM) or chronic migraine (CM) and initiating a physician-prescribed preventive treatment at primary care or neurology clinics in the United States are currently being enrolled in a study to assess the tolerability and effectiveness of migraine preventive therapies. Subjects are enrolled onsite at clinical sites and complete baseline assessments online. Baseline assessments include: demographic forms, migraine history, healthcare resource use, and PROs including Migraine Disability Assessment (MIDAS), Headache Impact Test (HIT-6™; score range: 36–78), Migraine Functional Impact Questionnaire (MFIQ; score range: 0–100), and Work Productivity and Activity Impairment Questionnaire (WPAI; score range: 0–100%). Migraine and treatment history are also reported by clinic staff through medical chart review. Subjects are followed for 6 months post-baseline, with monthly completion of questions related to migraine frequency, treatment tolerability, reasons for any change in treatment, and the PROs included at baseline. The enrollment target is 300 subjects. Summarized here are baseline characteristics of 101 subjects enrolled to date.

Results: The current sample includes 48 (47.5%) EM and 53 (52.5%) CM subjects, with mean ± SD age 42.0 ± 13.1 years. The majority are female (87.1%), white (73.3%), and employed full-time (58.4%). Mean ± SD age at first migraine diagnosis was 22.3 ± 11.1 years (EM: 23.5 ± 11.4; CM: 21.1 ± 10.8) and the majority have migraine without aura (65.3%). In the three months prior to enrollment, subjects reported mean ± SD of 15.8 ± 7.2 headache days per month (EM: 10.0 ± 2.4; CM: 21.1 ± 6.0), of which 11.4 ± 6.0 (EM: 7.6 ± 2.8; CM: 14.8 ± 6.2) were migraine days. Prior to

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**Headache Education for Clinicians and Patients**

**PO-02-100**

**Characteristics of patients newly initiating a preventive treatment for migraine: Baseline data from the Assessment of Tolerability and Effectiveness in Migraineurs using Preventive Treatment (ATTAIN) study**

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</table>

**Table:** All-cause total direct USD costs: propensity score-adjusted comparisons
conclusion: the majority of subjects (71.3%; EM: 75.0%; CM: 67.9%) were naive to treatment with migraine preventive medications; 58.3% of treatment naive subjects were initiated on topiramate. The most commonly prescribed migraine preventive treatments were topiramate (58.3%), beta blockers (14.6%), and tricyclic antidepressants (10.4%) for EM subjects, and topiramate (37.7%), onabotulinumtoxinA (24.5%), and tricyclic antidepressants (15.1%) for CM subjects. At baseline, EM and CM subjects reported severe headache impact (HIT-6 score > 59; EM: 85.4%, CM: 92.5%) and severe disability (MIDAS Grade IV (≥21); EM: 64.6%, CM: 83.0%). Functional impacts on activity were also reported based on MFIQ Global item (EM: 55.2 ± 29.2; CM: 55.7 ± 27.1) and WPAI activity impairment score (EM: 58.5% ± 29.4; CM: 55.1% ± 29.6).

Conclusion: This web-based longitudinal, observational study is currently ongoing and seeks to generate insights into the real-world tolerability and effectiveness of preventive migraine treatments. Baseline assessments indicate high burden of illness among both EM and CM subjects, with migraine contributing to severe disability, functional impact, and activity impairment.


Headache Education for Clinicians and Patients

PO-02-101

Headaches in Argentina. Preliminary Study

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Objectives: According to the data from the WHO (World Health Organization) (2010) primary headaches are among the most prevalent diseases worldwide. We conducted a National headache survey during 2014 with the aim of establishing the prevalence and some epidemiologic data of headache in Argentina.

Methods: We conducted a descriptive epidemiological study in different geographic areas of Argentina through a standardized questionnaire. Face-to-face interviews were performed to the general population randomly between May and July 2014. Subjects, who answered to have headaches, were asked about pain duration, frequency and severity, as well as the quality of life and self-medication.

Results: A total of 2020 subjects were interviewed. In this study 92% respondents reported to have headaches (52% female subjects vs. 48% male subjects) with no significant differences between the compared geographic areas. A total of 10% referred to have frequent headaches (more than 50 episodes/year). 22% reported to have moderate to severe pain, 94% missed work at least one day over the last year. 72% percent reduced their quality of life, and 80% were self-medicated. Only 38%, 5% sought medical help.

Conclusion: Our study showed a similar prevalence of headaches in our country compared to data from WHO. Upon analysis of the data, we concluded that the impaired quality of life is associated with the high frequency and severity of headache episodes. The self-medication is related to the severity and duration of the pain, and/or the frequency of each episode. Among those who sought medical help, more than half of the patients consulted a general practitioner.

Disclosure of Interest: None Declared
Headache Education for Clinicians and Patients

PO-02-102

Individual self-prediction of migraine attacks: longitudinal analysis of cohort of migraine patients using a digital platform

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Objectives: As a critical component towards self-management of their condition we examine the individual ability of patients to predict their attacks 24 hrs in advance. Prediction of attacks might be expected to be difficult as migraine premonitory symptoms, and the potential risk factors that trigger them, show significant inter-individual variation (1) and possibly also intra-individual variation. Accurate prediction may impact quality of life, allow optimal timing of medication dosing and may also lead to understanding of the profiles and “best practice” of good predictors. Thus, the objective is to understand and compare ability of episodic migraineurs to self-predict attacks on an individual level.

Methods: Individuals with migraine registered to use a digital platform (Curelator Headache™) via website or the App Store (iOS only) and on a daily basis for at least 90 days entered about lifestyle factors, possible headaches, and medications as well as migraine expectation for the next 24 hours (low/moderate/high). Patients with at least 10 low and 10 high expectations instances of migraine were included in the analysis. Prediction was considered successful when 24 hr expectation of migraine was high and an attack occurred on the next day; or 24 hr expectation was low and was followed by a migraine free day.

Results: Of 497 episodic migraineurs examined in the study, 192 met the criteria for analysis. Good predictors were defined as having an accuracy of ≥75% at predicting an attack; bad predictors were defined as those with ≤25% accuracy predicting a migraine. In this study we found 18% (n = 34) were good predictors and 21% (n = 41) were defined as bad predictors, and both groups stood up as different from the rest of the sample with statistical significance (p < 0.001).

Conclusion: A substantial proportion (61%, n = 117) of users predict their migraine with only moderate accuracy (≥25% but ≤75%). A small group (21%, n = 41), were considered bad predictors with <25% accuracy. A somewhat smaller group (18%, n = 34) were found to be good predictors with >75% accuracy. A next step would be to understand the in possible differences risk factors and premonitory symptoms that these two groups may exhibit and are possibly using for prediction of their attacks.


Reference


Headache Education for Clinicians and Patients

PO-02-103

Reducing Impaired Days: Results from the STRIVE Trial, A Phase 3, Randomized, Double-Blind Study of Erenumab for Episodic Migraine

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Objectives: To evaluate the effect of erenumab, a preventive treatment for episodic migraine (EM) in adults, on monthly days with impairment as measured by the Migraine Physical Function Impact Diary (MPFID).

Methods: The MPFID is a 13-item patient-reported outcome (PRO) measure that assesses the impact of migraine on two domains: everyday activities (EA) and physical impairment (PI), over the previous 24 hours. MPFID was completed using an electronic diary every evening during a global, placebo controlled double-blind, 6 month, phase 3 trial (STRIVE trial; NCT02456740) in which 955 adults with EM aged 18–65 years were randomized 1:1:1 to subcutaneous, monthly placebo or erenumab 140 mg or 70 mg. Reponses to items in the MPFID EA and PI domains are on a 1–5 scale, with higher numbers indicating greater negative impact. A day with a response ≥3 on at least one item in a domain was defined an “impaired day” (ID) for that domain, (i.e. EA-ID and PI-ID). Mean monthly number of IDs were summarized for the 4-week baseline period and each subsequent 4 week period. Changes from baseline in mean monthly EA-ID and PI-ID over the final 3 months (month 4–6) of the double-blind treatment phase (DBTP) were assessed as pre-specified exploratory
endpoints in the STRIVE trial; primary and secondary endpoints are reported separately. All p-values are descriptive and were not adjusted for multiplicity.

**Results:** At baseline, subjects in the erenumab and placebo groups had a similar number of mean monthly EA-ID (140 mg: mean = ± 6.62 ± 4.20; 70 mg: 7.21 ± 4.56; placebo: 7.12 ± 4.85) and PI-ID (140 mg: 5.81 ± 4.32; 70 mg: 6.09 ± 4.60; placebo: 6.20 ± 5.05). Over the final 3 months of the DBTP, greater reductions from baseline in EA-IDs and PI-IDs were observed in the erenumab 140 mg and 70 mg groups compared to placebo. For EA-IDs, subjects treated with erenumab 140 mg (LS mean = −3.01 days (95% confidence interval (CI): −3.45,−2.57)) and 70 mg (−2.83 days (−3.27,−2.39)) experienced larger reductions compared to placebo (−1.71 (−2.16,−1.27), p < 0.001 for both). Greater reductions in mean monthly PI-IDs days were also observed in the erenumab groups (140 mg: LS mean = −2.51 days (95% CI: −2.93,−2.09); 70 mg: −2.25 days (−2.68,−1.83)) compared to placebo (−1.16 (−1.59,−0.74), p < 0.001 for both).

**Conclusion:** Compared to the placebo group, EM subjects treated with erenumab 140 mg and 70 mg experienced greater reductions from baseline in mean monthly MPFID EA-ID and PI-ID during the 6 month DBTP of the STRIVE trial. Numerically greater reductions were observed in the 140 mg compared to the 70 mg group. Erenumab treated patients experience reductions in functional impairment due to migraine, as measured by MPFID, which complements improvements observed with standard efficacy measures.

**Disclosure of Interest:** A. Hareendran Conflict with: Pfizer Ltd, Conflict with: Employee of Evidera, D. Buse Conflict with: Buse has received grant support and honoraria from Allergan, Avanir and Eli Lilly. She is an employee of Montefiore Medical Center, which has received research funding by Allergan, CoLucid, Endo Pharmaceuticals, GlaxoSmithKline, MAP Pharmaceuticals, Merck, NuPath, Novartis, Ortho-McNeil, and Zogenix, via grants to the National Headache Foundation., Conflict with: Allergan, Avanir, Amgen, Dr. Reddy’s laboratories, Eli Lilly, Conflict with: Non-remunerative Positions of Influence: Buse is on the editorial board of the Current Pain and Headache Reports, Journal of Headache and Pain, Pain Medicine News, and Pain Pathways magazine., R. Lipton Conflict with: National Institutes of health, the National Headache Foundation, the Migraine Research Fund, Conflict with: Serves as a consultant, serves as an advisory board member, or has received honoraria from Alder, Allergan, American Headache Society, Autonomic Technologies, Boston Scientific, Bristo Myers Squibb, Cognimed, CoLucid, Eli Lilly, eNeura Therapeutics, Merck, Novartis, Pfizer, and Teva, Conflict with: Receipt of royalties: Royalties from Wolff’s Headache, 8th Edition (Oxford University Press, 2009), M. Bayliss Conflict with: Martha Bayliss, MSc, is an employee of Optum, a division of UnitedHealth Group, which has consulting engagements with many pharmaceutical companies, including Amgen., Conflict with: Optum, a division of UnitedHealth Group, Conflict with: Non-remunerative Positions of Influence, D. Mikol Conflict with: Amgen Inc., Conflict with: Amgen Inc., D. Revicki Conflict with: Amgen, Conflict with: Amgen, Allergan, Conflict with: Employee of Evidera, F. Zhang Conflict with: Amgen Inc., Conflict with: Amgen Inc., P. Desai Conflict with: Amgen Inc., Conflict with: Amgen Inc., H. Picard Conflict with: Amgen Inc., Conflict with: Amgen Inc., A. Kawata Conflict with: Employee of Evidera

**Headache Education for Clinicians and Patients**

**PO-02-104**

**Prevalence and Impact of Headache in Republic of Ireland**

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**Objectives:** Headache disorders such as migraine are among the most common disorders of the nervous system, bringing a heavy burden not only to individuals but also to society. The population of the Republic of Ireland is approximately 4.7 million however the impact and burden of headache disorders in Ireland is unknown

**Methods:** In order to estimate the prevalence and burden of headache within the republic of Ireland we conducted a telephone survey with a population sample that was generated by random digit dialling. The survey was answered by 1013 people, aged 15 or older. The population was spread across the four provinces of Ireland and balanced by age, sex and social demographic.

**Results:** 226 (22.3%) of the respondents reported at least one headache episode in the previous year. Of those 150 (14.8%) fulfilled the criteria for migraine, with 44% having at least one migraine a month. There was a 3:1 ratio of women to men reporting headache. Only one third of the headache sufferers had received an appropriate diagnosis from a doctor or other healthcare professional. Over half were given a diagnosis of migraine and a further 10% were diagnosed with tension headache. Other headache sufferers were diagnosed with epilepsy and vertigo. 135 (60%) of those reporting a headache had taken a medication in the past month for their headache with 15% of those reporting that they were currently taking a prophylactic or preventative treatment. Headaches were reported to be significantly impacting on ability to work and participation in social activities. The impact was similar in both the migraine and non-migraine groups.

**Conclusion:** This study provides an estimate of the prevalence of primary headache and migraine in Ireland. As already shown in many other Western countries, primary headache is common and there is an under-diagnosis of this often disabling condition. This under-diagnosis is
also apparent amongst those who have at least one headache a month. Migraine is the most disabling neurological condition worldwide, causing significant impact on day to day functioning, quality of life and productivity.

**Disclosure of Interest:** N. Murphy Conflict with: Employee of Novartis, R. Maclver Conflict with: Employee of Novartis, E. Tompkins: None Declared, M. Ruttledge: None Declared

**Headache Education for Clinicians and Patients**

**PO-02-105**

**Alcohol as a trigger for migraine**

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**Objectives:** To determine the self-reported prevalence of alcohol as a migraine trigger and self-restricted alcohol use in a large, well-defined, migraine cohort.

**Methods:** We conducted a cross-sectional, web-based, questionnaire study among 2197 migraine patients diagnosed according to ICDH-3. We assessed alcoholic beverages consumption and self-reported triggering potential, reasons behind alcohol abstinence, and time duration between alcohol consumption and migraine attack onset.

**Results:** Alcoholic beverages were reported as a trigger by 35.6% of migraine patients. One quarter of patients either stopped consuming or never consumed alcoholic beverages because presumed triggering effects. Wine, especially red wine (77.8% of patients) was recognized as the greatest trigger among the alcoholic beverages. However, in only 8.8% of patients red wine consistently led to an attack. Time of onset was rapid (<3 hours) in one third of patients, independent of beverage type.

**Conclusion:** Alcoholic beverages, especially red wine, are recognized as a migraine trigger factor by patients and have a substantial effect on patient behavior. Time of onset of provoked migraine attacks may suggest different mechanisms than for hangover-headache. Low consistency of provocation suggest that alcoholic beverages acting as singular trigger is insufficient or fluctuations in the trigger threshold might cause variations in triggering success.

**Disclosure of Interest:** None Declared

**Headache Education for Clinicians and Patients**

**PO-02-106**

**Association between work-related stress and headache among medical staff in Ulaanbaatar**

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**Objectives:** The headache is the third cause of years lost due to disability. For primary headache in the workplace one of the most commonly identified trigger is stress. The goal of this study is to determine the association between stress and headache among medical staff in the Ulaanbaatar city hospitals, Mongolia.

**Methods:** A cross-sectional, hospital-based survey consisting of semi-structured questionnaires was administered to 159 medical staffs from randomly selected public hospitals during the period from January to February 2017. The first part of the questionnaires included demographic data and the one-year headache profile, including headache duration, frequency, location, characteristics of accompanying symptoms, and aggravating factors. The subtyping questionnaire of primary headache was based on International Classification of Headache Disorders-III (ICHD-III) criteria. The questionnaire of the 22-item Maslach Burnout Inventory (MBI) was used to measure emotional exhaustion (EE), depersonalization (DP), and personal accomplishment (PA). The Student’s t-test, one-way analysis of variance (ANOVA), and chi-square test were used for statistical analysis.

**Results:** Seventy-six out of 156 responders (48.7%) had experienced primary headaches in the previous year. The prevalence rates of migraine, tension type headache (TTH), chronic headache and probable medication overuse headache, were 22.4% (n = 35), 26.3% (n = 41), 12.2% (n = 19) and 7.1% (n = 11), respectively. There were no demographic differences between the sufferers and non-sufferers. Most of staff had scores which indicated they were burnt out. Nearly one fifth (20.5%) reported EE, 22.4% reported DP while almost one quarter (26.3%) experienced reduced PA. Chronic Headache sufferers had more EE and PA than non-headache sufferers (p = 0.01). The primary headaches are triggered by changes in sleeping habits, stress and flu, most of responders commonly uses non-steroidal anti-inflammatory drugs to relieve their pain.
Conclusion: The primary headache prevalence is high among medical staff in Ulaanbaatar. Burnout, which results from prolonged exposure to chronic work stress, may be associated with chronic headache, further researches in this field is needed.

Disclosure of Interest: None Declared

Headache Education for Clinicians and Patients

PO-02-107

Willingness to pay for effective headache treatment in Estonia – preliminary results

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Objectives: The objectives of our study were to estimate the willingness to pay for effective headache treatment in Estonian population and investigate factors influencing the outcome.

Methods: The data were derived from a population based survey conducted in Estonia form January 2016 till March 2017. The participants were asked about their age, sex, education, monthly income, occurrence, frequency and intensity of headaches. Participants were asked to play a “bidding game”, which determined how much they would pay for effective headache treatment per month. The “bidding game” results were compared in respect to the age, sex, education, income, occurrence, frequency and intensity of the headaches of the participants using Kruskal-Wallis rank sum test, medians and means of the “bidding game” sum.

Results: 672 participants completed the survey (379 (56.4%) women). Of all the participants, 311 (46.3%) had had headaches during the previous year (205 (65.9%) women). The “bidding game” sum was statistically significantly different in only 2 domains of the study – the occurrence of the headaches (means 24.8 vs 36.6 for people with headaches vs without headaches, \( p = 0.01 \)) and the income of the participants (means 24.4, 33.2, 44.6, 44.7 and 54.2 for the income groups of 0–499, 500–999, 1000–1499, 1500–1999 and >2000 € per month respectively, \( p < 0.001 \)). There were no statistically significant differences in the “bidding game” sum in respect to the age (means 28.6, 31.9, 35.1, 30.6 and 24.1 for the age groups of 18–29, 30–39, 40–49, 50–59 and 60–65 years respectively, \( p = 0.48 \)), sex (means 33.4 and 29.2 for men and women respectively, \( p = 0.98 \)), education (means 10.0, 28.3, 32.3, 28.1 and 32.4 for the primary, basic, secondary, vocational and higher education groups respectively, \( p = 0.70 \)) or frequency (means 32.5, 25.8 and 32.6 for the frequency of 0–1, 2–14 and >15 days with headache per month respectively, \( p = 0.58 \)) or intensity of the headaches (means 38.8, 29.0 and 34.1 for mild, moderate and severe pain respectively, \( p = 0.18 \)).

Conclusion: Predictably, higher income was related to higher willingness to pay for effective headache care. Surprisingly, people who had not experienced headaches during the previous year showed higher readiness to pay for effective headache care than those who had had headaches. It might be speculated, that the reason for this is that those suffering from headaches are more incapacitated precisely because of the disorder and thus have a reduced socioeconomic capacity, which prevents them from using their limited resources for headache care. This in turn means that governmental support is essential in adequate headache care system in Estonia.

Disclosure of Interest: None Declared

Headache Education for Clinicians and Patients

PO-02-108

“What’s under the hat?” Evaluation of an online European campaign for increasing public awareness for headache disorders. Perplexities about the usefulness of a story-telling approach for revealing the headache-related burden

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Objectives: “What’s under the hat?” is a headache awareness campaign conceived and launched in 2015 by the European Headache Alliance, an umbrella organisation of patient organisations. The aims of the campaign were a) to increase awareness of and compassion for the real and everyday impact of headache disorders amongst the general public; b) to help those affected by headache disorders to know that they are not alone and that headache disorders are treatable. The campaign asked those living with a headache disorder such as migraine or cluster headache, to share their story online in video or photo and text format, with the person wearing a hat. Stories were shared mainly on Facebook and Twitter with the tag #underthehat. In this study we evaluated if the patients’ participation and stories posted in a video or text format on the online campaign platforms reached the campaign objectives.
Methods: The participation to the campaign was evaluated by using social-media metrics. In addition we conducted a qualitative analysis of patient stories posted during the first 8 months of the campaign and asked a selected team to rate the stories based on their appropriateness, appeal and clarity.

Analysis: Exemplificative voices from the What’under the hat? campaign
Cristiana (Italy) “due to my headaches I just can see the life running far from me. .I’m not able to make any project for the future”
Elisabeth (Ireland) “when I was young I missed an enormous amount of school and felt isolated, guilty and frustrated. Being unable to imagine how I would function normally as an adult was terrifying;”
Lucia (Spain): “headache is like a demon that prevented me to study, to work, to have a family, to have a normal life. .”
Nicki (Italy): “I don’t tell anymore to my friends and colleagues that I got a headache. . . They don’t understand . . .”
Michelle (UK): “no treatment has been effective for me. .I’m so angry. .I would like to change this condition but I can’t do anything helpful”

Results: The facebook page reached less than 200 users, less than 400 interactions and 710 likes. In twitter 747 tweets were obtained with the #underthehat. The only active organizations were from Italy, Spain, UK, Ireland and Finland. Only 30 stories (15 videos), mainly posted by women (92%), were received analyzed. Most patients give an account of the dramatic impact of headache on their working and private life. Headache is often personified as an invisible persecutor that may be accepted but not integrated in the self. The predominant feelings portrayed in the stories are anger, unhappiness and resignation. Furthermore, many people report a lack of empathy from their social group and colleagues. The appropriateness and clarity of patients’ stories were rated as ‘very good’ whereas their appeal was scored as ‘sufficient’.

Conclusion: Headache patients have shown to be reluctant to share their sufferings in a social media context. The personal stories posted online reached the campaign aims and represent a potential powerful source of information for educating the general public about the burden and impact of headache disorders. However, a concern emerged that the hopelessness evident in the stories may wrongly suggest that headache disorders whilst common and disabling cannot be managed or treated.

Disclosure of Interest: None Declared

Headache Education for Clinicians and Patients
PO-02-109
Development of a novel, weighted and quantifiable scale for measuring QOL among patients with chronic migraine
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Objectives: Lack of knowledge about chronic migraine headache may cause significant misunderstandings between patients and their healthcare providers. For patients with chronic migraine, a positive quality of life (QOL) may be continually threatened and disturbed. Attempts have been made to measure the effectiveness of headache therapy in number of ways. However, none of them are universally accepted or have been adopted as the gold-standard of QOL-oriented quantitative measures of severity of chronic migraine.

The purpose of the present study is to establish a novel, readily usable, quantifiable and reliable QOL-oriented scale for measuring the severity of chronic migraine headache.

Methods: Six variables including daily physical functioning, daily community activities, enjoyment of life, somatic symptoms which are found to predict QOL are selected from the review of scales currently available and from the opinion of 30 migraine experts (25 neurologists and 5 neurosurgeon).

After categorization of selected variables, evaluation of the distribution and sensitivity of variables utilizing 22 active patients (aged 27–52; 38.8 ± 12.3 years old, M:F = 10:12) who had frequent chronic migraine headache according to the criteria of the International Classification of Headache Disorders 3rd edition (Beta version).

After modification of the scale with modified variables, testing of inter- and intra-rater reliability by 8 pairs of doctors using 10 new stroke patients (aged 29–49; 37.2 ± 11.1 years old, M:F = 3:7).

Ranking of a set of 16 virtual patients with a different combination of variables according to severity by 27 presently symptomatic patients with chronic migraine (aged 27–58; 39.2 ± 12.4 years old, M:F = 10:17) and 30 headache specialists was performed.

From these rankings, conjoint analysis derived averaged importance and weights of each of the items of the scale.

Results: As a result of conjoint analysis, the relative importance against the QOL of migraineurs was calculated. For patients with chronic migraine, daily physical functioning (33.4%) was clearly the most important factor for determining the QOL of migraineurs. Somatic
symptoms (20.6%), work-place efficacy (19.2%), corporeal pain (9.5%), enjoyment of life (9.3%), daily community activities (8.0%) are the next important factors for determining the QOL.

On the other hand, for migraine specialists, daily physical functioning (29.1%) was the most important factor for determining the QOL of migraineurs. Somatic symptoms (23.5%), corporeal pain (14.5%), work-place efficacy (12.7%), enjoyment of life (10.6%), daily community activities (9.6%) are the next important factors for determining the QOL of migraineurs.

Total score of the scale ranges from 12.8 (the best QOL) to 20.0 (the worst QOL).

**Conclusion:** The present study revealed:

1. The difference of relative importance against the QOL of migraineurs between doctors and patients.
2. The relative importance of variables may be different among the countries and may change chronologically even in the same country.
3. The understanding of the difference between doctors and patients may lead to the better relationships for treatment with chronic migraine headache.
4. It also help the mutual understanding of medical practice and research in headache between nations.

The present study revealed the possibility of our scoring system with higher consistency, reliable validity and superior quantitativeness from the Clinimetical point of view.

**Disclosure of Interest:** None Declared

**Headache Education for Clinicians and Patients**

**PO-02-110**

**Medication use and overuse patterns in a cohort of US and UK migraine patients using a digital platform**

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**Objectives:** Overuse of acute medications may worsen migraine and lead to medication overuse headache (MOH) (1). Few population studies have studied the risk of MOH across migraine treatment classes, and drugs involved in MOH vary from region to region (2). Here we describe medication use and identification of overuse (MO) in users of a digital platform for migraine (Curelator Headache™). The objective is to compare medication use and possible overuse patterns in individuals’ with migraine from the US and the UK.

**Methods:** Individuals with migraine registered to use the platform (Curelator Headache™) via website or the App store (iOS only) and used it daily for at least 90 days, entering details about headaches and medications used acutely and chronically. Acute medication use was analyzed at the level of individual drug names and MO was defined according to ICHD-3 beta criteria; other reported drugs were not included in the analysis.

**Results:** Individuals from the USA (n = 261) and the UK (n = 216) entered 20,353 (USA) and 17,965 (UK) headache instances. Only 6 (2.3%) US and 4 (1.8%) UK users did not use any acute medication for their headaches. Triptans (29.8% US, 35.4% UK) and NSAIDs (27.8% US, 29% UK) were the most frequently used classes of medication: opioid use was significantly different in the US and UK (5.9% US, 0.8% UK, p < 0.0001). The top two medications used were sumatriptan and ibuprofen in both cohorts. Overall, potential overuse of acute medication was identified in 79 (30.3%) and 45 (20.8%) US and UK patients respectively. In individuals with headache on ≥15 days/month, MO was identified in 60% and 51% in the US and UK, respectively. In the US, individuals with MO used significantly more classes and individual medications than non-MO users (p < 0.0001). MO was more common with NSAIDs (41.2%) and analgesic combinations (29.4%) in the US, while in the UK NSAIDs (52.8%) and triptans (42.7%) were most frequently overused. In the US, top medications overused were ibuprofen (19.3%), oxycodone (16.6%), sumatriptan (15.2%) and tramadol (11.9%), while in the UK these were ibuprofen (33.1%), paracetamol/codeine (21.4%), naproxen (13.8%) and zolmitriptan (12.1%).

**Conclusion:** Using a digital platform (Curelator Headache™) MO was identified in 114 migraine subjects and could be used to alert patients and their clinicians, which is clinically useful (1). US and UK medication use and overuse patterns are different but within literature-reported rates. An electronic diary system may complement previous studies investigating the role of MO in developing chronic migraine or MOH.


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Conflict with: Alder Biopharmaceuticals; Allergan; Amgen Inc.; Avanir Pharmaceuticals, Inc.; Curelator, Inc.; Depomed; Dr. Reddy’s Laboratories; ElectroCore Medical, LLC; eNeura Inc.; INSYS Therapeutics; Pfizer, Inc.; Lilly USA, LLC; Supernus Pharmaceuticals, Inc.; Teva Pharmaceuticals; Theranica; Trigemina, Inc.; Labrys Biologics; Medscape, LLC; Medtronic, Inc.; Neuralieve; NINDS

References

Headache Education for Clinicians and Patients

PO-02-111

Epidemiology differences between migraineurs followed by the (Curelator Headache™) who completed 3 months daily electronic follow up vs. drop-outs
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2Curelator Inc, Cambridge, United States

Objectives: Migraine is a very common condition with high prevalence throughout the world. An important issue of medical research is to obtain reliable data and adequate follow up. Data collection for headache research has been historically obtained by questionnaires utilizing retrospective data, which are not very reliable, given that data is not collected on real time and is prone to recall bias. Paper headache diaries, used clinically by physicians are also not completed daily and patients are prone to the same caveat when trying to report headache frequency and other factors during their office visit. Some attempts were made to develop and utilize electronic methods for recording data in a prospective way like the platform used here (Curelator Headache™), which requires users to enter data daily, irrespective of the presence of symptoms. Current technology utilizes smart phone as a personal data entry device and can function as a powerful tool to track headaches, however many patients end up losing interest and after a short period of time drop the use of these headache diaries. A platform that demands daily tracking of both risk factors and symptoms from users was used in this cohort, and sought to determine if there were differences between a group of individuals who completed a headache tracking period daily for at least 90 days and continued being tracked, and their counterparts who dropped out within 90 days.

Methods: The digital platform offered to headache patients in the present study (Curelator Headache™) was used to record profile demographic data, as well as real time daily collection of headache data including frequency, possible triggers, treatment and disability score (MIDAS) among other variables. Patients were followed daily for at least 90 days and those completing data collection at that time were defined “completers”, those who did not complete the 90 days data collection and stopped entering date were “non-completers”. Non-completers were further stratified in try-outs (<3 tracked days), early drop-outs (>3 and ≤30 tracked days) and late drop-outs (>30 and <90 tracked days). Demographics and headache data between groups were compared statistically utilizing t-test and Mann-Whitney tests for continuous variables and chi-square for categorical variables.

Results: 2678 individuals with migraine were registered with the platform, 88% were women. At 90 days, only 20.7% were still following the platform daily. There were differences between “completers” and “non-completers” for age (median), female (%) and employed (%). Differences were also found in mean pain level (median), caffeine (%) and visited ER (%). Table:

<table>
<thead>
<tr>
<th>Group</th>
<th>Completers</th>
<th>All Drop-outs</th>
<th>p-value</th>
<th>Try-outs</th>
<th>Early Drop-outs</th>
<th>Late Drop-outs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>41</td>
<td>34</td>
<td>&lt;0.0001*</td>
<td>34</td>
<td>35*</td>
<td>36.5*</td>
</tr>
<tr>
<td>Female (%)</td>
<td>90.5%</td>
<td>88.6%</td>
<td>0.06</td>
<td>87.0%</td>
<td>87.6%</td>
<td>90.5%</td>
</tr>
<tr>
<td>Employed (%)</td>
<td>36.9%</td>
<td>52.3%</td>
<td>&lt;0.0001*</td>
<td>49.4%</td>
<td>63.7%</td>
<td>60.5%</td>
</tr>
<tr>
<td>MIDAS Grade (mean)</td>
<td>3.52</td>
<td>3.48</td>
<td>0.90</td>
<td>3.46</td>
<td>3.51</td>
<td>3.46</td>
</tr>
<tr>
<td>MIDAS Grade (median)</td>
<td>4.00</td>
<td>4.00</td>
<td>1.00</td>
<td>4.00</td>
<td>4.00</td>
<td>4.00</td>
</tr>
<tr>
<td>Mean pain Level (median)</td>
<td>6.08 (1.83)</td>
<td>6.69 (1.84)</td>
<td>&lt;0.0001*</td>
<td>6.78 (1.85)*</td>
<td>6.52 (1.76)*</td>
<td>6.32 (2.00)*</td>
</tr>
<tr>
<td>Caffeine (%)</td>
<td>88.8%</td>
<td>92.5%</td>
<td>0.012*</td>
<td>92.9%</td>
<td>92.4%</td>
<td>89.5%</td>
</tr>
<tr>
<td>Nicotine (%)</td>
<td>6.5%</td>
<td>13.5%</td>
<td>&lt;0.0001*</td>
<td>15.0%</td>
<td>10.3%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Visited ER (%)</td>
<td>10%</td>
<td>16%</td>
<td>0.003*</td>
<td>16%</td>
<td>15%</td>
<td>10%</td>
</tr>
</tbody>
</table>

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493 (18.4%) individuals reliably completed data entry, compared to 2185 drop-outs (1535 try outs, 702 early drop-outs and 304 late drop-outs). An additional 356 patients also enrolled and are ongoing data collection, but did not yet reach 90 days. Completers were older, less likely to be employed (36.9% vs 52.3%), had slight less severe pain, although they visited the ED less frequently (10% vs 16%), utilized less caffeine and smoked less cigarettes when compared to all non-completers (drop-outs). When comparing completers to late drop-outs, completers were older and less likely to be employed, but there was no difference in pain level, caffeine consumption, smoking and ED visits.

**Conclusion:** Our study identifies differences between patients completing daily electronic follow up compared to those who drop out utilizing a very demanding electronic platform (Curelator HeadacheTM). Being able to identify potential drop out participants has paramount public health impact in developing reliable future research and also to promote initiatives to retain these group of individuals.

**Disclosure of Interest:** J. Vieira: None Declared. G. Boucher Conflict with: Curelator Inc, P. Prieto Conflict with: Curelator Inc

**Headache Education for Clinicians and Patients**

**PO-02-112**

**Tyramine as a risk factor for migraine attacks: an exploration**

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**Objectives:** Since the initial study by Hanington in 1967 (1) which suggested an association between foods containing tyramine and migraine attacks, questions have been raised about the prevalence of this sensitivity in the migraine population (2). Adding to lack of clarity is that the tyramine content of food varies greatly depending on freshness and processing, not all foods containing tyramine are considered common migraine triggers and some foods have been incorrectly identified as containing tyramine (3). Hence despite much suspicion there is no agreement about whether tyramine is a migraine trigger. To explore this question we used a digital platform (Curelator HeadacheTM) to statistically compare daily intake of tyramine containing foods and occurrence of migraine attacks.

The objective of this study is to determine in individuals with migraine 1) how many suspect tyramine as a migraine trigger and 2) for how many an association of tyramine intake with attacks can be identified statistically.

**Methods:** Individuals with migraine registered to use Curelator Headache via website or the App Store (iOS only) and answered questions about personal suspected triggers, including tyramine, and their importance (1 = low; 10 = maximal). They then used Curelator Headache daily for 90 days, entering details about headaches and tracking factors that may affect migraine attack occurrence. After 90 days all factors were analyzed (univariate analysis - see Ref 4) and for each individual the association of tyramine intake with attacks was determined.

**Results:** Of 528 individuals with migraine, tyramine was suspected as a trigger by 240 (45.5%): it was mildly suspected (1–3) by 20.6%, moderately (4–6) by 18.2%; strongly (7–10) by 6.6%. Of those who suspected tyramine, 129 entered sufficient data and tyramine was shown to be associated with increased attack risk in 20 (15.5%), with decreased risk in 20 (15.5%) and no association was identified in 89 (69%). In the other 111 there was insufficient data for analysis, indicating either avoidance of tyramine or lack of reporting. There was no clear association between degree of suspicion of tyramine and the percentage of individuals in whom an association was identified.

Of 288 individuals who did NOT suspect tyramine as a trigger, 139 entered sufficient data for analysis and we found an association of increased risk in 14 (10.1%) and decreased risk in 13 (9.4%). In 149 there was not enough data for analysis - again indicating either avoidance of tyramine or lack of reporting.

**Conclusion:** Tyramine is widely suspected as a trigger but in only a small number of individuals was an association with attacks identified statistically. However intake of tyramine containing foods was reported infrequently by almost half of individuals making analysis for them impossible: this is possibly due to avoidance of such foods.


**References**

(2) Kohlenberg RJ. Headache 22:30–34, 1982
(3) McCabe-Sellers et al J Food Comp Analysis 2006;19:S58-S65

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PO-02-113

Characteristics of Migraine According to the Age: A Clinic-based Study in Korea

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Objectives: Past studies suggested that the profile of migraine changes over the life span, and migraine remits in majority. We aimed to investigate if the core characteristics of migraine differ according to the age at onset.

Methods: Using the consecutive headache registry, we identified patients who were diagnosed with migraine in Samsung Medical Center headache clinic from October 2015 to April 2016. Patients were grouped into three categories; group A, patients younger than 50 years; group B, patients 50 years old or older with headache began before 50 years; and group C, patients with new-onset headache after 50. Components of diagnostic criteria for migraine were assessed using International Classification of Headache Disorders, 3rd edition (ICHD-III), beta version and compared between the groups.

Results: Three-hundred twenty patients were included in this study (190 for group A, 77 for group B, and 53 for group C). There were no significant differences in unilateral, pulsatility, nausea and/or vomiting, and photophobia and phonophobia, and aura in three groups. Duration of attack and aggravation by routine physical activity were less typical in group C (85.3%, 81.8%, and 58.5% for group A, B, and C; both p < 0.001). Intensity of headache were less severe in group B and C, compared with group A (85.9%, 70.0%, and 51.9%, for group A, B, and C, p < 0.001). The proportions of chronic migraine and medication overuse headache were not different among the groups.

Conclusion: In this cross-sectional study using a large number of migraine subjects, clinical features of unilateral, pulsatility, nausea and/or vomiting, photophobia and phonophobia, and aura did not differ across the age at age of onset, serving as core features of migraine. Duration of attack and peripheral sensitization were less typical in late-onset migraine, while headache intensities decreased in older patients regardless of age of onset. These features may be helpful to easily identify migraine in patients older than 50 years presenting with new-onset headache.

Disclosure of Interest: None Declared

PO-02-114

Study of Headache after the Great East Japan Earthquake in Iwate coast area. (2) The change of migraine-related factor (2012 ~ 2015)

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2Department of Hygiene and Preventive Medicine, Iwate Medical University
3Iwate Medical University, Morioka, Japan

Objectives: To investigate related factors with migraine in the people lived in disaster area after the Great East Japan Earthquake.

Methods: We conducted medical inquiries concerning headaches every year from 2012 to 2015 headache-related factors among municipalities with the greatest earthquake-related damage in Iwate prefecture including Yamada Town, Rikuzentakata City and Heita District of Kamaishi City. We got replies from 5915 individuals in 2012, 5588 in 2013, 5286 in 2014, 5318 in 2015. We investigated prevalence of migraine and compared about age, gender, mental factors (stress, nervousness, sleep disorder, and K6 score), habit of alcohol and smoking, daily physical exercise, post-traumatic stress disorder (PTSD)–related factors caused by the earthquake and social network factors (having friends, thinking of helping and trust neighbors each other) between the group with and without migraine.

Results: The prevalence of subjects who had migraine declined gradually from 2012 to 2015 (p < 0.05). Migraineurs were younger (p < 0.001) and more frequent in women (p < 0.001). Migraine was related with stress (p < 0.001), nervousness (p < 0.001), high score of K6 (p < 0.001) and PTSD by he earthquake (physical symptoms) (p < 0.05) in every year; and were related with nocturnal awakening (p < 0.05) in 2012, 2013, 2014 (p < 0.05). Migraine wasn’t related with habit of smoking and exercise, but was related with drink habit in every year (p < 0.05). Proportion of subjects who trust neighbors were few in migraineurs in every year. Proportion of subjects who can help each other and have friends (p < 0.001) were few in migraineurs in 2013, 2014 (p < 0.001).

Conclusion: The present study revealed that prevalence of migraine in subjects suffered by the Great East Japan Earthquake declined gradually from 2012 to 2015. Migraine was related with mental factors, PTSD and social network.

Disclosure of Interest: None Declared
Headache Education for Clinicians and Patients

PO-02-115

Algorithms to improve identification of Idiopathic Intracranial Hypertension patients in the Swedish National Patient Registry

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2Centre for Pharmacoepidemiology, Department of Medicin, Solna, Karolinska Institutet
3Department of Clinical Neuroscience, Department of Neurology, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden

Objectives: Idiopathic intracranial hypertension (IIH) is a rare disorder mainly affecting young, obese females. By definition, the cause behind development of high intracranial pressure is unknown for IIH patients. Large scale studies are hard to conduct due to the rarity of IIH and because IIH is known to often be misdiagnosed, which has made assessment of risk factors difficult. The purpose of this study was to produce algorithms to better predict true IIH patients among those given an IIH diagnosis in the Swedish National Patient Register (NPR) to improve the validity of the IIH diagnosis in future register-based studies.

Methods: Individuals with a recorded IIH diagnosis between 2006 and 2013 in Stockholm County were identified using the NPR (ICD-10 code G93.2). Validation was done through medical record reviews, using the original modified Dandy Criteria. We randomized the patients into two groups, one group to produce the algorithm (algorithm group, n = 105) and one group for validation (test group, n = 102). We tested variables which it was possible to extract from registries (NPR and Prescription Register) and used forward stepwise logistic regression. The outcome was whether the diagnosis was correct or not. The model then provided a predicted probability of the diagnosis being correct for each patient.

Results: 207 patients were identified of which 135 had confirmed IIH. This gave a positive predictive value (PPV) of 65.2% (95% CI: 58.4–71.4). The variables most useful for correctly identifying patients were; age, having received the diagnosis code twice or more and treatment with acetazolamide. The algorithm which included information from NPR and Prescription Register could predict the diagnosis correctly 88.2% (95% CI: 80.3–93.3) of the time when testing on the test group. When we reapplied the algorithm on the group used to make the predicted probabilities the percent correctly identified was slightly lower. Using only NPR data the probability of correct prediction was again slightly lower (see Table 1).

Conclusion: We produced two algorithms that can with high accuracy predict whether an IIH diagnosis in the NPR is correct. This can be a useful tool when performing large registry based studies on patients with IIH given that some misclassification will inevitably affect the accuracy of such studies.

Disclosure of Interest: A. Sundholm: None Declared, S. Burkill: None Declared, S. Bahmanyar: None Declared, I. Nilsson Remahl Conflict with: Lectures and Advisory board for Allergan, Linde Healthcare

Abstract number: PO-02-115
Table: 1 Algorithm predicting correct or incorrect if patients have IIH disorder or have been given a wrong diagnosis code

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Test group n = 102</th>
<th>Algorithm group n = 105</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency: (95% CI)</td>
<td>Frequency: (95% CI)</td>
</tr>
<tr>
<td>Algorithm 1: Incorrect</td>
<td>12 (6.7–19.8)</td>
<td>21 (13.3–29.9)</td>
</tr>
<tr>
<td>Correct</td>
<td>90 (80.3–93.3)</td>
<td>84 (71.1–86.7)</td>
</tr>
<tr>
<td>Algorithm 2: Incorrect</td>
<td>15 (8.9–23.1)</td>
<td>21 (13.3–29.9)</td>
</tr>
<tr>
<td>Correct</td>
<td>87 (76.9–91.0)</td>
<td>84 (71.1–86.7)</td>
</tr>
</tbody>
</table>

Headache Education for Clinicians and Patients

PO-02-116

Perception of the effect of exercise in patients with migraine at a Headache Clinic in Argentina

Fiorella Martin Bertuzzi1,* and Eduardo D Doctorovich1

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Objectives: In International Headache Society classification (version III-beta) one of the migraine criteria is that physical activity may worsen headache. On the other hand, regular exercise is often recommended in migraine treatment. At the moment, there’s conflicting evidence about the effect of exercise in migraine treatment. We aim to describe patients’ perception of the effect of physical activity (PA) in their pain. Secondarily, we tried to

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find a relationship between type of migraine, age or sex in the effect of exercise in migraine.

Methods: This study was conducted at a specialist Headache Center in Buenos Aires, Argentina, between August 2016 and January 2016. The participants were asked to complete a 3 questions self-administered survey. Patients were asked how PA impacts in a mild-moderate or severe migraine headache (PA was defined as "climb up a floor of stairs" or "walking fast 200 meters") and wherever if they noted if regular exercise improves frequency, intensity or duration of migraine headaches. Additionally, age and sex were requested and patients were classified in three categories, migraine without aura (MWOA), migraine with aura (MWA) and chronic migraine (CM), for a trained neurologist, according the International Classification of Headache Disorders version 3 beta.

Results: Overall, we evaluated 115 participants: 85 with MWOA (73,9%), 10 MWA (8,7%) and 20 CM (17,4%). Mean age was 40,1 years (range 17–70 years) and 87,8% were females. Patients answers are resumed in tables 1 and 2. In the analysis by groups, there was no correlation between effect of PA and type of migraine, sex or age.

Conclusion: Diagnostic criteria of migraine includes an item of "aggravation by or causing avoidance of routine physical activity", but in clinical practices is not uncommon find patients without this classic characteristic. We find 55% of patients that report that mild to moderate headaches did not get worse, and even 16% getting better with PA. In our analysis, there were no differences in the effects of PA adjusted by type of migraine, age or sex. It is uncertain if the PA has a real effect on migraine treatment. In our experience over half of patients perceive that regular physical activity ameliorate their migraines.

Disclosure of Interest: None Declared

Headache Education for Clinicians and Patients

PO-02-117

Dopaminergic symptoms in migraine: a case series on 446 consecutive patients

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Objectives: Dopamine (DA) is considered to play a major role in migraine pathogenesis as suggested by clinical, genetic, biochemical and pharmacological evidence. The present study was designed to assess frequency and characteristics of DAergic pre-synaptic (yawning, somnolence, neck discomfort/stiffness) and post-synaptic (intense nausea, vomiting) symptoms in migraineurs during the different attack phases (prodromes, headache stage, postdromes), and to investigate whether migraineurs with DAergic symptoms represent a distinct migraine clinical phenotype.

Methods: We studied all patients affected by episodic and chronic migraine consecutively seen at our Headache and Pain Unit from 1 June to 31 December 2016. Following a careful physical and neurological examination, all patients were evaluated with face-to face interviews using a semi-structured questionnaire addressing three main issues: 1) life-style, behavioral and socio-demographic factors, including age, sex, civil status, occupation, body mass index, blood pressure, sport activity, use of coffee, alcohol, smoking, illicit drugs, sleep disturbances, menopause, contraceptive use; 2) comorbidities and concomitant medications; and 3) clinical migraine features.
encompassing family history, disease duration, site, quality and intensity of pain, attack duration and frequency, presence, type and duration of aura, prodromes, accompanying symptoms, postdromes, DAergic symptoms, allodynia, unilateral cranial parasympathetic symptoms, triggers and alleviating factors, previous and current acute or preventive treatments, patients’ satisfaction with triptans. The presence of DAergic symptoms was determined by asking the following question: “During prodromes, headache stage or postdromes do you also have at least one of the following symptoms: yawning, somnolence, neck discomfort/stiffness, severe nausea or vomiting?”.

Results: We investigated 446 migraine patients (F/M: 348/98; migraine without aura: 269 pts; migraine with aura: 71 pts; chronic migraine: 142 pts; medication overuse headache, MOH: 114 pts). One-hundred-sixty-three of 35 pts; chronic migraine: 142 pts; medication overuse headache, MOH: 114 pts). One-hundred-sixty-three of 35 pts; chronic migraine: 142 pts; medication overuse headache, MOH: 114 pts). Seventy out of 163 DA+ patients (42.9%) had at least one symptom, 21 (12.9%) 2 symptoms and 98 (60.1%) ≥3 symptoms. Seventy out of 163 DA+ patients (42.9%) had both pre- and post-synaptic DAergic symptoms during the attack: the most frequent was yawning (94 pts, 57.7%) followed by somnolence (79 pts, 48.4%), severe nausea (71 pts, 43.6%), neck discomfort/stiffness (58 pts, 35.6%) and vomiting (40 pts, 24.5%). DAergic symptoms occurred during prodromes in 14.7% patients, headache stage in 74.3% and postdromes in 11.1%. DA+ patients had longer attack duration (p < 0.0052), more severe pain intensity (p = 0.0335) and more frequent osmophobia (p < 0.0001) than general migraine population, showing a positive trend for allodynia (p = 0.0576) and comorbidities (p = 0.0639). Migraineurs with and without DAergic symptoms did not differ for other migraine clinical variables.

Conclusion: This study, the first specifically aimed at identifying DAergic symptoms in migraine, reveals that more than 1/3 or migraineurs afferents to a headache center has DAergic symptoms (usually ≥3) during the different migraine attack phases. DAergic symptoms are usually presynaptic (yawning and somnolence being the most frequent) and occur mainly during the headache stage. Migraine attacks are longer, more severe and more frequently associate with osmophobia in DA+ patients than general migraine population.

Disclosure of Interest: None Declared

Headache Education for Clinicians and Patients

PO-02-118

Quality indicators in headache care: an implementation study in six Italian specialist-care centres

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Objectives: Headache disorders are highly prevalent, and have a substantial and negative impact on health worldwide. They are largely treatable, but differences in structure, objectives, organization and delivery affect the quality of headache care. In order to recognize and remedy deficiencies in care, the Global Campaign against Headache, in collaboration with the European Headache Federation, recently developed a set of quality indicators for headache services. These require further assessment to demonstrate fitness for purpose. This is their first implementation to evaluate quality in headache care as a multicentre national study.

Methods: Between September and December 2016, we applied the quality indicators in six Italian specialist headache centres (Bologna, Firenze, Modena, Padova, Roma Campus Bio-Medico and Roma Sapienza). We used five previously developed assessment instruments, translated into Italian according to Lifting The Burden’s translation protocol for hybrid documents. We took data by questionnaire and from the medical records of 360 consecutive patients (60 per centre), and by questionnaire from their health-care providers (HCPs), including physicians, nurses and psychologists.

Results: The findings, comparable between centres, confirmed the feasibility and practicability of using the quality indicators in Italian specialist headache centres. The questionnaires were easily understood by HCPs and patients, and were not unduly time-consuming. Diagnoses were almost all (>97%) according to ICHD criteria, and routinely (100%) reviewed during follow-up. Diagnostic diaries
were regularly used by 96% of physicians. Referral pathways from primary to specialist care existed in five of the six clinics, as did urgent referral pathways. Instruments to assess disability and quality of life were not used regularly, a deficiency that needs to be addressed.

**Conclusion:** This Italy-wide survey confirmed in six specialist centres that the headache service quality indicators are fit for purpose. By establishing majority practice, identifying commonalities and detecting deficits as a guide to quality improvement, the quality indicators may be used to set benchmarks for quality assessment. The next step is extend use and evaluation of the indicators into non-specialist care.

**Disclosure of Interest:** None Declared

**Headache Education for Clinicians and Patients**

**PO-02-119**

**Visual Sensitivity and Cutaneous Allodynia in Migraine**

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2Tergooi Ziekenhuis, Hilversum, Netherlands

**Objectives:** Migraine patients report visual sensitivity and cutaneous allodynia, during and in-between attacks. Allodynia is believed to be caused by central sensitisation, the process assumed to underlie the transformation from episodic to chronic migraine and likely causing enhanced cortical excitability. Increased visual sensitivity is thought to be caused by cortical hyperexcitability and may thus also result from central sensitization. We expected these phenomena of altered sensory processing to be correlated in migraine patients. Furthermore, we hypothesised a correlation between the number of migraine headache days and visual sensitivity and cutaneous allodynia.

**Methods:** Patients with episodic (N = 19) or chronic (N = 18) migraine who were screened for a clinical trial with prophylactic migraine treatment recorded the number of migraine headache days over 4 weeks using a headache diary. Ictal and interictal visual sensitivity and ictal cutaneous allodynia during the same timespan were recorded using the Leiden Visual Sensitivity Scale (L-VISS; range 0–36 points) and a questionnaire on allodynia (range 0–12 points), respectively. Spearman’s correlation coefficients between these parameters were calculated.

**Results:** Mean number of migraine headache days was 9.8 days (SD 4.3), the median ictal and interictal L-VISS scores were 18.0 (interquartile range 9.5) and 7.0 (interquartile range 9.5), respectively, and the median allodynia score was 3.0 (interquartile range 5.0). The number of migraine headache days correlated with ictal (R = 0.566, p < 0.001) and interictal (R = 0.397, p = 0.015) L-VISS score, but did not correlate with allodynia (R = 0.138, p = 0.415). Allodynia did however show a correlation with ictal (R = 0.514, p = 0.001) and interictal (R = 0.531, p = 0.001) L-VISS score.

**Conclusion:** We found an association between visual sensitivity and cutaneous allodynia in episodic and chronic migraine patients. In our cohort, ictal and interictal visual sensitivity but not ictal cutaneous allodynia were correlated with the number of migraine headache days. There appears to be a complex interaction between central sensitization, sensory processing and number of migraine headache days.

**Disclosure of Interest:** None Declared

**Headache Education for Clinicians and Patients**

**PO-02-120**

**Establishment of an italian chronic migraine database: a multicenter pilot study**

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5National Institute of Health, Rome, Italy

**Objectives:** To optimize chronic migraine (CM) ascertainment, provide specific clinical management and healthcare procedures, and rationalize economic resources allocation, we performed an exploratory multicenter pilot study coordinated by the Italian National Institute of Health, aimed to establish an Italian CM database, the first step for a future Italian CM registry.

**Methods:** We enrolled all consecutive patients affected by CM referred to 4 Italian headache centers. Using face-to-face interviews, detailed information were gathered on life-style, behavioral and socio-demographic factors, comorbidities and concomitant medications, migraine features before and after chronicization and healthcare resource use.

**Results:** We enrolled 63 patients affected by CM (F/M = 51/12; 47.4 ± 14.6 yrs). Previous episodic migraine started at the age of 15.2 ± 6.6 yrs, had a frequency of

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5.6 ± 5.4 days/month, and evolved into CM at the age of 36.6 ± 14.1 yrs. Chronicization factors included affective disorders (19%), stressful events (9.5%), menopause (4.8%), cancer (3.2%) and others (3.2%). Most frequent comorbidities were insomnia (30.2%), depression (22.2%), anxiety (17.5%), endocrine disorders (17.5%), hypertension (12.7%), dyslipidemia (11.1%) and previous head/cervical trauma (9.5%). Mean CM attack frequency was 23.6 ± 5.4 days/month. Migraine episodes were severe (60.3%), very disabling (92%), associated with photo- and phonophobia (84.1%), osmophobia (54%), allodynia (50.7%), nausea (73%) and vomiting (31.7%). CM patients used triptans (73%), NSAIDs (50.8%) and analgesic combinations (30.2%) as acute treatment. Most patients (58.5%) overused analgesics: triptans (33.2%), NSAIDs (11.1%), analgesic combinations (6.3 %), NSAIDs + triptans (4.7%), triptans + analgesic combinations (3.1%). Patients with CM had used on average 2 prophylaxis among anticonvulsants (66.7%), amitriptyline (50.8%), botulinum toxin (41.3%), beta-blockers (39.7%), calcium-antagonists (36.5%), acupuncture (20.6%), antiserotonin drugs (12.7%) and nutraceuticals (6.3%). Migraine treatments had been prescribed by GP in 50.8% of cases, headache specialists in 47.6% and other specialists in 19%. Self-medication had occurred in 41.2% of patients. Diagnostic procedures had been requested by headache specialists in 52.4% of cases, GPs in 49.2%, other specialists in 28.6%, or had been performed by patients themselves (19.04%): 57.1% had undergone brain MRI, 38% brain CT-scan, 26.9% EEG, 19% cervical MRI, 7.9% cervical spine or temporomandibular joint x-rays. 27% of patients had been hospitalized for CM, 9.5% admitted to DH, and 36.5% to ED. 11% of patients got illness benefit exemption or disability allowance. Univariate analysis revealed that patients affected by more severe CM (≥ 21 headache days/month) had more frequently MO (p = 0.01) and MO positive family history (p = 0.01), insomnia (p = 0.05), ipsilateral lacrimation during the attacks (p = 0.03) and had used more frequently topiramate (p = 0.05), valproate (p = 0.01) and antiserotonin drugs (p = 0.05) than those with mild CM. When considering monthly migraine days as independent variable, regression analysis showed that patients with severe CM had higher alcohol intake (p = 0.033), more frequent insomnia (p = 0.017) and analgesic overuse (p = 0.018) than those with mild CM.

**Conclusion:** This multicenter pilot Italian study on CM identifies areas with inadequate health care provision, indicates the need for rationalizing healthcare strategies and resource use and prompts for the establishment of an Italian CM registry.

**Disclosure of Interest:** None Declared

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**Headache Education for Clinicians and Patients**

**PO-02-121**

**Follow-up study of 12–18 years on subtypes of headache in a population of children below 6 years old: preliminary results**

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**Objectives:** Headache is a common problem in childhood; up to 25% of school children suffer from chronic recurrent headache but the diagnosis of early onset headache disorders can be delayed due to the non specific nature of symptoms. Studies about primary prescholar headaches are rare. As well as, in this paediatric population, there are only few follow-up studies. Aim of this study is to analyze the follow-up of a pediatric cephalalgic population below 6 years old, previously studied in depth.

**Methods:** We contacted a population of children admitted in our headache center, between 1997 and 2003, when they were below 6 years old. We evaluated the evolution over time of headache's subtypes and using a 12–18 years-long follow-up study, we tried to identify a possible predictor throughout the duration of follow-up. We administered a semi-structured questionnaire by phone interview from November 2015. Children with secondary headaches have been excluded

**Results:** We found 96 children's medical records. To date, only 22/96 (22,9%) patients responded to the semi-structured interview. The actual mean age is 17 years old (range 22–14 years old). There were 12 males (54,54%) and 10 females (45,45%). We found 14 cases with of migraine, 2 patients with primary stabbing headache and 6 cases with more than one headache's subtype. As preliminary result, we found that 4 of 22 (18,1%) patients without headache and 13 patients of 14 (92,8%) that still have migraine. 10/14 (71,4%) of migraineurs exhibited cranial autonomic symptoms

**Conclusion:** Description of the evolution of headache from childhood to adulthood has been a focus of interest for several authors; there is still a paucity of literature data on the evolution and prognosis of headache starting in childhood. From the preliminary result obtained in our study we found that of 14 patients with migraine interviewed, 92% today still suffers from migraines and 71% of these complains autonomic symptoms. This finding shows that prescholar migraineurs after a follow-up of
several years, still complain migrainous attacks and they present a significant cranial parasympathetic involvement.

Disclosure of Interest: None Declared

Headache Education for Clinicians and Patients

PO-02-122

Classification of cases with a diagnosis of acute headache, to emergency division in Regional Hospital Durres, Albania

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Objectives: Symptoms of headache that is relatively frequent to emergency care and assessment and differentiation of these cases are done by gravity pain and neurological signs that had accompanying. Evaluation of cases made with CT, MRI and EEG according to the evaluation of neurologist doctor. Often headache are considered a contingency of "small" in relation to major emergencies presented in the service of emergency. About 1–2% of the cases presented with acute headache have a life threatening Diagnose.

Methods: To demonstrate how often a strong acute headache may mask a serious pathology we have seen in our study cases presented with a diagnosis of the above in the period November 2014-December 2015, in the emergency care, in Regional Hospital Durres. In total where 70000 cases gone in emergency(al categories). With the diagnosis of cefalese were 3674 patients (5.2% of cases), of which 2612 cases (71%) were women, and 1062 (29%) males. From cases with headache 2645 patients (72%) had not accompanying with neurological deficits and were considered and treated as primary headache and were later flown home. In the case of the symptoms associated cefalea n = 1029 (28%) presented symptoms as ataxia, nystagmus, meningitis, visual disturbance, coifusional state, convulsions, etc.). Of these 116 cases with associated symptoms (11.2%), or =3.1% of total cases with cefalea resulted in serious pathology. Of these, 24 patients (20.6% of 116) were diagnosed bleeding subarachnoid, 6 cases (3.4%) intraparenchymal hemorrhage, 11 (9.4%) subdural hematoma 39 (33.6%) cerebral ischemia, 12 (10.3%) neuroinfection, 12 (11.2%) primary cerebral neoplasia, 5 cases with brain defects (4.3%), 1 case with carotid artery dissection (0.8%), 5 cases arachnoidal cyst (4 3%), 1 case with hydrocephalia (0.8%). All cases were examined with CT and MRI of the head. Examinations made for other accompanied symptoms headache, had excluded cerebral serious problems.

Results: In the case of the symptoms associated cefalea n = 1029 (28% of all cases with headache), 116 of these (11.2%), or =3.1% of total cases with headache resulted in serious pathology. Examinations made for other accompanied symptoms headache, had excluded cerebral serious problems. n = 913 (88.8%)

Conclusion: These data show the importance of careful assessment of the cases presented with a diagnosis of acute headache in emergency service and the evaluation of each case suspicious of examinations appropriate to have the correct diagnosis, this and in collaboration with specialists other.

Disclosure of Interest: None Declared

Headache Education for Clinicians and Patients

PO-02-123

Clinical profile of headache in a Displaced Population: A Case series of 26 patients in a public hospital of Bogota, Colombia

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Objectives: Background: Headache is a common complaint of patients presenting to the clinical practice. According to a study by Colombia’s National Centre for Historical Memory, more than five million civilians were forced from their homes between 1985 – 2012, generating the world’s second largest population of internally displaced persons.

Aim: Analyze and classify the clinical features of headache in a displaced population in a public hospital of Bogota-Colombia

Methods: We conducted an observational, descriptive, and cross-sectional study from July to December of 2016. The data for all patients were prospectively registered. Diagnosis of headache was according to the International classification of headache disorders, 3th edition (ICHD-3 Beta).

Results: Twenty-six (9.7%) out of 277 patients with headache in our headache unit, were victims of forced displacement. Ninety-six percent were women with mean age of 48.7 years (SD = 16). The mean time prior to consult was 1.4 years and 69.2% of them meet the criteria for chronic daily headache (CDH). Among patients with CDH, 70.6% (n=12) complain about phonophobia (p = 0.06), but there was no difference in other symptoms. 73% patients were classified as having primary headache being Chronic migraine the most frequent diagnosis (42.3% for migrainous attacks and they present a significant cranial parasympathetic involvement.

Disclosure of Interest: None Declared

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Pain tend to intensify with stress (58.3 %); 33.3 (n:8) has medication overuse and 45% (n:10) complain about sleep disorders. In the group of secondary headache de most frequent diagnosis was posttraumatic headache.

**Conclusion:** In a displaced population, headache is a common cause of consultation and apparently, are more frequent the primary headaches as in the general population. In this population, the semiological profile is characterized by women with chronic daily headache, with phonophobia, medical overuse and sleep disorders. Phonophobia and posttraumatic headache may be related with armed conflict.

**Key Words:** Headache, displaced population, chronic daily headache, phonophobia.

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**Disclosure of Interest:** None Declared

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**Headache Education for Clinicians and Patients**

**PO-02-124**

A Retrospective Analysis of Emergency Department Visits and Revisits for Migraine in New York City

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**Objectives:** Headache is the fifth most common cause of emergency department (ED) visits; however, prior research demonstrates suboptimal care of headache patients in the ED. ED revisit rates are considered one marker of ED quality of care. We sought to examine (1) the number of revisits to the emergency department (ED), (2) the timeframe of revisits to the ED, and (3) whether poverty was associated with migraine ED revisits.

**Methods:** We conducted a retrospective analysis of patients with a diagnosis of migraine in 18 NYC EDs from 1/1/2015–6/30/2015. The primary outcome was headache revisit within 6 months. A secondary outcome was patient poverty status. Descriptive analyses were conducted.

**Results:** 402,705 patients visited the EDs during this time period with any discharge diagnosis. 33.2% (133,744/402,705) had one revisit and 24.1% (96,811/402,705) revisited twice or more. Within our nested migraine cohort, there were 1052 migraine discharge diagnoses (80.8% female). 26.3% (277/1052) of migraine discharge diagnosis patients had one revisit and 12.5% (131/1052) had two or more revisits. 92.3% (971/1052) of the patients were below the federal poverty line, and 53.1% were in the high or very high poverty group.

**Conclusion:** ED revisit rates for migraine discharge diagnoses were lower than the ED revisit rate for the overall discharge diagnosis for any disorder but the absolute numbers are still considerable. Over half of the patients who visited the 18 EDs in New York City are considered to be at a high or very high level of poverty based on the Federal Poverty Line.

**Disclosure of Interest:** None Declared

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**Prevalence and clinical characteristics of headache in general medicine and dental students in Kyrgyz State Medical Academy and International University of Kyrgyzstan**

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**Objectives:** To determine prevalence and characteristics of all types of headache in students of 2nd, 3rd and 4th years of medical universities Kyrgyz State Medical Academy (KSMA) and International University of Kyrgyzstan, International School of Medicine (IUK, ISM) in Kyrgyzstan.

**Methods:** A questionnaire was administered to randomly selected students of general medicine and dental faculty, which included index HIT6, VAS, index HALT, Zung depression scale. Diagnoses were assigned according to the criteria of the International Headache Society.

**Results:** 768 students participated in our study with mean age 21 ±3.2 years, and 77% responded positively about headache, 49% males and 51% females. Among 592 students with headache, 56.7% had tension headache (TH) with pericranial muscles tensions, 11.6% TH without pericranial muscles tensions, 23.8% had autonomic cephalgias, 7.2% had migraine. TH localized in frontal zone in 81% of students. Female students with migraine had menstrually related attacks more frequently than students with non-migraine headache (78.1% versus 19.5%). Women students suffered from migraine-types of headache twice more than men (p=0.001). Significant headache risk-factors were loud noise OR 4 (95%CI 2.1–3.18), lack of sleep OR 8 (95%CI 4.2–9.1), staying in suffocated room OR 7 (95%CI 5.6–8.9), staying in a crowded place OR 5 (95% CI 3.2–6.2). Protective methods were massage OR 0.6 (95% CI 0.51–0.9), warm shower OR 0.8 (95% CI 0.61–0.82). 78% of students did not link use of alcohol with headache.
manifestation \( (p = 0.01) \), but the positive connection was found in starting of headache after 4th class (after 5 h of studying), \( p = 0.0001 \). We found positive correlation between long-term depression and headache \( (p = 0.001) \). KSMA students displayed more expressed and frequent headache in both genders than students of IUK ISM \( (p = 0.01) \). 38% of students do not use treatment. Among treatment students tend to use non-steroid anti inflammatory pills (68%).

**Conclusion:** Tension headache is prevalent in students of medical universities in both genders in Kyrgyzstan, it connects with long-term depression and more than 5 h of studying. We educated 238 students with headache post isometric relaxation techniques for pain relieving.

**Disclosure of Interest:** None Declared

**Headache Education for Clinicians and Patients**

**PO-02-126**

**Burden of Chronic Migraine in Tertiary Headache Outpatient Clinics: Experience of 10 years a Multicenter Study**

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**Objectives:** The burden of headache is a major public health problem worldwide. Headache, more specifically chronic headache, is associated with direct and indirect costs and negatively affects on quality of life. International Classification of Headache Disorders (ICHD) diagnostic criteria had provided marked awareness about headache since firstly published. Classification schemes not only provide accurate diagnosis of headache subtype, but also comprehensively classified syndromes. This standardization facilitated multicenter-studies globally last decade and shed light on understanding of pathophysiology of headache. Population based studies report globally 45–50% of adult population have active headache, nearly 10% for migraine, %30–35 for tension type headache and 3% for chronic headache. However, distribution for tertiary headache centers expected to be different from many aspects.

In this large study we stated 10 years’ experience of three tertiary headache centers. We analyzed patient data retrospectively and re-classified subjects according to ICHD-3 beta. We aimed (1) to reveal distribution of primary and secondary headache, (2) to classify primary headache, (3) to state frequency of chronic headache according to ICHD-3 beta.

**Methods:** This study is conducted a part of ongoing Turkish Headache Database Study recording and analyzing headache syndromes according to ICHD standards at tertiary headache centers in Turkish population. Electronic database examined retrospectively for 2007–2017 years and 28546 enrolled patients’ data included to survey. The accurate diagnosis re-evaluated according to ICHD 3 beta by headache-experienced neurologists. To avoid mistakes, we excluded all patients whom have insufficient data or could not be diagnosed accurately.

**Results:** Study group consisted 8711 patients, 6954 women and 1674 men (80.6% and 19.4%). Mean age was 38.2 ± 14.2 years. The primary headache disorders covered 6959 patients (79,89%) and 1752 patients diagnosed secondary headache syndromes (%20,11). Secondary headache patients were significantly older, male/female ratio were significantly higher than primary headache patients \( (p < 0,001) \). Headache onset (months) were significantly longer at primary headache disorders (48 months & 24 months), \( (p < 0,001) \). Three thousand-six hundred and seventy four patients have migraine (42,18%), 3163 patients have tension type headache (36,1%), 90 patients have trigeminal autonomic cephalalgias (1,03%). Other primary headache syndromes observed rarely. Chronic migraine diagnosed 8,9% of study group, covered 775 patients (24,5% of migraine patients), when we added migraine plus medication overuse headache patients to chronic migraineurs (112 patients, 1,22%), chronic migraine frequency reached 28% of migraine patients and 10,2% of study group.

**Conclusion:** This study exposes that Chronic Migraine is more prevalent in Tertiary Headache centers and reached up to 10% of all patients. This high prevalence demonstrates urgent need to new arrangements for diagnosis and treatment schemes. Population-based studies report tension type headache is the most common headache syndrome, contrarily in this study the most frequent headache disorder was migraine.

**Disclosure of Interest:** None Declared
Elevation of apolipoprotein E during migraine attacks
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Objectives: Our previous proteomics analysis revealed that the serum apolipoprotein E (Apo E) protein level during migraine attacks was significantly higher than the preictal level. In this study, we aim to compare the serum level of Apo E protein in migraineurs during attack and attack-free period with that of control subjects.

Methods: All patients were carefully interviewed and examined, and diagnosis was made using the ICHD-3 beta. Sera were prepared from peripheral blood samples obtained from 4 migraine with aura patients (MA) and 8 migraine without aura (MO), 5 tension type headache (TTH), and 3 healthy controls. We performed Western blot analysis for Apo E and α-fodrin, the latter of which we previously reported as a possible migraine biomarker using an RNA microarray method.

Results: The protein levels of Apo E and α-fodrin tend to be higher than those of controls (TTH patients and healthy controls). Notably, the level of α-fodrin protein in the patients with MA during attack free-period was only significantly higher than controls and other types of headache patients.

Conclusion: These findings suggest that migraine attacks alter serum ApoE level. Moreover, Apo E may serve as a biomarker of migraine that is useful in differential diagnosis of headache disorders.

Disclosure of Interest: None Declared

5-HT2B-induced calcium increase and ERK phosphorylation in primary cells with relevance to a migraine mouse model
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Objectives: Recent research showed that the 5-HT2B receptor may play a crucial role in the pathophysiology of migraine. These findings are emphasized by clinical studies demonstrating, that mCPP (meta-chlorophenylpiperazine), a partial 5-HT2B receptor agonist, led to a migraine-like headache in migraine patients. We have established a chronic migraine model, in which hypoxic treatment sensitizes mice towards a migraine-like status in which mCPP can induce PPE (plasma_protein_extravasation) in the murine dura mater. This readout serves as an indicator for a sterile neurogenic inflammation of the dura mater in animal models.

Consequently, investigations of 5-HT2B receptor signalling pathways came into focus. Studies from heterologous cell systems provided some evidence that its activation may lead to ERK (extracellular-signal regulated kinase) phosphorylation and calcium release via IP3, but the latter was in contrast to the few results from experiments with endogenously expressing cells like pulmonary artery endothelial cells (ECs). To investigate this further, primary cell cultures of murine lung and dural ECs were established.

Methods: Calcium-imaging, western blotting (pERK/ERK), immunocytochemistry (pERK), single-cell PCR and primary murine endothelial cell culture.

Results: Activation of the 5-HT2B receptor on murine pulmonary EC triggered ERK phosphorylation and elevation of cytoplasmic calcium in the analysed cell population. Single-cell analysis revealed mRNA expression of the 5-HT2B receptor in pulmonary and dural primary ECs.

Conclusion: Effects of 5-HT2B receptor activation on murine ECs may comprise cell proliferation and increased transcription, which may lead to dural vascularisation in the animal. An altered vascular system in the murine dura mater may contribute to the migraine-like status in the hypoxic mouse model.

Disclosure of Interest: None Declared

Both anti-CGRP and anti-CALCRL antibodies suppress cortical spreading depression
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Objectives: Cortical Spreading Depression (CSD), is a transient propagating synaptic excitation followed by depression, which is regarded as an important pathophysiological basis of migraine. Both calcitonin-gene related peptide (CGRP) and CALCRL-containing receptor
are the known targets for migraine prophylaxis; however, their mechanism action in migraine is not fully understood. This study aimed to explore if CGRP and CGRP receptor could regulate cortex susceptibility to CSD in rodents.

**Methods:** CSD was induced by K\(^+\)-medium. Intrinsic optical imaging was used for CSD recording in the mouse brain slice and electrophysiology for CSD recording in the rat.

**Results:** The results show that functional inhibition of CGRP by an anti-CGRP antibody markedly prolonged the CSD latency in the mouse brain slice; this inhibition was not observed when the antibody was co-incubated with exogenous CGRP. Corresponding to this, an anti-CALCRL antibody also prolonged the CSD latency in the mouse brain slice. Consistently, prolongation of CSD latency was also observed after pretreatment of the anti-CALCRL antibody perfused into the intracerebroventricle of rats in addition to a significant reduction of CSD number and propagation rate.

**Conclusion:** This data demonstrates that functional inhibition of both CGRP and CALCRL-containing receptors suppress cortex susceptibility to CSD, indicating their key role in central mechanism of migraine.

**Disclosure of Interest:** None Declared
PO-02-131

Facial TRPM8 stimulation ameliorates thermal hyperalgesia in a mouse migraine model

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Objectives: Transient receptor potential cation channel melastatin 8 (TRPM8), a nonselective cation channel that mediates cool perception, is expressed in trigeminal ganglion (TG) neurons. Genome-wide association studies reproducibly identified TRPM8 as a candidate susceptibility gene for migraine. In the present study, we aimed to investigate the role of TRPM8 in migraine pathophysiology.

Methods: We produced a migraine model by dural inflammatory soup (IS: 1 mM each of histamine, serotonin, and bradykinin, and 0.1 mM prostaglandin E2 in 10 mM HEPES buffer, pH 5.5) administration in wild-type C57BL/6 and TRPM8 knockout (KO) mice. Sham-operated animals without IS administration were used as controls. Temporal profiles of facial heat pain threshold temperature were recorded using a peltier device-based apparatus with its surface temperature regulated by a computer. After baseline measurement, mice were subjected to 5 minute-long topical application of icilin solution (10 μM) or DMSO to the face prior to every threshold temperature determination. Measurement was carried out at 6 hours, 1 day, 2 days, and 6 days after IS administration or sham operation. A histological study using retrograde tracers (Fluorogold and DiI for the dura and face, respectively) was also performed to identify TG neurons innervating these regions. Furthermore, immunostaining for transient receptor potential cation channel vanilloid 1 (TRPV1), a marker for nociceptive neurons, was conducted. All numerical data were expressed as mean ± SD.

Results: In wild-type mice, the threshold temperature for heat pain was gradually reduced, reaching a nadir on Day 2 post-IS treatment (41.3 ± 1.9°C vs. 43.6 ± 1.0°C at the baseline, N = 30 each, P < 0.001, ANOVA with a Bonferroni correction). The IS-induced thermal hyperalgesia was abrogated by pretreatment with icilin in wild-type mice. Such an inhibitory effect of icilin was not observed in TRPM8 KO mice. In sham-operated mice, there were no significant changes in threshold temperature. Our tracer study revealed that 14.3 ± 10.8% of all TG neurons (N = 3015 from 12 animals) were labelled with Fluorogold, indicating that these neurons innervated the dura. Furthermore, 60.0 ± 28.8% of these TG neurons were found to send collaterals to the face as well. Of these TG neurons innervating both the dura and face, 46.1 ± 34.9% were positive for TRPV1.

Conclusion: TRPM8 activation is capable of correcting trigeminal nociceptive hyperactivity due to migraine-associated meningeal inflammation. Therapeutic interventions to the face seem to be an effective measure for modifying dural nociceptive neuronal activity. Taken together, TRPM8 activation in the facial region is likely to be a promising therapeutic strategy for migraine.

Disclosure of Interest: None Declared

Headache Pathophysiology - Basic Science

PO-02-132

Persistent Naproxen sodium treatment dose not induce mechanical allodynia in mice

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Objectives: Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for migraine treatment. The excessive intake of acute migraine therapy may lead to disease chronification and progression to medication overuse headache (MOH). NSAIDs have been proposed to be a risk factor for MOH in patients having high baseline migraine frequency. However, the study of prolonged NSAID induced MOH in animal models has not been fully established. To examine the effect of a long-acting NSAID on the progression of MOH-like phenotype in mice, we aimed to explore alterations in mechanosensitivity resulting from repeated exposure to naproxen sodium.

Methods: Male and female C57BL/6J mice (N = 36) were injected intraperitoneally with naproxen sodium (100 mg/kg), sumatriptan (0.6 mg/kg) or saline control daily for 15 or 11 days, respectively, followed by a recovery period. Hind paw mechanical withdrawal thresholds were measured every second day using von Frey filaments. On the testing day, mice were acclimatized in the apparatus for 1 hour, followed by the application of filaments perpendicularly to the plantar surface of the hind paw for 3 seconds. Positive response was defined as lifting or flicking of the paw after stimulation, commencing with the 0.6 g filament and following the “up and down” method. To evaluate the mechanical threshold, the pattern of filaments was calculated using the Claplan analysis method. All behavioral testing occurred in light conditions between 09:00 and 12:00 to avoid circadian variations.

Results: We first demonstrated that repeated exposure to sumatriptan induced a latent sensitization of hind paw mechanical withdrawal thresholds ($F_{(1,140)} = 11.92$, $p < 0.001$).
P ≤ 0.001) in agreement with published data. However; there was no significant difference in mechanical withdrawal thresholds in response to sustained administration of naproxen sodium when compared to control mice (F(1, 21) = 1.39, P = 0.252).

**Conclusion:** Repeated exposure to daily naproxen for 15 days does not induce mechanical hypersensitivity in mice. This long acting NSIAD may represent an alternative therapeutic agent for those at risk of MOH or undergoing withdrawal.

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**Disclosure of Interest:** None Declared

**Headache Pathophysiology - Basic Science**

**PO-02-133**

**The α6 subunit-containing GABAA receptors: A novel target for migraine treatment**

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**Objectives:** The α6 subunit-containing GABA_A receptors (α6GABA_ARs) are expressed in both neurons and satellite glia of the trigeminal ganglia (TG) in addition to cerebellar granular cells. The α6GABA_A-R-positive neuronal cell bodies in the TG project axons to the temporomandibular joint as well as to the trigeminal nucleus caudalis and upper cervical region (Vc–C1), which form the trigeminal cervical complex (TCC). Previous studies, including ours, have shown that activation of the TCC plays an important role in the pathogenesis of migraine. However, the pathophysiological role of α6GABA_ARs in migraine remains unclear. Recently, a pyrazoloquinolinone Compound 6 was identified to be a positive allosteric modulator (PAM) highly selective to α6GABA_ARs. We examined its effect on a migraine model induced by intra-cisternal injection (i.c.) of capsaicin to elucidate the role of α6GABA_ARs in the pathogenesis of migraine. Besides, two α6GABA_A-R PAMs, Ro15–4513 and loreclezole, were used as positive controls of Compound 6, and diazepam, an α6GABA_A-R-insensitive benzodiazepine, was used as negative control.

**Methods:** The migraine model induced by intra-cisternal (i.c.) capsaicin in Wistar rats (250–300 g) was used. The rat was pretreated with the drug or vehicle by intraperitoneal injection (i.p.) 30 min before being stimulated by i.c. instillation of capsaicin (10 nmol, 100 µl). Two hours after capsicain instillation, the dura mater, TG and TCC in rats were dissected for immunohistochemical measurements. The neuronal number with positive immunoreactivity (ir) of c-Fos, an activated neuron marker, in the TCC was quantified by the formulas established in our previous study, representing the central end response of the trigeminovascular system (TGV). In the periphery, the immunoreactivity of calcitonin gene-related peptide (CGRP-ir) was measured by immunohistochemistry and immunofluorescence in the dura mater and TG, respectively.

**Results:** Capsaicin i.c. instillation significantly increased the c-Fos-ir neuronal number in the TCC, increased the CGRP-ir in the TG, and depleted the CGRP-ir in the dura mater. Compound 6, at 3 and 10 mg/kg (i.p.), but not 1 mg/kg, significantly attenuated the elevation in the number of c-Fos-containing TCC neurons and CGRP-ir of TG as well as reversed CGRP depletion in the dura mater. Importantly, all the three effects of Compound 6 were mimicked by Ro15-4513 and loreclezole, two α6GABA_A-R PAMs, but not by diazepam, an α6GABA_A-R-insensitive benzodiazepine.

**Conclusion:** These results showed that α6GABA_A-R PAM can attenuate capsaicin-induced responses in both central and peripheral ends of the TGV, suggesting α6GABA_ARs play a role in the pathogenesis of migraine, and are novel and promising targets of migraine treatment. α6GABA_A-R PAMs, like Compound 6, may be potential novel antimigraine agents.

**Disclosure of Interest:** None Declared

**Headache Pathophysiology - Basic Science**

**PO-02-135**

**The CGRP receptor antagonist olcegepant modulates cortical spreading depression in vivo**

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Objectives: The neuropeptide calcitonin gene-related peptide (CGRP) plays a key role in migraine pathophysiology. CGRP is released during migraine attacks, and agents that inhibit CGRP signaling have demonstrated efficacy as migraine therapy. We examined the effects of the CGRP receptor antagonist olcegepant on the neural and vascular components of cortical spreading depression (CSD) in mice in vivo.

Methods: Neural and vascular responses to CSD in anesthetized mice were recorded using optical intrinsic signal (OIS) and local field potential recording techniques. The effects of systemically administered olcegepant (0.02 mg/kg IP) on spontaneous cortical bursting and accompanying vascular activity, and on single and repetitive CSD events were examined.

Results: Olcegepant did not have any significant effect on baseline spontaneous cortical bursting activity or accompanying vascular oscillations prior to CSD. Treatment with olcegepant significantly reduced (by 35%) repetitive CSD frequency evoked by continuous KCl stimulation as compared with vehicle treated controls. Examination of single CSD events before and after administration of olcegepant in the same animal showed that olcegepant increased the initial vasoconstriction associated with the CSD wave, and prolonged the sustained vasoconstriction that occurred after the initial CSD wave.

Conclusion: These findings support a role for CGRP in CSD, including both its neural and vascular components.

Disclosure of Interest: None Declared

Headache Pathophysiology - Basic Science

PO-02-136

Distribution of CGRP and its receptor components CLR and RAMP1 in the rat retina

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Objectives: With CGRP and its growing role in migraine, it is vital to understand their roles in various parts of the retina since different visual phenomenon are found in migraine patients. This study aims to investigate the distribution of CGRP and its two receptor components in the rat retina.

Methods: Rat retinas were used and processed visually by immunohistochemistry and quantitatively with flow cytometry using antibodies against CGRP, CLR, or RAMP1.

Results: Immunohistochemistry showed that CGRP was mainly confined to ganglion cell layer, vessels in the inner-most part of the retina and to occasional cells within the inner nuclear layer, while CLR and RAMP1 co-expressed in the optic nerve and in the inner most layer of the retina, specifically the nerve fiber layer. Retinal vessels showed CLR and RAMP1 immunoactivity. Moreover, CLR expression dominated over RAMP1 and thereby revealing that CLR expression alone occurred. Double labelling with vimentin revealed co-expression between CGRP and vimentin, indicating that CGRP is expressed in Müller glial cells. No co-expression between vimentin and CLR or RAMP1 was found. Two-color flow cytometry showed that 13.6% of CLR-positive events were expressing RAMP1. Furthermore, 96.3% of RAMP1 positive events expressed CLR. These results suggest that almost all RAMP1 positive events expressed CLR.

Conclusion: The functional role of CGRP and its receptor is still unknown, but recent developments in antibody genetics and new antagonists may provide excellent tools to unravel this. However, our results indicate that CGRP is expressed in glial cells and the receptor elements in neurons. In addition, the localization of RAMP1/CLR immunoreactive cells gives a decent appreciation of functional CGRP receptors distribution in the rat retina.

Disclosure of Interest: None Declared

Headache Pathophysiology - Basic Science

PO-02-137

Trigeminal ganglia of familial hemiplegic migraine type 1 R192Q mutant mice express markers of the M1 macrophage polarisation stage

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Objectives: One of the hallmarks of migraine are recurrent pain attacks, a condition supported by a tissue background prone to neuronal sensitisation and neurogenic inflammation. Transgenic mice that express a missense R192Q mutation in the α1A subunit of voltage-gated Cav2.1 calcium channels are the model of familial hemipLEGic migraine type 1 (FHM1 R192Q mutant mice). Trigeminal ganglia from these mutant mice, compared to ganglia of wild type mice, are characterised by a larger number of lba-immonopositive macrophages, higher expression levels...
of CD11b, ED1 and F4/80 markers in non-neuronal satellite glial cells and increased secretion of pro-inflammatory cytokine TNFα. Recent evidences suggest that the tissue balance of different macrophage polarisation stages is an important indicator for inflammation outcome.

**Methods**: We have used FHM1 R192Q mutant mice to study macrophage polarisation markers, namely the M1 pro-inflammatory markers CD16 and CD32 and the M2 pro-resolving CD206. Expression of the inducible form of the nitric oxide synthase gene (iNOS) was also tested. Real-time PCR analysis of intact trigeminal ganglia samples from FHM1 R192Q mutant and WT mice have been performed. All experiments were carried out in accordance with the regulations of the local Animal Welfare act accordingly to the 3R roles and following the ARRIVE guidelines.

**Results**: We observed a large heterogeneity of CD16- and CD206-expressing cells in ganglia from mutant mice compared to wild type ganglia. In addition, mutant mice expressed significantly larger amount of the pro-inflammatory CD32 and iNOS transcripts. In contrast, trigeminal ganglia from a CGRP knockout mice expressed significantly lower levels of the CD16 transcripts.

**Conclusion**: These results suggest that soluble mediators, such as CGRP, have a strong role in the control of the differentiation of pro-inflammatory monocytes in trigeminal ganglia. Pro-resolving strategies aimed at lowering the neurogenic inflammation background in the trigeminal ganglia could be considered to ameliorate migraine prognosis.

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**Disclosure of Interest**: None Declared

**Headache Pathophysiology - Basic Science**

**PO-02-138**

**Exteroceptive suppression of voluntary masseter muscular activity in migraine: A pilot study**

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**Objectives**: We aimed to explore the differences in the trigeminal system by studying the exteroceptive suppression of the voluntary masseter muscular activities between migraine patients and controls.

**Methods**: Ten patients (1M/9F, mean age 34 years old) with migraine without aura and 9 healthy volunteers (3M/6F, mean age 31 years old) were recruited into the study. In the exteroceptive suppression test, activities of the ipsilateral masseter muscle were recorded while the electric stimuli were applied to the area supplied by the infraorbital nerve (V2 branch). The exteroceptive suppression of voluntary masseter muscular activities constitutes dual phases of the silent periods in the electromyography (EMG), i.e. exteroceptive suppression period 1 (ES1) and ES2. Between these two suppression periods, a period with transient increased EMG activities emerged, i.e. the interposed EMG activity (IE). The latency and duration of IE and the ratio of IE, defined as the ratio of the IE duration to the overall exteroceptive suppression duration (i.e. IE latency + IE duration + ES2 duration), were measured. In this study, we compared the difference in these measurements between migraine patients and controls. In addition, the measurements were correlated with the headache profile in patients with migraine.

**Results**: Both left and right mean IE durations were significantly longer in migraine patients than those in controls (left 31.02 ± 6.82 ms vs. 24.70 ± 6.89 ms, p < 0.001; right 27.3 ± 6.56 ms vs. 25.32 ± 8.22 ms, p = 0.02). A trend of shorter left IE latency (26.45 ± 2.8 ms vs. 27.1 ± 3.99, p = 0.126) and a significantly higher left IE ratio were found in migraine patients (0.33 ± 0.07 vs. 0.28 ± 0.084, p < 0.001) compared to the controls. In patients with migraine, a positive correlation between right IE ratio and number of migraine days per month (r = 0.316, p = 0.037) and a negative correlation between left IE latency and number of days with painkiller usage per month (r = −0.302, p = 0.044) were demonstrated.

**Conclusion**: Our pilot study showed migraine patients, compared to the controls, had longer IE duration, shorter IE latency and higher IE ratio. These findings suggest hyper-excitability in the spinal trigeminal complex system in migraine patients. Further study recruiting more cases is warranted to confirm our results.

**Disclosure of Interest**: None Declared
**Headache Pathophysiology - Basic Science**

**PO-02-139**

**Intercital levels of cgrp are no related with changes in cerebral vasoreactivity in chronic migraine**

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**Objectives:** CGRP is a potent vasodilator of cranial vasculature. Intercital CGRP (calcitonin-gene related peptide) levels have been reported as a reliable biomarker of chronic migraine (CM). Cerebral CO2 Vasoreactivity (CVR) reflects the vasodilation of microvasculature and its impairment is a marker of endothelial dysfunction. In CM, both an increase in CGRP levels and a decrease in CVR have been described. The aim of this study is to determine whether CGRP levels correlate with CVR in CM.

**Methods:** This series includes women meeting current IHS diagnostic criteria for CM. CGRP levels were determined in blood samples obtained from right cubital vein between 9–12 am with an ELISA kit from USCN following manufacturers instructions. CVR was assessed by Breath Holding Index (BHI) on transcranial Doppler in middle cerebral arteries (MCA), posterior cerebral arteries (PCA) and in the basilar artery (BA). To examine correlations between BHI and CGRP, Pearson correlation coefficient test was used.

**Results:** A total of 94 women fulfilling CM criteria (aged 43.09 ± 12.01 years) were included. CGRP levels were 64.51 ng/ml (range 11–157). Mean BHI were: MCA 1,528 ± 0.408, PCA 1,420 ± 0.406, BA 1,450 ± 0.352. There was no correlation between BHI and CGRP levels for the different arteries explored: MCA r = 0.000, PCA r = −0.024, BA r = −0.054 (p > 0.05)

**Conclusion:** In our series of CM there was not relationship between intercital CGRP levels and CVR. This finding suggest that CGRP alone is not responsible for the endothelial dysfunction described in migraine. The role of other neuropeptides alone or in combination with CGRP needs to be studied.

**Disclosure of Interest:** D. Larroza Campo: None Declared, C. Ramón Carbajo: None Declared, E. Cernuda Morollón: None Declared, P. Martinez-Camblor: None Declared, J. Pascual Gómez Conflict with: Supported by the PI14/00020 FISSS grant (Fondos Feder, ISCIII, Ministry of Economy, Spain)

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**Headache Pathophysiology - Basic Science**

**PO-02-140**

**The role of the transient receptor potential ankyrin type-I (TRPA1) channel in migraine pain: evaluation in an animal model**

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**Objectives:** To date, the pharmacological treatment of migraine remains somewhat unsatisfactory, partly because the pathophysiology of this disabling disease is still poorly understood. Clinical and experimental studies have pointed to the possible involvement of the transient receptor potential ankyrin type-I (TRPA1) channels in migraine pain. The present study is aimed to further investigate the role of TRPA1 in the mechanisms of migraine pain in an animal model of migraine using a novel TRPA1 antagonist (ADM_12) as a probe.

**Methods:** The effects of ADM_12 on nitroglycerin-induced hyperalgesia at the trigeminal level were investigated in rats using the quantification of nocifensive behavior induced by the orofacial formalin test. Gene expression of CGRP and SP in peripheral and central areas relevant for migraine pain were also evaluated.

**Results:** The findings show that in rats made hyperalgesic with nitroglycerin, ADM_12 has an anti-hyperalgesic effect of in the second phase of orofacial formalin test. This effect is associated to a significant inhibition of nitroglycerin-induced increase in c-fos, CGRP and SP mRNA levels in medulla-pons, cervical spinal cord and in trigeminal ganglion.

**Conclusion:** The present findings support a critical involvement of TRPA1 channels in the pathophysiology of migraine, and show their active role in counteracting hyperalgesia at the trigeminal level.

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**Disclosure of Interest:** None Declared
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PO-02-141

The role of peripheral CGRP on the vasculature in a preclinical mouse model of migraine

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Objectives: The neuropeptide calcitonin gene-related peptide (CGRP) is a key player in migraine. While migraine can be induced by peripherally administered CGRP (intravenous) and can be treated using CGRP antagonists that act peripherally, the relevant sites of CGRP action remain unknown. To address the role of CGRP both within and outside the central nervous system, we used a mouse model of photophobia. Photophobia is an abnormal discomfort to non-noxious levels of light and is experienced by approximately 90% of migraine patients. We have previously shown that peripheral (intraperitoneal, IP) injection of CGRP resulted in light aversive behavior in wild-type CD1 mice similar to aversion previously seen following central (intracerebroventricular, ICV) injection. Importantly, two clinically effective migraine drugs, the 5-HT1B/D agonist sumatriptan and a CGRP-blocking monoclonal antibody, attenuated the peripheral CGRP-induced light aversion and motility behaviors. Our goal for this study, is to identify the mechanism of action of peripheral CGRP using light aversion.

Methods: Intraperitoneal injections 0.1 mg/kg CGRP, Vehicle, 1 mg/kg Phenylephrine, CGRP + Phenylephrine was given to mice 30 minutes prior to placement in the light aversion chambers. Radio telemetry devices were implanted in mice and blood pressure was used as a readout for changes in vascular tone after injection of drugs in mice.

Results: As previously mentioned, ICV CGRP, but not IP CGRP, induced light aversion in mice that have elevated levels of the CGRP receptor component hRAMP1 in the nervous system. We have now used transgenic CGRP-sensitized mice that have globally elevated levels of hRAMP1 (global hRAMP1) in all tissues. Interestingly, sensitivity to low light after IP CGRP in these mice was observed. We have now begun investigating the role of the vasculature in peripheral CGRP-induced light aversion by using two approaches (1) injection of phenylephrine to minimize vasodilation induced by CGRP (2) genetic overexpression of the CGRP receptor in the vasculature.

Conclusion: These results suggest that CGRP can act in both the periphery and the brain by distinct mechanisms. This also suggests that peripheral CGRP actions may be transmitted to the CNS via indirect sensitization of peripheral nerves and likely not on CGRP receptors in the nervous system to cause migraine-like photophobia.

Disclosure of Interest: None Declared

Headache Pathophysiology - Basic Science

PO-02-142

Peripheral CGRP-induced pain detection in a preclinical mouse model of migraine

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Objectives: Migraine is a complex neurological disorder that afflicts over 6% of men and 18% of men in the United States. Having a myriad of symptoms, migraine is denoted by debilitating, unilateral pain, lasting up to 72 hours, and at least one of two symptoms: nausea and/or vomiting, or photophobia and phonophobia. Photophobia is a condition where low to normal levels of light cause discomfort and light aversion in the perceiver. This photosensitivity is a subjective experience for each migraineur and is a common trigger. Calcitonin gene-related peptide (CGRP) is a neuropeptide that is elevated during migraine. Clinical evidence suggests that CGRP plays a key role in migraine etiology. In particular, intravenous injection of CGRP has been shown to induce migraine-like headache in migraineurs but only fullness-of-head in non-migraineurs. Currently we have an established mouse model for CGRP-induced photophobic behavior. However, we have yet to quantify pain expression post CGRP administration. We hypothesized that our mice would exhibit increased expression of pain after CGRP administration and that this expression may be increased in the presence of light.

Methods: Mice were acclimated to a customized restraint and recorded using multiple cameras during dark and light conditions. Mice were then given an intraperitoneal injection of CGRP (0.1–0.5 mg/kg) or PBS and underwent the same conditions. Using the Mouse Grimace Scale and point-to-point measurement software, mice were independently scored by blinded observers for pain expression. Additionally, mice were co-injected with Sumatriptan, the gold standard for migraine treatment, to observe if symptoms of pain would be alleviated.

Results: CGRP caused a significant increase in pain expression compared to saline control in both dark and
light conditions. A difference between dark and light was not observed.

**Conclusion:** These data validate the grimace and squint assays as sensitive tools to measure CGRP induced discomfort in mice. The data further suggest that peripherally administered CGRP exerts an effect in a light-independent manner in addition to its photophobia-inducing properties.

**Disclosure of Interest:** None Declared

**Headache Pathophysiology - Basic Science**

**PO-02-143**

**Plasma CGRP, Histamine, L-Kynurenine and Kynurinic acid levels in migraine without aura patients**

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**Objectives:** There is a great need to find and validate biomarkers in clinical migraine research. Currently, only description of headache intensities, location of headache and at least one of the associated symptoms like nausea, vomiting, photophobia and phonophobia, are the diagnostic criteria to verify migraine headache. A significant change in the plasma calcitonin gene-related peptide (CGRP), histamine, L-Kynurenine (LK) and Kynurinic acid (KA) are reported in migraine patients. But there are also conflicting studies showing no change in these markers during migraine attack. In present study, we wanted to study comprehensive list of potential biomarkers in the plasma of migraine without aura patients, both during attack and interictally, by using advance LC-MS/MS and ELISA methods.

**Methods:** Four sets of blood samples were collected from the cubital vein. The first set during a migraine attack, second set two hours after treatment with subcutaneous sumatriptan, third set after at least five migraine free days/free from any other headache for at least 24 hours and the last set after a cold pressure test. Plasma was immediately separated in tubes containing protease inhibitors. Samples were placed on dry ice and transported back to the hospital from patient’s home. Subsequently, samples were stored in -80-degree freezer. LC-MS/MS methods for CGRP, histamine, LK and KA were developed at the University of Washington, USA. CGRP ELISA assay was performed in-house at Rigshospitalet-Glostrup, Denmark.

**Results:** We have identified two surrogate peptides, NNFVPTNVGSK and SGGVVK, to detect human CGRP by LC-MS/MS. In human plasma samples, small peaks of NNFVPTNVGSK and SGGVVK, matching to spiked heavy labelled peptides, were identified. But peaks were below limit of quantification. Subsequently, CGRP was extracted from plasma and ELISA assay was performed. Pooled plasma from non-migraineurs was used as a matrix to get a CGRP standard curve. Lower limit of quantification for CGRP was 15 pg/ml. In most of the samples, CGRP concentration was below lower limit of quantification. Lower limit of quantification for histamine, KA and LK were 5 nM, 30 nM and 250 nM. Plasma histamine levels were below limit of quantification. There was no significant change in plasma KA (99 nM vs 96 nM) and LK (750 nM vs 730 nM) levels during and outside migraine attack.

**Conclusion:** CGRP and histamine levels were below limit of quantification. Recovery of spiked CGRP in plasma is approximately 10 %. We recommend that when recovery is low, unknown values should be calculated from standard curve derived from known amount of CGRP spiked in similar volume of plasma and extracted similarly as samples. There is a great need to come up with protocols harmonizing neuropeptide extraction from plasma and subsequent ELISA assay protocols. Our results cast considerable doubt upon previous positive studies of these markers during migraine attack.

**Disclosure of Interest:** None Declared

**Headache Pathophysiology - Basic Science**

**PO-02-144**

**Cortical spreading depression alters expression of inflammatory gene transcript in the dura: (a) sex effects (b) effects of pretreatment with onabotulinumtoxinA**

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**Objectives:** Cortical spreading depression (CSD) has long been thought to be the neural event that underlies migraine aura, the non-painful sensory phenomena that can precede the migraine attack. It is thought to initiate the headache phase of migraine by activating the nociceptive pathway that provides the sensory innervation to the intracranial meninges. We recently raised the possibility
that cortical spreading depression (CSD) activates meningeal nociceptors indirectly, by changing the molecular environment in the dura. Accordingly, the purpose of this study was to determine whether CSD alters the molecular environment in the dura, and if so, how such changes respond to treatment with onabotulinumtoxinA.

Methods: To answer these questions, we first induced a single wave of CSD in naïve male and female mice, and an hour later removed the dura and measured expression of gene transcripts (mRNA) encoding proteins that play roles in immune and inflammatory responses. We then repeated these experiments in male and female mice pre-treated with onabotulinumtoxinA seven days earlier. Gene expression was considered altered (elevated or suppressed) if the number of copies of mRNA of that gene was altered by more than 1.5 fold and a p value of \(< 0.01\).

Results: A comparison between mice in which CSD was induced (after craniotomy) and sham mice (in which craniotomy was performed but CSD was not induced) revealed that 31 genes were altered in female mice (27 were upregulated, 4 were downregulated) and 17 in male mice (7 were upregulated, 10 were downregulated). A comparison between OnabotulinumtoxinA-treated and untreated mice showed that onabotulinumtoxinA reversed some of the CSD effects. In female mice, it downregulated 7 of the upregulated genes. In male mice, it downregulated 4 of the upregulated genes, and upregulated 4 of the downregulated genes. Functional analysis revealed that the altered genes are involved in inflammatory responses, immune cell trafficking, and lymphoid tissue structure.

Conclusion: The findings suggest that CSD-induced activation of inflammatory pathways in the dura is more robust in females than males, and that pre-treatment with onabotulinumtoxinA can prevent such activation. In the context of migraine headache, it may be that activation of dural nociceptors by CSD is secondary to a so-called ‘inflamed’ environment. In the context of onabotulinumtoxinA mechanisms of action, the findings point to a possible involvement in ‘calming’ the environment in the dura by reducing inflammatory responses.

Disclosure of Interest: A. Melo-Carrillo: None Declared, A. Schain: None Declared, M. Bhasin: None Declared, R. Burstein Conflict with: TEVA, Allergan, Trigemina, SST, Depomed, Dr. Reddy, Conflict with: TEVA, Allergan, Trigemina, Dr. Reddy

Headache Pathophysiology - Basic Science

PO-02-145
Cortical spreading depression closes the paravascular space and impairs glymphatic flow: Implications for migraine headache and treatment
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Objectives: To determine the effect of cortical spreading depression (CSD), the neural correlate of migraine aura, on the physical and functional attributes of the brain’s “glymphatic” waste clearance system, a recently described network of paravascular space (PVS) tunnels through which cortical interstitial solutes are cleared from the brain.

Methods: Using state-of-the-art 2-photon in vivo imaging through the lightly thinned skull, we studied the PVS, the blood vessel lumen, and the subarachnoid space before, during, and after CSD. We used ubiquitously expressing GFP or tdTomato mice which can be used to identify such fluid-filled spaces by lack of fluorescence. We then inject 3kDalton dextran dyes into the brain to determine the effect of CSD on the rate of flow through the glymphatic system.

Results: We show that CSD induces a closure of the paravascular space around cortical pial blood vessels, that is not related to the stereotypical changes in blood vessel lumen. The overlying subarachnoid space is less affected. This closure is accompanied by a reduction in the rate of clearance of intraparenchymal solutes from the cortex. We also show that the glymphatic system is unaffected by approved migraine prophylactics.

Conclusion: Our findings not only demonstrate a link between migraine and the glymphatic system, but also suggest a novel mechanism for regulation of glymphatic flow through PVS constriction or dilatation independent of vasculature. Because CSD is involved in the production of many potentially harmful interstitial molecules, the additional blockage of their route of clearance could exacerbate their effects on cortical structural changes, gliosis, and headache instigation.

Disclosure of Interest: A. Schain: None Declared, A. Melo-Carrillo: None Declared, A. Strassman: None Declared, R. Burstein Conflict with: TEVA, Allergan, Trigemina, SST, Depomed, Dr. Reddy, Conflict with: TEVA, Allergan, Trigemina, Dr. Reddy

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Hydrogen sulfide as a new modulator in an animal model of trigeminal nociception

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Objectives: Hydrogen sulfide (H2S) is a neuromodulator acting through nitroxyt (HNO) when it reacts with nitric oxide (NO). HNO activates TRP channels of the ankyrin type I (TRPA1) causing release of calcitonin gene-related peptide (CGRP) from primary afferents. Activation of meningeal nociceptors projecting to the human spinal trigeminal nucleus (STN) may lead to headaches. In a rodent model of meningeal nociception, the activity of STN neurons was used as readout for the interaction between H2S and NO.

Methods: In anesthetized rats extracellular recordings from single neurons in the STN were made. Na2S producing H2S in the tissue and the NO donor DEA-NONOate were infused intravenously. H2S was also locally applied onto the exposed cranial dura mater or the medulla. Endogenous production of H2S was inhibited by oxamic acid and NO production by L-NAME to manipulate endogenous HNO formation.

Results: Systemic administration of Na2S was followed either by increased ongoing activity (in 73%) or decreased activity (in 27%) of units. Topical application of Na2S onto the cranial dura mater caused a short-lasting activation followed by a long-lasting decrease in activity in the majority of units (70%). Systemic administration of DEA-NONOate increased neuronal activity, subsequent infusion of Na2S added to this effect, whereas DEA-NONOate did not augment the activity after Na2S. The stimulating effect of DEA-NONOate was inhibited by oxamic acid in 75% of units, and L-NAME following Na2S administration returned the activity to baseline.

Conclusion: Individual spinal trigeminal neurons may be activated or (less frequently) inhibited by the TRPA1 agonist HNO, presumably formed by H2S and NO, whereby endogenous H2S production may be rate-limiting. Activation of meningeal afferents by HNO paradoxically tends to decrease spinal trigeminal activity, consistent with the elevation of the electrical threshold caused by TRPA1 activation in afferent fibers. The effects of H2S-NO-TRPA1 signaling seem to depend on the site of action and the type of central neurons, and the role of H2S in headache generation appears ambiguous.

Disclosure of Interest: None Declared

Presence of Oxytocin Receptors on PACP-38 positive Shenopalatine Ganglia Neurons

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Objectives: Objectives: Activation of parasympathetic sphenopalatine ganglia (SPG) neurons is implicated as a critical step in the pathogenesis of cluster and some migraine headaches. In particular, activation of these neurons appears to release PACAP-38 onto the dura matter, where it causes mast cell degranulation and subsequent vasodilation. When infused, PACAP-38 induces headache as well as facial flushing in patients. Thus, mechanisms by which inhibition of SPG neuronal activity and subsequent release of PACAP-38 is potentially of great clinical utility. We have previously demonstrated that oxytocin, acting at oxytocin receptors on trigeminal ganglia neurons inhibits those neurons, reduces the release of CGRP and inhibits craniofacial pain in rodents and migraine headache in patients. Thus, it is of interest to determine whether SPG neurons also possess oxytocin receptors and whether these receptors are co-localized with PACAP-38. Here we performed immunohistochemical experiments examining the expression of oxytocin receptors and PACAP-38 on SPG neurons.

Methods: Methods: Rats were injected bilaterally with 50 µL of CFA into the vibrissal pads to induce robust inflammation which has been shown to induce overexpression of oxytocin receptors. Two days later, rats were deeply anesthetized and transcardially perfused with fixative. Their SPG was removed and cryoprotected overnight in 20% sucrose. Thereafter SPG was cryosectioned (10 µm) and slices were processed for PaCAP-38 and oxytocin receptor immunofluorescence using specific antibodies. Sections were also stained with DAPI to show nuclei. Sections were then examined using epifluorescence microscopy for immunoreactivity to the two antigens. Z stacks were also created to determine intracellular localization

Results: Results: Examination of sections demonstrated clear expression of oxytocin receptors on most SPG neurons. In addition, as previously reported, many cell also showed expression of PACAP-38. Extracellular PACAP-38 was also observed. More than 50% of oxytocin receptor positive neurons were also positive for PACAP-38. Z-stack analysis demonstrated that while cellular PACAP-38 was primarily located cytoplasmically, oxytocin receptors were located along neuronal cell membranes as well as in the cytoplasm.

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Conclusion: These results indicate oxytocin receptors are present on SPG neurons and that many of these neurons also contain PACAP-38. Given the demonstrated inhibitory effect of oxytocin on peripheral neuronal firing, it is possible that oxytocin might also inhibit the firing of SPG neurons, inhibit PACAP-38 release, and have a therapeutic effect on cluster headache.


Headache Pathophysiology - Basic Science

PO-02-148

Peripherally administered Calcitonin Gene-Related Peptide induces pain and pain-depressed behaviors in mice

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Objectives: Migraine is a complex neurological disorder inducing severe headaches that last for 4 to 72 h and has at least two of the following characteristics: unilateral localization, pulsating quality, moderate to severe pain intensity, and aggravation by movement. In addition, migraine is accompanied by at least one of two symptoms: nausea and/or vomiting, or photophobia and phonophobia. The neuropeptide calcitonin gene-related peptide (CGRP) is a well-established key player in migraine pathogenesis. CGRP levels are elevated during spontaneous migraine attacks, and peripherally administered CGRP antagonists are able to relieve both the pain and the associated symptoms of migraine. Interestingly, an intravenous injection of CGRP in migraineurs causes spontaneous migraine symptoms. To this day, the relevant sites of CGRP action remain unclear. Our team has previously shown that both peripherally and centrally administered CGRP induced an immediate light-aversive behavior in mice, in correlation with the photophobia observed in patients. The goal of the present study is characterize other migraine relevant symptoms in mice after peripheral CGRP injection.

Methods: We used the Mouse Grimace Scale in order to investigate pain induced by peripheral CGRP. Orbital tightening, nose bulge, cheek bulge, ear position and whiskers orientation were the different modalities scored on a scale of 0 to 2. We also used an activity wheel (number of wheel turns over 2 hours) in order to investigate whether mice would be discouraged to engage in an otherwise pleasurable activity (non-essential movements) after peripheral injection of CGRP, mimicking the clinical observation that movement exacerbates migraine symptoms. In complement, animals’ activity was recorded over time using an automated activity assay (essential movements).

Results: We report that peripheral administration of 0.1 mg/kg i.p. CGRP significantly induces pain in CD1 mice starting 10 minutes after the injection, compared to vehicle administrated animals. In those conditions, CGRP is also able to decrease the amount of wheel turns immediately after injection, and for at least 45 minutes. Preliminary results show that the overall activity of the animals is decreased during the first hour after the injection of CGRP. This decrease however is relatively small compared to the one observed with the activity wheel, suggesting a discrimination between essential and non-essential movements.

Conclusion: Peripheral injection of CGRP in mice seems to recapitulate many clinically relevant symptoms observed in migraine headache patients. Those findings further validate the possible action of CGRP in the periphery in the development of migraine symptoms.

Disclosure of Interest: None Declared
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**Late-Breaking Abstracts of the 2017 International Headache Congress**

**Headache Pathophysiology – Basic Science**

**OC-LB-001**

**Novel migraine therapeutic target discovery by single-cell RNA sequencing of trigeminal ganglia**

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**Objectives:** Pain experienced in migraine involves the sensitization of trigeminal afferent neurons, but the extraordinary cellular diversity within trigeminal ganglia has limited our understanding of the molecular substrates through which this process occurs. Recent advances in single-cell RNA sequencing technology have enabled the massively parallel identification and molecular profiling of nearly all cells within heterogeneous tissues. We are using this powerful tool to identify unique gene expression patterns within individual trigeminal ganglion cell types, and aim to leverage this insight towards the discovery of fundamentally new targets in headache pathophysiology.

**Methods:** Single-cell RNA sequencing was performed on postmortem mouse and human trigeminal ganglia. Approximately ten thousand cells were collected with a custom-designed microfluidics device (inDrops) and sequenced using next-generation Illumina sequencing. Unsupervised principle component analysis and graph clustering generated groups of cells based on their measured gene expression patterns. Novel marker genes were then identified using gene set enrichment analysis.

**Results:** Bioinformatic analysis of mouse and human data from trigeminal ganglion single-cell RNA sequencing identified clusters of cells that represent neuronal, glial, vascular, and meningeal cell subtypes. Individual cell types are clearly delineated based on their gene expression profiles, which enabled the interrogation of specific subtypes of neurons (e.g. CGRP+ nociceptors) or glia (e.g. satellite glia). Each of these unique cell populations are confirmed by selective expression of known marker genes. After each cell type was determined, genome-wide enrichment analysis was performed to determine the set of genes that are selectively enriched in each cell type. Indeed, we have identified the genes that are highly enriched in both mouse and human CGRP+ neurons. These data establish a new resource for querying the expression level of genes within specific cell types of the mouse and human trigeminal ganglia.

**Conclusion:** The gene expression patterns of individual mouse and human trigeminal ganglia cells were reliably described by single-cell RNA sequencing. These data enabled the discovery of novel genes that are uniquely expressed within specific trigeminal cell subtypes such as CGRP+ neurons. Future studies are aimed at investigating the role of these genes in CGRP+ neuronal function and migraine pathophysiology.

**Disclosure of Interest:** None Declared

**Migraine Acute Therapy**

**OC-LB-002**

**Non-invasive Vagus Nerve Stimulation (nVNS) for the Acute Treatment of Migraine: A Randomised Controlled Trial**

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Objectives: Pilot studies and clinical experience have suggested the safety, tolerability, and preliminary efficacy of non-invasive vagus nerve stimulation (nVNS; gammaCore™) for the treatment of migraine. nVNS is an attractive option for patients, with its ease of use, flexibility, and favourable adverse event profile. We explored the efficacy, safety, and tolerability of nVNS in the acute treatment of migraine in a multicentre, double-blind, randomised, controlled trial (RCT).

Methods: 248 subjects with episodic migraine with or without aura were recruited for this prospective, parallel-group study conducted at 10 Italian tertiary headache centres. Entry criteria and efficacy end points were consistent with existing guidelines and previous nVNS studies. Within 20 minutes from migraine pain onset, subjects self-administered a 120-second stimulation to the right side of the neck that was immediately followed by a 120-second stimulation on the left side. Subjects were instructed to repeat both stimulations if pain did not improve at 15 minutes, and the subjects had the option of administering a third set of stimulations at 120 minutes if not pain free. Rescue medication use before 120 minutes was considered treatment failure. Up to 5 migraine attacks were treated in the double-blind period.

Results: Acute nVNS treatment (n = 120) led to significantly higher pain-free rates than sham (n = 123) for the first treated migraine attack at 30 minutes (12.7% vs 4.2%; P = 0.012) and 60 minutes (21.0% vs 10.0%; P = 0.023), with a nearly significant difference at 120 minutes (30.4% vs 19.7%; P = 0.067; primary end point; sensitivity analysis). Due to the inconsistency between the 120-minute finding and the 2 earlier findings, a post hoc repeated-measures test was performed, confirming that nVNS was superior to sham at 120 minutes (odds ratio: 2.3; 95% CI: 1.2, 4.4; P = 0.012). nVNS was superior to sham for the rate of mild/no pain at 120 minutes (40.8% vs 27.6%; P = 0.030) and 50% responder rates for no pain (32.4% vs 18.2%; P = 0.020) and mild/no pain (47.6% vs 32.3%; P = 0.026).

Conclusion: This RCT demonstrates that nVNS is rapidly effective, well tolerated, and practical for the acute treatment of episodic migraine with or without aura. nVNS was superior to sham for pain freedom at 30 and 60 minutes but not at 120 minutes (primary end point). A repeated-measures test validated the primary end point, indicating the superiority of nVNS over sham through 120 minutes. This study provides a clinical rationale for nVNS use in the acute treatment of episodic migraine.

Funding: This study was sponsored by electroCore, LLC.


Headache Epidemiology, Outcomes and Burden

OC-LB-003

Factors Associated with Acute Medication Overuse in Persons with Migraine: Results from the 2017 Migraine in America Symptoms and Treatment (MAST) Study

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Objectives: Overuse of prescription and OTC medications to treat migraine attacks can lead to more frequent and/or persistent migraine. Objectives were to 1) estimate rates of medication overuse (MO) in a non-clinic sample of persons with migraine; 2) determine the association of headache frequency and other variables with presence of MO.

Methods: MAST Study participants were recruited from a nationwide online research panel. Stratified random sampling identified a representative cohort aged ≥18 years meeting modified ICHD-3β criteria for migraine. Those averaging ≥1 headache days per month over prior 3 months and using acute migraine medication(s) were eligible. ICHD-3β criteria identified persons with migraine and those having MO (or not) based on their frequency of acute headache medication use. Variables of interest included sociodemographics (age, gender, race, income, BMI, education, health insurance, smoking), past 30-day headache frequency category (1–4, 5–9, 10–14, ≥15 days/month), severity (0–10 pain intensity rating), migraine symptom severity score (MSSS) sum, psychological symptomology (PHQ-4, symptom score ≥6) and presence of allodynia (ASC-12, symptom score ≥3). Binary logistic regression identified the variables associated with MO in a hierarchical manner. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each variable.

Results: 117,150 responded to an email survey, 95,821 responses were usable and 14,396 met inclusion criteria. Mean age was 43.4 yrs, 73.1% were women, 81.5% were Caucasian, 70.8% were employed full- or part-time. There were 2,854 (19.8%) who met criteria for MO. Covariates were entered sequentially to an initial model predicting MO as a dichotomous outcome. Headache frequency (≥15 headache days per/mo vs. 1–4 days/mo; OR 14.51, CI 12.68, 16.62), pain intensity (OR 1.17, CI 1.13, 1.21) and MSSS (OR 1.04, CI 1.02, 1.06) were associated with MO. Respondents with psychological symptomology were 58% more likely to meet criteria for MO (1.58, 95% CI 1.42, 1.76), and respondents with cutaneous allodynia were 15% more likely to meet criteria (OR 1.15, CI 1.04, 1.27). Characteristics associated with less risk of MO included Caucasian race (OR 0.80, CI 0.71, 0.90), having health insurance (OR 0.74, CI 0.63, 0.87) and not smoking (0.71, 0.63, 0.87). In prior research, females were at greater risk for allodynia and individuals with allodynia were at greater risk for MO. Thus, we hypothesized that females would have greater odds of MO. However, modeling revealed male gender was associated with increased MO (OR 1.19, CI 1.06, 1.32). To explore this unexpected finding, a final model included a sex x allodynia interaction, which was significant (OR 1.31, CI 1.05, 1.62). Men with allodynia were found to be more likely to meet MO criteria vs. women with allodynia (unadjusted percents: 30.0% and 23.6% respectively).

Conclusion: At cross-section, roughly 20% of persons with migraine met criteria for medication overuse. As expected, persons with frequent headaches were more likely to meet MO criteria. However, after adjusting for headache frequency, headache intensity, and sociodemographics, a significant association between MO and psychological distress and cutaneous allodynia remained. Being Caucasian, having health insurance and not smoking were associated with reduced risk of MO. Of note, men with allodynia were more likely to meet criteria for MO than women with allodynia. In this cross-sectional study we cannot determine temporal sequence or causality for these associations, however treating modifiable predictors of MO is likely good clinical practice.

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**Headache Pathophysiology – Basic Science**

**OC-LB-004**

A unique inbred rat strain with sustained cephalic hypersensitivity as a model of chronic migraine-like pain

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**Objectives:** Animal models of migraine-like pain enabling study of behaviour typically involve the systemic administration of vasoconstrictors or dorsal administration of inflammatory algogens. However, neither method mediates sustained effects on behaviour that might be required to drive long-term pathophysiological changes within trigeminovascular pain circuits. We acquired a breeding pair of spontaneous trigeminal allodynia (STA) rats which have previously been reported to exhibit episodic, fluctuating periorbital thresholds to mechanical stimulation indicative of migraine-like pain. We wanted to perform an independent comparative behavioural and pharmacological validation of this unique inbred strain.

**Methods:** Experiments were performed using two generations of STA rats bred in house to minimize epigenetic influences on behaviour: F2 STA and control SD males were also tested. An automated von Frey algesiometer and Randall-Selitto paw pressure applicator were used to measure periorbital (left and right sides) and hindpaw sensory thresholds (g) to cutaneous mechanical stimulation respectively. A hot plate (48°C) was used to measure hindpaw latency (s) as an index of thermal sensitivity. General behaviour was evaluated using the automated behavioral registration system LABORAS.

**Results:** The periorbital threshold to mechanical stimulation in F1 female STA rats (74 ± 9 g, mean ± SEM, n = 14) was 2 fold lower compared with Charles River or Taconic control SD rats (159 ± 21 g, n = 10 and 181 ± 12 g, n = 13; both P < 0.001). Hypersensitivity was specific for the cephalic region and unaffected by oestrus cycle status. In F2 female STA rats (n = 17), cephalic hypersensitivity manifested shortly after puberty (Day 48 post-partum) and was sustained into early adulthood (Day 130) compared with age-matched control SD rats (n = 8); F2 male STA rats were similarly sensitive. No difference in periorbital thresholds between the left and right sides of F2 female STA rats occurred indicating that the hypersensitivity was bilateral in its distribution. Noxious thermal stimulation of the hindpaw in F2 female STA rats was performed to exclude that lack of sensitivity was not due to stimulus modality. Remarkably, they were shown to exhibit a sustained hindpaw hypoesthesia compared with control SD rats, indicative of a clear loss in sensory function. STA rats also gained weight less rapidly than age-matched SD controls, suggesting that other phenotypic differences might exist between the sub-strains. Notably, characterization of general behaviour using LABORAS revealed no obvious differences in various motor-related behaviours between F2 female STA and control SD rats. Finally, we used a blinded cross-over paradigm to test efficacy of migraine-specific drugs against cephalic hypersensitivity in F2 female STA rats. Accordingly, both the 5HT1B/1D agonist sumatriptan (1 mg/kg, s.c.) and the CGRP receptor antagonist rizatriptan (1 mg/kg, i.p.) produced a robust reversal of periorbital thresholds in F2 female STA rats compared with vehicle treatment (both P < 0.001 and n = 13).

**Conclusion:** Periorbital thresholds to mechanical stimulation in STA rats did not fluctuate episodically as described previously. Rather, following puberty they remained lower than control SD rats and the associated hypersensitivity sustained at least into early adulthood. This unique strain appears to possess a phenotype indicative of migraine chronicity which is exquisitely sensitive to migraine therapeutics, and could prove to be an invaluable resource in preclinical migraine drug discovery.

**Disclosure of Interest:** None Declared

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Neuromodulation for Headache

OC-LB-005

Acute treatment of migraine with e-TNS: A multi-center, double-blind, randomized, sham-controlled trial

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Objectives: There is an unmet need for non-invasive, well-tolerated and effective acute treatments for migraine. e-TNS (external trigeminal nerve stimulation) has shown encouraging results in open-labelled pilot studies (1–3). The objective of the current study was to assess the efficacy and safety of e-TNS as an acute treatment of migraine attacks with or without aura in a multi-center, double-blind, randomized, sham-controlled trial.

Methods: Subjects aged 18 to 65 years old with a diagnosis of episodic or chronic migraine, with or without aura, were recruited if they were experiencing an acute migraine attack lasting for at least 3 hours. Eligible patients were randomized 1:1 to verum or sham stimulation and treated with e-TNS applied via the Cefaly® neurostimulator device (CEFALY Technology, Seraing, Belgium), for a 1-hour treatment session at the clinic. Patients scored their pain intensity on a visual analogue scale (0=no pain to 10=maximum pain). Pain level was assessed before the treatment was applied (baseline score), after the 1 h treatment, at 2 h after the beginning of the treatment phase, and at 24 h after treatment. Rescue medication intake was also recorded during the 24 h observation period. The primary outcome measure was the mean change in pain score at the 1 h time point, compared to baseline. Secondary outcome measures were the mean change in pain score at the 2 h and 24 h time points compared to baseline, as well as the proportion of patients not requiring rescue medication within 24 h of treatment.

Results: 106 patients were randomized and included in the intention-to-treat (ITT) analysis. The primary outcome measure (mean pain intensity after the 1 h e-TNS session compared to baseline) was significantly reduced in the verum group compared to sham (−3.46 ± 2.32 vs. −1.78 ± 1.89, p < 0.001; or −59% vs. −30%, p < 0.001). Pain intensity was also significantly reduced in the verum group compared to sham at 2 h and 24 h. Rescue medication intake within the 24 h period was not significantly lower in the verum group. 99 patients were included in a modified intention-to-treat (mITT) analysis (randomized patients who underwent the 1 h stimulation treatment and provided headache sores at baseline and at the 1 h point). Mean pain intensity was significantly reduced in the verum group compared to sham at 1 h (−3.83 ± 2.13 vs. −1.85 ± 1.89, p < 0.001; or −65% vs. −32%, p < 0.001) and at 2 h and 24 h time points. In addition, the percentage of patients who were pain-free at 24 h was significantly higher in the verum group compared to sham (32% vs. 13%, p < 0.05). Regarding safety, one minor adverse event (nausea) occurred; there were no serious adverse events, nor were any subjective complaints or side effects reported in either group within the 24 h period.

Conclusion: The results of this multi-center, double-blind, randomized, sham-controlled trial demonstrate that e-TNS is an effective and well-tolerated treatment for the acute treatment of migraine.

*Disclosure: This study received funding from CEFALY Technology

Disclosure of Interest: D. Chou Conflict with: outside the submitted work: research funding from Teva, Alder, and Capnia, Conflict with: advisory boards: Eli Lilly, Amgen, Teva, Allergan, and Pernix, Conflict with: speaking honorarium from Medscape, M. Yugrakh: None Declared, G. Gross: None Declared, D. Winegarner: None Declared, V. Rowe: None Declared, D. Kuruvilla: None Declared

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Headache Pathophysiology – Basic Science

OC-LB-006

TRPA1 and not TRPV1 activation inhibited by aspirin in human volunteers

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Objectives: Transient receptor potential ankyrin 1 (TRPA1), an emerging target for migraine therapy, is
activated by cinnamaldehyde (CA) and results in a reproducible increase in dermal blood flow (DBF) after local CA application. This study investigates the mediators involved in this response in healthy volunteers.

**Methods:** Part I: Randomized, 2-way cross-over study using aspirin (1 g, non-selective, irreversible COX-inhibitor) and aprepitant (375 mg, NK1-antagonist) in 13 healthy male volunteers. Part II: randomized, 3-way cross-over study using aspirin, indomethacin (100 mg, non-selective, reversible COX-inhibitor) and celecoxib (400 mg, reversible COX2-inhibitor) in 15 healthy male volunteers. During all visits (separated by a wash-out of 14 days) drugs were administered orally. CA (2 ml/20 ml) and capsaicin (1000 mg/20 ml) were applied topically on the volar surface of the forearms during screening and subsequent study periods. DBF was assessed using laser Doppler imaging (LDI) at baseline and at fixed time points for 60 minutes after CA application. Data are expressed as Area Under the Curve (AUC) (mean / SEM, perfusion units (PU)*min) and analyzed with One-way ANOVA with post-hoc Bonferroni.

**Results:** Part I: After aspirin intake, CA-induced DBF was almost completely blocked (p < 0.001), in contrast to aprepitant, when comparing to no drug intake. Part II: Inhibition of CA-induced DBF response by aspirin was confirmed (p < 0.001), compared to no drug intake. Additionally, indomethacin was also able to reduce the DBF response (p < 0.05), while celecoxib was not, compared to no drug intake. Interestingly, a difference was also found between aspirin and indomethacin p < 0.05, indicating that aspirin is a stronger inhibitor. Capsaicin-induced DBF was not reduced by intake of any drug, compared to no drug intake.

**Conclusion:** In healthy volunteers, COX-1 dependent vasodilating prostaglandins play an important role in CA-induced DBF and thus TRPA1 activation, while COX-2 and Substance P do not seem to contribute substantially to the response. These results are of interest because:

1. In mice, prostaglandins were reported not to play a role in CA-induced DBF, which contributes to the emerging hypothesis that there are striking differences between human and rodent TRPA1 homologues complicating TRPA1-targeted drug discovery;
2. Although both aspirin and indomethacin are both non-selective cox-inhibitors, aspirin seems to have a stronger inhibitory effect on CA-induced DBF, maybe since aspirin is an irreversible inhibitor and indomethacin is not;
3. Although both TRPA1 and TRPV1 are reported to be co-expressed on the same peptidergic nerve endings, the vasodilatation induced via their activation seems to be induced by different second messengers.

**Disclosure of Interest:** None Declared

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**Migraine Preventive Therapy**

**PO-01-178**

**A Randomized Pilot Study of Nuedexta® for the Prevention of Episodic Migraine**

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**Objectives:** Nuedexta® (dextromethorphan and quinidine) is a potent NMDA and Sigma-1 receptor antagonist with high CNS availability and a long half-life which can potentially inhibit glutamate activity in the nervous system. Glutamate is one of the most potent excitatory neuropeptides in the nervous system and is a precursor to gamma-amino-butyric acid (GABA). Glutamate binds with the N-methyl-D-aspartate (NMDA) receptor to open ion channels.
channels and increase CNS excitability. Inhibition of the NMDA receptor has been shown to block pain transmission and has been implicated in migraine pathophysiology, peripheral and central sensitization as well as cortical spreading depression. The less studied Sigma-1 receptor is involved in calcium signaling and is implicated in pain processing. This pilot study explores the potential of daily Nuedexta® in reducing the frequency of frequent episodic migraine.

**Methods:** This was a double-blind, placebo-controlled, randomized study conducted at 6 centers. Forty-five subjects, 18 to 65 years of age, with frequent episodic migraine (6–14 days per month), with or without aura as defined by ICHD-3beta, entered a 4 week baseline period to confirm the diagnosis and establish baseline migraine characteristics. Subjects could maintain other current stable migraine prophylaxis throughout the study. Eligible subjects were randomized in a 1:1 ratio to daily Nuedexta® or Placebo for 16 weeks, completing daily electronic headache diaries and returned monthly for evaluations.

**Results:** A comparison of the number of headache days from the baseline month to each of the treatment period months between the Nuedexta® arm vs. the placebo arm revealed a significant interaction effect, $F(3, 105) = 4.51$, $p = .01$, $\eta^2_p = .11$. Subjects randomized to Nuedexta® ($n = 20$) reported a significantly greater reduction in headache days ($−3.4$ days, $p < .001$) during treatment weeks 12–16 while there was no significant change for those receiving placebo ($−0.52$ days, $p = .69$). A similar trend was seen with a significantly greater reduction in the number of migraine days for those receiving Nuedexta® ($−2.95$ days, $p < .001$) vs. placebo ($−0.72$ days, $p = .57$). Half of the subjects in the Nuedexta® arm (10/20) reported at least a 50% reduction in the number of migraines at the end of treatment, which was statistically significant compared to the placebo arm ($3/17$, $p = .04$) in the placebo arm. Subjects in the Nuedexta® arm reported significantly higher Headache Health Scores™ compared to baseline during all treatment periods, while subjects in the placebo arm reported no significant change from the baseline month to each of the treatment period evaluations.

**Conclusion:** Data from this pilot study suggests Nuedexta® may have benefit for the prevention of episodic migraine. Subjects reported fewer migraine and headache days, as well as significant increases in Headache Health Scores™ indicative of overall improvements for subjects’ quality of life. These data further support a potential role of glutamate in the pathophysiology of migraine. Few adverse events were reported with Nuedexta® relative to placebo. These positive results suggest the need for larger additional studies on the role of NMDA receptor antagonists and sigma-1 antagonists in the prevention of episode and chronic migraine.

**Disclosure of Interest:** R. Cady Conflict with: Research Grant, T. Smith: None Declared, H. Manley: None Declared, J. Sly: None Declared, R. Cady: None Declared

**Migraine Preventive Therapy**

**PO-01-179**

Erenumab Reduces Weekly Migraine Days in Patients With Episodic Migraine During the First Week of Administration

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**Objectives:** Subcutaneous erenumab, a fully human monoclonal antibody against the CGRP receptor, significantly reduces headache frequency in patients with episodic migraine. Here, we evaluated the response to erenumab 70 mg and 140 mg administered by subcutaneous injection from baseline through 2 weeks in reducing migraine days in patients with episodic migraine ($≥4$ and $<15$ headache days per month).

**Methods:** This post hoc analysis of a phase 3, randomized, double-blind, placebo-controlled clinical trial of erenumab (NCT02456740) evaluated: 1) the proportion of subjects with $≥50%$ reduction in weekly migraine days and 2) the percentage of subjects with migraine days each day during the first 2 weeks of treatment. Stratified Cochran-Mantel-Haenszel with nonresponder imputation was used for $≥50%$ responder rates. To visualize trend in daily migraine rate, a 7-day moving average of the observed percentages of patients experiencing a migraine day was calculated with a centering method. Nominal p-values are reported without multiplicity adjustment.
Results: Baseline mean weekly migraine days was 2.1 days for all treatment arms. At week 1, 28% of patients on placebo (n = 316) had ≥50% reduction in weekly migraine days compared to 34% receiving erenumab 70 mg (n = 312; P = 0.097) and 43% receiving erenumab 140 mg (n = 318; P < 0.001), increasing to 30%, 45%, and 47%, for placebo, 70 mg, and 140 mg, respectively, at week 2 (P < 0.001 for both 70 mg and 140 mg vs placebo). Moreover, the percentage of patients experiencing a migraine day was lower for the erenumab groups within several days after initiation of treatment, supporting that the onset of erenumab efficacy occurs within the first week of treatment, earlier for the 140 mg dose than for the 70 mg dose (Figure).

Conclusion: Among patients with episodic migraine, efficacy is observed within the first week of erenumab treatment. These results are similar to those reported for patients with chronic migraine, and taken together suggest that erenumab has a rapid onset of efficacy in patients with migraine.


Migraine Preventive Therapy

PO-01-180
Efficacy of Erenumab (a fully human Mab targeting the CGRP receptor) in Chronic Migraine Patients with Prior Treatment Failure: a Subgroup Analysis of the Phase 2, Randomized, Double-Blind, Placebo-Controlled Study

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Objectives: To present results on prior prophylactic treatment failure (≥1, ≥2 and never failed) due to lack of efficacy and/or poor tolerability from a pre-specified subgroup analysis of the Ph 2 study of erenumab in patients with chronic migraine (CM).

Methods: Patients (N = 667; ≥18–65 years) with CM (>15 headache days/month; ≥8 migraine days) were randomized (2:2:3) to once-monthly s.c. erenumab 70 mg, 140 mg or placebo (Pbo). Efficacy endpoints were change in monthly migraine days (MMD), achievement of ≥50% reduction in MMD, change in monthly acute migraine-specific medication treatment days (MSMTDs), and change in cumulative monthly headache hours. Assessments compared weeks 9–12 to baseline.

Results: With erenumab 70 mg and 140 mg, there were greater reductions at week 12 in MMD and more patients achieved ≥50% reduction in MMD vs Pbo across subgroups. Greater reduction in monthly acute MSMTDs
was observed with erenumab 70 mg and 140 mg in patients who failed prophylactic medications vs Pbo. Cumulative monthly headache hours reduced with erenumab 140 mg vs Pbo in patients who failed prophylactic medications. Pbo effect was greatest in patients who never failed prophylactic medication. Across endpoints, reductions were greater with erenumab 140 mg than 70 mg.

**Conclusion:** Erenumab 140 mg showed better efficacy in patients who had failed ≥1 or ≥2 prophylactic medications.

EQ-5D-5L analyses were conducted using an analysis of covariance approach (with years since onset of migraine and baseline EQ-5D-5L score as covariates).

**Results:** The study included 375 patients in each of the fremanezumab treatment arms and 371 in the placebo arm. Compared with placebo, fremanezumab significantly improved MSQoL scores in patients with CM. The mean MSQoL score in the RR domain for each fremanezumab dose regimen was significantly increased versus placebo, from baseline to Week 12 (least-squares mean [LSM] ± standard error [SE] differences versus placebo: 5.6 ± 1.4 in the quarterly fremanezumab group and 6.3 ± 1.4 in the monthly fremanezumab group; both \( P < 0.0001 \)). Significant \(( P < 0.05)\) improvements in the RP and EF domains of MSQoL were also observed. Significant improvements in each domain of MSQoL were observed as early as 4 weeks after the first dose and was sustained at all pre-defined assessments in the fremanezumab groups. As measured by the EQ-5D-5L VAS, patients with CM experienced statistically significant improvement in overall health status with fremanezumab quarterly \((4.6 ± 1.1; P = 0.0402)\) and monthly \((4.8 ± 1.1; P = 0.0291)\) dosing as compared with placebo \((2.2 ± 1.1)\).

**Conclusion:** These results indicate that fremanezumab improves migraine-specific QoL and overall health status of patients with CM. These improvements highlight the positive impact of fremanezumab on CM patients’ ability to engage in and perform work and daily activities.


**Migraine Preventive Therapy**

**PO-01-182**

**The Positive Impact of Fremanezumab on Work Productivity and Activity Impairment in Patients With Chronic Migraine**

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**Objectives:** Migraine is a debilitating chronic disease that imparts a substantial indirect cost burden on corporations. The management and treatment of migraine costs US employers approximately $12 billion annually in productivity loss and accounts for up to 70–90% of total migraine-related annual costs. Chronic migraine (CM) creates an
especially high societal burden. In clinical trials, fremanezumab, a fully humanized monoclonal antibody that selectively targets calcitonin gene-related peptide, reduced the frequency, severity, and duration of headaches in patients with CM. The purpose of this analysis was to evaluate the effect of subcutaneous fremanezumab on work productivity loss and activity impairment in patients with CM, as measured by the Work Productivity and Activity Impairment (WPAI) questionnaire.

Methods: In this Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study (NCT02621931), eligible patients aged 18–70, with a history of migraine (≥12 months) and prospectively confirmed CM (≥15 headache days and ≥8 migraine days per month), were randomized 1:1:1 to receive subcutaneous injections of fremanezumab quarterly dosing (675 mg at baseline and placebo at Weeks 4 and 8), fremanezumab monthly dosing (675 mg at baseline and 225 mg at Weeks 4 and 8), or placebo at each time point over a 12-week treatment period. Change in WPAI score from baseline to 4 weeks after administration of the last dose of study drug was an exploratory endpoint. The WPAI questionnaire includes questions regarding the impact of health on the extent of work loss and productivity impairment during work and other activities, with higher scores indicating greater impairment.

Results: The full analysis set included 375 patients in each of the fremanezumab dosage groups and 371 patients in the placebo group. Patients with CM treated with fremanezumab reported larger reductions from baseline in overall work productivity loss (composite of absenteeism and impairment while working [presenteeism]) compared with placebo (–16.6% ± 2.9% [quarterly] and –15.9% ± 2.02% [monthly] vs –9.1% ± 2.02% [placebo]), resulting in significant treatment differences for each fremanezumab treatment arm versus placebo (quarterly: –7.5% ± 2.24%, P = 0.0009; monthly: –6.8% ± 2.26%, P = 0.0026). The change from baseline in presenteeism was greater with fremanezumab than with placebo (–15.7% ± 1.89% [quarterly] and –14.9% ± 1.82% [monthly] vs –10.0% ± 1.82% [placebo]), resulting in significant treatment differences for each fremanezumab treatment arm versus placebo (quarterly: –5.7% ± 2.03%, P = 0.0049; monthly: –4.9% ± 2.05%, P = 0.0169). In addition, fremanezumab significantly reduced impairment of activity outside of work in the quarterly dosing arm of the study compared with placebo (–15.0% ± 1.70% vs –11.0% ± 1.7%; treatment difference of –4.0% ± 1.85%, P = 0.0311).

Conclusion: In this Phase III study, fremanezumab treatment resulted in significant improvements in work productivity and activity impairment, demonstrating the positive impact of fremanezumab on the ability of patients with CM to function both at and outside of work.


Migraine Preventive Therapy

PO-01-183

Early Onset of Action of Fremanezumab (TEV-48125) Versus Placebo by the First Week for the Preventive Treatment of Chronic Migraine

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Objectives: Migraine is a prevalent disease which may progress over time. Migraine prevention is intended to reduce the frequency, severity, and disability associated with migraine attacks, and faster onset of action could increase the benefit to patients with migraine. Fremanezumab is a fully humanized monoclonal antibody targeting the calcitonin gene-related peptide (CGRP) ligand, a preventive treatment designed to specifically target a pathophysiologic mechanism of migraine. This analysis assesses the onset of action of fremanezumab in the prevention of migraine.

Methods: This is a 16-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to compare the efficacy, safety, and tolerability of 2 subcutaneous dose regimens of fremanezumab and placebo (PBO) in adults with CM. Patients maintained a daily diary during a 28-day baseline period, and throughout the treatment period. Patients were assigned randomly to 1:1:1 ratio to 1 of 3 treatment groups: (1) monthly dosing: an initial dose of 675 mg fremanezumab followed by 225 mg of fremanezumab at months 2 and 3, (2) quarterly dosing: a single dose of 675 mg of fremanezumab at month 1, followed by placebo injections at months 2 and 3, and (3) monthly administration of matching placebo. The mean change from baseline (28-day run-in period) to the 12-week randomization period in the monthly average number of migraine days the primary endpoint in the EM study and secondary endpoint in CM study, and results at Weeks 1, 2, 3 and 4 were also assessed using a mixed-effect model for repeated measures.

Results: Chronic migraine with fremanezumab experienced statistically significant reduction in the number of monthly headache days of at least moderate severity.
during the 12-week period after 1st dose, for both dosing regimens [monthly (−4.6 days) and quarterly (−4.3 days); \(p < 0.0001\)] vs. placebo (−2.5 days), and during the 4 week period after 1st dose, for both dosing regimens (\(p < 0.0001\)). At Week 1, fremanezumab resulted in significant reduction in the weekly number of headache days of at least moderate severity (−1.1 days; \(p < 0.0001\)) versus placebo (−0.5 days). At Week 2, fremanezumab resulted in significant reduction in the weekly number of headache days of at least moderate severity (−1.2 days; \(p < 0.0001\)) versus placebo (−0.5 days). At Week 3, fremanezumab resulted in significant reduction in the weekly number of headache days of at least moderate severity (−1.2 days; \(p < 0.0001\)) versus placebo (−0.6 days). At Week 4, fremanezumab resulted in significant reduction in the weekly number of headache days of at least moderate days (−1.1 days; \(p = 0.0006\)) versus placebo (−0.7 days). Posthoc analysis indicated that more patients reported no headache of at least moderate severity with fremanezumab (69%; \(p = 0.0036\)) versus placebo (61%) by the next day after the first injection.

**Conclusion:** These results indicate that the onset of action with fremanezumab occurred rapidly for the preventive treatment of migraine. The significant improvement was maintained throughout three months of treatment for both monthly and quarterly subcutaneous injections.

**Disclosure of Interest:** P. Yeung Conflict with: Teva Pharmaceuticals, E. Aycardi Conflict with: Teva Pharmaceuticals, M. Bigal Conflict with: Teva Pharmaceuticals, T. Blankenbiller Conflict with: Teva Pharmaceuticals, M. Grozinski-Wolff Conflict with: Teva Pharmaceuticals, Y. Ma Conflict with: Teva Pharmaceuticals, J. Brandes Conflict with: Teva Pharmaceuticals

**Migraine Preventive Therapy**

**PO-01-184**

**A Phase 3, Long-Term, Open-Label Safety Study of Self-Administered Galcanezumab Injections in Patients with Migraine**

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**Objectives:** To evaluate the long-term safety and tolerability of galcanezumab (GMB), a humanized monoclonal antibody that selectively binds to the calcitonin gene-related peptide, for up to 1 year of treatment in patients with migraine.

**Methods:** Patients 18–65 years of age, who were diagnosed with migraine (including chronic migraine) and without prior exposure to GMB, were randomized 1:1 to open-label treatment with GMB 120 mg, with an initial loading dose of 240 mg, or GMB 240 mg given subcutaneously once monthly for 12 months. The initial dose of GMB was administered by site personnel, and subsequent doses were self-administered with a pre-filled syringe or autoinjector. Safety and tolerability were assessed by the incidence of serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), and adverse events leading to study discontinuation (DCAEs). Pertinent laboratory values, vital signs, electrocardiograms (ECGs), and suicidality, assessed by the Columbia-Suicide Severity Rating Scale, were analyzed. In addition, change from baseline in the number of monthly migraine headache days (MHD), functioning (assessed by the Migraine Specific Quality of Life Scale), and disability (assessed by Migraine Disability Assessment) were evaluated.

**Results:** One hundred thirty-five patients were randomized to each dose group. Most of the patients were female (80%), with an average age of 42 years, and had an average of 10.6 MHD per month at baseline. Overall, 77.8% of the patients completed the study, and 4.8% discontinued due to AEs. The TEAEs reported in ≥10% of patients in the combined dose groups included injection site pain, nasopharyngitis, and respiratory tract infection. There were 10 SAEs, each of which occurred once, 3 in the 120 mg group and 7 in the 240 mg group. Overall, there were no clinically meaningful differences between GMB doses in laboratory values, vital signs, or ECGs. None of the patients reported suicidal behavior, but 1 patient did discontinue due to suicidal ideation in the GMB 120 mg group. The overall least squares mean change in monthly MHD over 12 months for GMB 120 mg was −5.6 and for GMB 240 mg was −6.5. In addition, level of functioning improved, and disability was reduced in both dose groups.

**Conclusion:** Treatment with self-administered GMB was safe and associated with reduction in the number of monthly MHD over 1 year of treatment. Overall, there were no clinically meaningful differences in tolerability and safety for GMB 120 mg compared to GMB 240 mg. This study is registered as NCT02614287 at ClinicalTrials.gov.

Migraine Preventive Therapy

PO-01-185

A Multicenter, Prospective, Randomized, Open-label Study to Compare the Efficacy, Safety, and Tolerability of OnabotulinumtoxinA and Topiramate for Headache Prophylaxis in Adults with Chronic Migraine: The FORWARD Study

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Objectives: To compare the efficacy, safety and tolerability of onabotulinumtoxinA and topiramate for preventive treatment of chronic migraine (CM) in adults.

Methods: The FORWARD Study (ClinicalTrials.gov, NCT02191579) is a multicenter, randomized, parallel-group, prospective study. Adults with CM were randomized (1:1 ratio) to receive either 155 U of onabotulinumtoxinA (31 sites in a fixed-site, fixed-dose paradigm across 7 head/neck muscles) every 12 weeks (±7 days) for 3 treatment cycles or 50–100 mg/day of topiramate administered daily up to week 36. Patients who discontinued topiramate crossed over to receive onabotulinumtoxinA no earlier than 12 weeks and up to 3 treatment cycles. Patients recorded frequency, duration, and severity of headache, acute medication use, and interictal burden daily using an electronic diary. Other measures were assessed at follow-up clinic visits. The primary efficacy measure was a dichotomous variable (responder/nonresponder) defined as the proportion of patients with ≥50% reduction in headache day frequency during the 28-day period before week 32 (weeks 29–32). Analyses were performed on the ITT dataset using logistic regression. A worst-case imputation method was utilized to impute missing data; this replaces the missing value with the baseline value if the responder rate was missing at week 32 for any reason. Adverse events (AE) were monitored. Presented efficacy data are based on the week 32 assessment (weeks 29–32) whereas the safety data include AEs from randomization and cross-over phases.

Results: 282 patients were enrolled (onabotulinumtoxinA n = 140; topiramate n = 142) at 35 US sites. Patients were primarily female (n = 239, 84.8%) and white (n = 229, 81.2%); baseline demographics and mean (SD) baseline headache days (onabotulinumtoxinA, μ = 22.1 [±4.6]; topiramate, μ = 21.8 [±4.8]) were similar across treatment groups. The primary reasons for withdrawal were ineffective treatment (onabotulinumtoxinA, n = 7 [5.0%]; topiramate, n = 28 [19.7%]) and adverse effects (onabotulinumtoxinA, n = 5 [3.6%]; topiramate, n = 72 [50.7%]). 80 topiramate patients crossed over to onabotulinumtoxinA through the week-32 assessment. OnabotulinumtoxinA treatment demonstrated significantly higher proportion of patients with a ≥50% reduction in headache frequency at the week-32 assessment compared to baseline vs topiramate (40.0% vs 12.0%, respectively; OR, 4.98 [95% CI, 2.70–9.17]; P < 0.0001; Figure). Treatment-related AEs were reported by 17.7% and 69.0% of onabotulinumtoxinA and topiramate patients, respectively. One serious AE (nephrolithiasis) for topiramate was reported as related.

Conclusion: In this open-label study, preventive treatment of adults with CM with onabotulinumtoxinA demonstrated more favorable tolerability and was significantly more effective than topiramate.

Migraine Preventive Therapy

PO-01-186

The Impact of Fremanezumab on Headache-Related Disability in Patients With Chronic Migraine Using the Headache Impact Test (HIT-6)

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Objectives: Patients with chronic migraine (CM) experience substantially impaired daily functioning and reduced quality of life, with the occurrence of daily or near-daily headache attacks. In clinical trials, fremanezumab, a fully humanized monoclonal antibody that selectively targets calcitonin gene-related peptide, reduced the frequency, severity, and duration of headaches in patients with CM. The impact of migraine cannot be fully understood only by assessment of the frequency of headaches. The 6-item Headache Impact Test (HIT-6) is a validated tool used to measure headache-related disability. This study uses HIT-6 to assess the effect of fremanezumab versus placebo on headache-related disability.

Methods: In this multicenter, randomized, double-blind, placebo-controlled, Phase III study, eligible patients with CM were randomized 1:1:1 to receive subcutaneous injections of fremanezumab quarterly dosing (675 mg at baseline and placebo at Weeks 4 and 8), fremanezumab monthly dosing (675 mg at baseline and 225 mg at Weeks 4 and 8), or placebo at each time point over a 12-week treatment period. As a secondary endpoint, change in HIT-6 score was evaluated from baseline (Day 0) to 4 weeks after administration of the last dose of study drug. HIT-6 scores range from 36 to 78, with higher scores indicating a greater impact of headache on the daily life of the respondent. Efficacy analyses for primary and secondary endpoints were performed in the full analysis set (FAS; all randomized patients who received at least one dose of study drug and had at least 10 days of post-baseline efficacy assessments on the primary endpoint) and repeated for the per-protocol analysis set (PPS; all patients who completed the study without violation of eligibility criteria or omission of drug administration). The data were analyzed using the analysis of covariance approach, with baseline HIT-6 score and years since onset of migraine used as covariates.

Results: Treatment with both fremanezumab dose regimens yielded significant improvements in disability, as measured by the reductions in HIT-6 scores from baseline to 4 weeks after administration of the last study dose. In the FAS, the least-squares mean ± standard error changes from baseline with fremanezumab quarterly (−6.4 ± 0.45 points) and (−6.8 ± 0.44 points) monthly dosing were larger than with placebo (−4.5 ± 0.45 points); this resulted in significant differences in HIT-6 score change from baseline for fremanezumab treated patients versus placebo (quarterly: −1.9 ± 0.49 points, P = 0.0004; monthly: −2.4 ± 0.49 points, P < 0.0001). Similar treatment differences with fremanezumab versus placebo were observed in the PPS (quarterly: −2.1 ± 0.51 points, P = 0.0001; monthly: −2.3 ± 0.51 points, P < 0.0001). P-values for treatment comparisons were based on the Wilcoxon rank-sum test.

Conclusion: In this Phase III study, fremanezumab treatment demonstrated a significant improvement in headache-related disability in patients with CM.


Migraine Preventive Therapy

PO-01-187

Fremanezumab blocks CGRP induced dilatation in human cerebral, middle meningeal and abdominal arteries.

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Objectives: Fremanezumab (TEV-48125) is a fully humanized anti-CGRP monoclonal antibody (mAb) that has shown positive results in prevention of frequent episodic migraine (Bigal et al., 2015a) and of chronic migraine (Bigal et al., 2015b). Previous preclinical studies have revealed CGRP antagonistic effects on cerebral (CA) (Edvinsson et al., 2007) and middle meningeal arteries (MMA)(Juhl et al., 2007). The aim was presently to evaluate the antagonistic effects of fremanezumab on human arteries.

Methods: Arteries were removed in conjunction with neurosurgery (CA and MMA n = 4) or reconstructive abdominal surgery (AA n = 5). Ring segments of the vessels were mounted in a sensitive myograph, and the functional responses studied using pre-contraction with 30 mM...
potassium chloride (KCl), and CGRP was given in increasing concentrations ($10^{-10}$ to $10^{-2}$ M). Increasing concentrations of fremanezumab or vehicle (0.01, 0.05, 0.1 mg/ml) were given 30 min prior to the CGRP administration.

**Results:** All included arteries responded with a strong stable contraction to the application of 30 mM KCl in buffer. During this precontraction CGRP caused a concentration-dependent relaxation which differed in potency between the types of arteries (CA/MMA = 100%; AA 80%). Increasing concentrations of fremanezumab showed a shift in the EC$_{50}$ value and at higher doses a reduction of E$_{max}$: CA/MMA = 99.2 nM at 0.01 mg/ml, and 5.6 nM at 0.05 mg/ml. The highest dose showed no relaxation at all to CGRP (total blockade). AA = 182 nM at 0.01 mg/ml and 3.05 nM at 0.1 mg/ml. Vehicle did not modify the responses. The highest dose blocked the response totally to CGRP.

**Conclusion:** This study has shown that CGRP relaxes human arteries 80–100% but with different EC$_{50}$: the potency range was CA/MMA < AA. The antagonistic effect and potency of fremanezumab was similar in the human arteries, suggesting that the antibody may have effect in all the studied vessels.

**Disclosure of Interest:** L. Ohlsson: None Declared, L. Edvinsson Conflict with: Study supported by a grant from TEVA, Conflict with: Collaboration, E. Kronvall: None Declared, O. Nilsson: None Declared

**Migraine Preventive Therapy**

**PO-01-188**

**Longer term outcomes for patients with chronic migraine treated with OnabotulinumtoxinA BOTOX and implications for a Headache Service:** Real-life data for 120 patients treated at Sunderland Royal Hospital, UK

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**Objectives:** OnabotulinumtoxinA BOTOX has been demonstrated to be an effective treatment for chronic migraine. A study of the longer term outcomes of 120 patients who received up to five cycles of OnabotulinumtoxinA BOTOX between March 2013 and March 2017 was done to help predict longer term service demand and consider implications for local headache services. The number of patients who successfully transformed into episodic migraine following OnabotulinumtoxinA BOTOX treatment were calculated. Out of this cohort of patients, the number who then relapse back into more than 15 headache days per month was calculated. This number together with the number of partial responders requiring ongoing OnabotulinumtoxinA BOTOX treatment will help predict service demand.

**Methods:** 120 adults with chronic migraine were injected with OnabotulinumtoxinA BOTOX as per PREEMPT Protocol between March 2013-March 2017. Outcomes following the second, third and fifth treatments were defined according to NICE Guidance as transformation to episodic migraine (treatment success) based on <15 headache days/month for three months, partial response to treatment (treatment success) based on >30% reduction in headache days, and no response to treatment (treatment failure) based on <30% reduction in headache days. Headache Impact test scores were collected prior to every treatment with OnabotulinumtoxinA BOTOX. Secondary outcomes were adverse events and reductions in oral migraine prophylactic or analgesia.

**Results:** After the first two cycles of treatment with OnabotulinumtoxinA BOTOX, 83.8% of patients were defined as treatment success which included 31.6% whom successfully transformed into episodic migraine, and 52.2% whom had a significant partial response. 15% of patients did not respond significantly to treatment. Outcomes after the third (episodic 32.1%, partial 55.1%, no response 11.4%) and fifth (34.6%, partial 55.1%, no response 10.2%) cycles show a comparable pattern of response to that following the second cycle. For those patients who transformed into episodic migraine, 86.4% of these patients relapsed back to more than 15 headache days per month up to six months later. The average length of time patients remained in an episodic migraine pattern was 3 months (range 3–17 months).

There was a reduction of the average HIT score by 5 points. Side effects were reported in 41% patients and were mild and tolerable in most cases. 35% patients were able to reduce or discontinue oral preventative (15.8%) or analgesia/triptan treatment (19.1%).

**Conclusion:** OnabotulinumtoxinA BOTOX remains a very effective treatment for chronic migraine. The majority of patients who respond to treatment require regular treatment in the long term. This study showed a consistent pattern of response over five cycles of treatment with 83.8% to 89.7% of patients achieving treatment success and requiring ongoing treatment. There is a trend for better outcomes with increasing number of treatment cycles. This allows future predications for service demand which may require increasing numbers of trained injectors and clinic capacity. Support in the community may be required in the long term. Cost effectiveness of the treatment can be measured in the reduction of oral medications, increased work productivity and reduced GP or emergency hospital admissions.
Disclosure of Interest: None Declared

Migraine Preventive Therapy

PO-01-189

The effectiveness of 12-week Tai Chi training in the prophylaxis of episodic migraine: a pilot randomized controlled trial in Chinese women

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Objectives: Tai Chi is a body-mind exercise. Its prophylactic efficacy on migraine attack remains largely unknown. The purpose of this study was to test the effectiveness of 12-week Tai Chi training in the prophylaxis of episodic migraine in Chinese women.

Methods: A two-arm individual level randomized controlled trial was designed. Eighty-two local women aged 18 to 65 years and diagnosed with episodic migraine were randomized to the Tai Chi group or the waiting list control group. A modified 32-short form Yang-style Tai Chi training with 1 hour per day, 5 days per week for 12 weeks was adopted as intervention. The control group received a “delayed” Tai Chi training at the end of the trial. The primary outcomes were the difference in migraine days between 4 weeks before baseline and 9–12 weeks after randomization, and the proportion of subjects with at least a 50% reduction of the number of attacks per month. The changes of headache intensity (measured by Visual Analogue Scale) and duration (hours) were also analyzed.

Results: Of 189 women screened, 82 eligible women completed the baseline assessment. After randomization, 9 women withdrew immediately, finally 40 in Tai Chi group and 33 in control group were involved in the analysis. On average, women in Tai Chi group had 3.6 (95% CI: 2.7 to 4.4) days reduction of migraine attack, whereas no significant between-group differences were found (both P > 0.05). The intensity and duration of headache had 0.6 (95% CI: −1.2 to 0.0, P < 0.05) units and 1.2 (IQR: −1.5 to 1.1, P < 0.05) hours reduction in Tai Chi group, respectively. Whereas no significant between-group differences were found (both P > 0.05).

Conclusion: The 12-week Tai Chi training significantly decreased migraine attack frequency. Its effectiveness on headache alleviation and duration shortening needs further larger sample investigations.

Disclosure of Interest: None Declared

Migraine Preventive Therapy

PO-01-190

A Phase 1 Study to Assess the Pharmacokinetics, Safety, Tolerability and immunogenicity of Fremanezumab (formerly TEV-48125) doses (225 mg, 675 mg and 900 mg) in Japanese and Caucasian Healthy Subjects

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Objectives: Fremanezumab (formerly TEV-48125) is a fully humanized IgG2a monoclonal antibody that selectively blocks both CGRP isoforms (α- and β) from binding to the CGRP receptor. Fremanezumab was effective and well-tolerated as a preventive treatment of episodic migraine and chronic migraine in phase 2 and phase 3 trials. The present study evaluated the pharmacokinetic profile, safety, and immunogenicity of fremanezumab doses tested in the phase 2 and 3 trials (225 mg, 675 mg and 900 mg) following single administration in Japanese (n = 32) and Caucasian (n = 32) healthy subjects.

Methods: Japanese and Caucasian healthy subjects were enrolled into 1 of 4 cohorts: cohorts 1 and 3 were Japanese and cohorts 2 and 4 were Caucasians. Subjects in each cohort were randomly assigned to 1 of 4 treatments: 225, 675, or 900 mg fremanezumab, or placebo. In the first cohort only, a dose escalation scheme was applied where study drug was not escalated to the next dose level unless the safety and tolerability of the previous doses were acceptable by sponsor and clinical team. Caucasian subjects were matched to Japanese subjects based on gender, age (±10 year) and BMI (±20%). PK and immunogenicity sampling and safety & tolerability assessments occurred during 13 clinic visits including 1 inpatient visit from day −1 to day 6 and 12 ambulatory visits between post treatment days 8–225.

Results: Sixty-two subjects out of 64 completed the study; 2 Japanese subjects (1 225 mg and 1 900 mg fremanezumab) withdrew consent because of family emergencies. Overall median Tmax was similar across doses and ranged from 5 to 7 days. Mean half-lives were similar across doses (range 32.23 to 36.15 days). No differences due to race/ethnicity. Increases in Cmax and AUCs were slightly greater than dose proportional for both Japanese and Caucasian subjects. Fremanezumab exposures were generally higher with lower body weights. No deaths or
SAEs; most frequently occurring AEs (≥2 subjects) were injection site reactions, abdominal pain, headache, upper respiratory tract infection, constipation and nasopharyngitis. Local tolerability of the SC fremanezumab injection was comparable between Japanese and Caucasian subjects. No treatment-induced anti-drug-antibodies occurred and there were no clinically meaningful changes in laboratory findings.

**Conclusion:** Overall fremanezumab was safe and well tolerated following SC single doses (225, 675, or 900 mg). Pharmacokinetic exposure parameters per dose were similar for Japanese and Caucasians. Half-life following SC injections support the once monthly SC injections of 225 mg and quarterly SC injections of 675 mg as a treatment doses.


**Migraine Preventive Therapy**

**PO-01-191**

**Cognitive Behavioral Therapy Experience in Patients With Refractory Chronic Migraine**

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**Objectives:** Cognitive Behavioral Therapy (CBT) for pain management is a form of therapy which aims to modify thoughts and behavior for realistic and balanced way and change in behaviors. CBT in migraine intends to arrange the behavioral interventions for controlling headache attacks. There are limited studies to assess the efficacy for CBT for patients with pharmacotherapy resistant chronic migraine in our population. We investigated the effects of CBT for patients with refractory chronic migraine on pain severity, attack frequency, disability, anxiety, and depression.

**Methods:** Fourteen patients with chronic migraine were referred from headache clinic to psychiatry department who participated regularly for follow-up therapy sessions once in 2 weeks for six months. After 2 sessions of psychiatric evaluation, subjects had CBT sessions lasting 30 minutes for 12 times and were taught for relaxation exercises. Hamilton Depression and Anxiety Inventories, for assessing the severity of pain visual analogue scale (VAS) and for evaluating migraine related disability Migraine Disability Assessment Test (MIDAS) were used before and after CBT.

**Results:** The number of male subjects was 5 and female subjects 9 and their mean age was 34.35 ± 8.17. The average disease duration was 13.07 ± 7.18 and 12 patients had a previous psychiatric evaluation. Seven patients had depression, 4 patients had anxiety disorders and 1 patients had trauma-related disorders. Nine patients were under migraine prophylactic therapies. Before CBT, Hamilton Depression scores were 29.07 ± 7.74 and after 14.21 ± 7.7 which was statistically significant. Before CBT, Hamilton Anxiety scores were 26.8 ± 11.7 and after 11.7 ± 2.6 which was statistically significant (p = 0.000). Before CBT, VAS scores were 7.74 and after CBT, 20.12 ± 16.6 (p = 0.000).

**Conclusion:** CBT reduced migraine severity, number of attacks and disability statistically significant in patients with chronic migraine. CBT should be included in headachtreatment more often.

**Disclosure of Interest:** None Declared

**Migraine Preventive Therapy**

**PO-01-192**

**Effect of iron administration for migraine with iron deficiency**

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**Objectives:** To examine the effects of iron replacement therapy in migraines complicated by iron deficiency.

**Methods:** Patients with migraine who visited our clinic were enrolled in the study after consent. Plasma hemoglobin, MCV, and ferritin levels were obtained. Iron replacement was offered to patients whose ferritin levels were less than 25 ng/ml at the time of enrollment. If a patient opted for the therapy, 50 mg/day of sodium ferrous citrate was administered for 3 months. We continued other

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ongoing therapies for the rest of the patients (patient who declined iron therapy and patients whose ferritin levels were 25 ng/ml or more). In both groups, we did not alter the regimen for migraine including acute-phase treatment and preventional therapies. Overt iron deficiency was defined as ferritin levels of less than 25 ng/ml with hemoglobin levels of less than 13 g/dl for men and less than 12 g/dl for women; subclinical iron deficiency was defined as ferritin levels less than 25 ng/ml with hemoglobin levels of 13 g/dl or more for men and 12 g/dl or more for women. Outcomes were measured by number of headache days per month (NHD/M) 3 months after enrollment, and was classified into 4 groups: “cured” if NHD/M was 0, “improved” if NHD/M decreased but remained more than 1 day per month, "not changed" if there was no change in NHD/M, and "unknown" if NHD/M could not be measured.

Results: 63 patients (13 men and 50 women) with migraine were enrolled in the study. Of them, overt iron deficiency was found in 7 patients (1 men and 6 women), and subclinical iron deficiency in 14 patients (0 men and 14 women). Prevalence of iron deficiency (overt and subclinical) in the patients with migraine was 33.3% (21/63). All patients with iron deficiency opted to receive iron replacement. After 3 months of therapy/observation, 11/21 patients in the iron replacement group were “cured”, 8/21 “improved”, 2/21 “did not change”, and 0/21 “unknown”; 11/42 patients in non-intervention group were “cured”, 15 “improved”, 13 “did not change”, and 3 “unknown”. Therefore, migraine was cured in 52% (11/21) patients in the iron administration group, while the proportion was merely 26% (11/42) in the non-intervention group. If therapeutic effect was defined as the sum of "cured" and "improved" groups, more therapeutic effect was found in 90% (19/21) the iron replacement group compared to 62% 26/42 in non-intervention group (p = 0.0215).

Conclusion: In patients with migraine complicated by overt or subclinical iron deficiency, oral iron replacement therapy led to improved control of symptom of migraine.

Disclosure of Interest: None Declared

Migraine Preventive Therapy

PO-01-193

Cognitive Behavioral Therapy in Turkish Patients With Refractory Chronic Migraine

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Objectives: Cognitive Behavioral Therapy (CBT) for pain management is a form of therapy which aims to modify thoughts and behavior for realistic and balanced way and change in behaviors. CBT in migraine intends to arrange the behavioral interventions for controlling headache attacks. There are limited studies to assess the efficacy for CBT for patients with pharmacotherapy resistant chronic migraine in our population. We investigated the effects of CBT for patients with refractory chronic migraine on pain severity, attack frequency, disability, anxiety, and depression.

Methods: Fourteen patients with chronic migraine were referred from headache clinic to psychiatry department who participated regularly for follow-up therapy sessions once in 2 weeks for six months. After 2 sessions of psychiatric evaluation, subjects had CBT sessions lasting 30 minutes for 12 times and were taught for relaxation exercises. Hamilton Depression and Anxiety Inventories, for assessing the severity of pain visual analogue scale (VAS) and for evaluating migraine related disability Migraine Disability Assessment Test (MIDAS) were used before and after CBT.

Results: The number of male subjects was 5 and female subjects 9 and their mean age was 34.35 ± 8.17. The average disease duration was 13.07 ± 12.18 and 12 patients had a previous psychiatric evaluation. Seven patients had depression, 4 patients had anxiety disorders and 1 patients had trauma-related disorders. Nine patients were under migraine prophylactic therapies. Before CBT, Hamilton Depression scores were 29.07 ± 7.74 and after 14.21 ± 7.7 which was statistically significant. Before CBT, Hamilton Anxiety scores were 26.8 ± 11.7 and after 11.7 ± 2.6 which was statistically significant (p = 0.000). Before CBT, MIDAS scores were 55.5 ± 20.4 and after CBT, 20.12 ± 16.6 (p = 0.000).

Conclusion: CBT reduced migraine severity, number of attacks and disability statistically significant in patients with chronic migraine. CBT should be included in headache treatment more often.

Disclosure of Interest: None Declared
Migraine Preventive Therapy

PO-01-194

A Phase 3, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Eptinezumab in Frequent Episodic Migraine Prevention: Primary Results of the PROMISE I (PRevention Of Migraine via Intravenous eptinezumab Safety and Efficacy 1) Trial

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Objectives: Calcitonin gene-related peptide (CGRP) is associated with the facilitation of pain transmission and neuronal sensitization in both central and peripheral sensory pathways, and is believed to have an important role in migraine pathophysiology. PROMISE-1 is a Phase 3 study to evaluate the efficacy and safety of eptinezumab, an anti-CGRP monoclonal antibody, for the prevention of frequent episodic migraine (FEM).

Methods: Adult patients with 4 to 14 headache days per month, of which 4 or more met ICHD-II criteria for migraine, were randomized to receive eptinezumab 300 mg, 100 mg, 30 mg, or placebo by intravenous (IV) infusion every 12 weeks for 4 total doses. The current analyses use double blind data through Week 24 (2 doses). The primary endpoint was the mean change in migraine days over Weeks 1–12 compared to a 28-day baseline. Key secondary endpoints include: the percent of patients who achieved ≥75% reduction in monthly migraine days over Weeks 1–4 and Weeks 1–12; the percent of patients who achieved ≥50% reduction in monthly migraine days over Weeks 1–12; and the percent reduction in the proportion of patients experiencing migraine on the first day after infusion. Statistical significance versus placebo was prespecified at the two-sided p value <0.05.

Results: 888 patients were included in the efficacy evaluation. Baseline migraine days averaged 8.5 days/month across groups. There were highly significant decreases in monthly migraine days for Weeks 1–12 in the eptinezumab 300 mg, 100 mg, and 30 mg groups vs the placebo group (−4.3, −3.9, and −4.0 vs −3.2; p = 0.0001, p = 0.0179, and p = 0.0045*, respectively). The 75% migraine responder rates over Weeks 1–4 were significantly greater in the eptinezumab 300 mg, 100 mg, or 30 mg groups vs the placebo group (31.5%, 30.8%, and 30.0% vs 20.3%; p = 0.0066, p = 0.0112, and p = 0.017*, respectively). The 75% migraine responder rate was maintained in the 300 mg group over Weeks 1–12 (300 mg, 29.7%, p = 0.0007; 100 mg, 22.2%, p = NS; 30 mg, 24.7%, p = 0.0272*, placebo, 16.2%). A significantly higher proportion of patients given eptinezumab had a ≥50% reduction in migraine days over Weeks 1–12 (300 mg, 56.3%, p = 0.0001; 100 mg, 49.8%, p = 0.0085*; 30 mg, 50.2%, p = 0.0064* placebo, 37.4%). The percent-ages of patients with a migraine on Day 1 decreased by ≥50% in the eptinezumab 300 mg and 100 mg groups (53.6% and 51.3%, respectively) and 44.6% in the 30 mg group vs. 20.7% with placebo (p = 0.0087*, p = 0.0167*, and p = 0.074* respectively). Adverse event rates for epti-nezumab were similar to placebo.

Conclusion: In PROMISE-1, eptinezumab demonstrated efficacy for migraine prophylaxis across several measures. Reductions in migraine activity were seen as early as Day 1 and maintained at similar levels over Weeks 1–4 and Weeks 1–12. Adverse event rates for eptinezumab were similar to placebo and its safety profile was consistent with previous studies.

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Migraine Preventive Therapy

PO-01-195

A Phase 3 Placebo-Controlled Study of Galcanezumab in Patients with Chronic Migraine: Results from the 3-month Double-Blind Treatment Phase of the REGAIN Study

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Objectives: To determine if galcanezumab (GMB), a humanized monoclonal antibody that selectively binds to the calcitonin gene-related peptide (CGRP), is superior to placebo in the prevention of chronic migraine at doses of 120 mg or 240 mg/month.

Methods: This was a Phase 3, double-blind, randomized, placebo-controlled, 3-month study with a 9-month open-label extension. Eligible patients 18–65 years of age with chronic migraine, defined as ≥15 headache days per month, of which at least 8 met criteria for migraine, were randomized 2:1:1 to subcutaneous injections of placebo (N = 558), GMB 120 mg (N = 278), or GMB 240 mg (N = 277) given once monthly for 3 months. The primary endpoint was the overall mean change from baseline in the number of monthly migraine headache days (MHD) during the 3-month double-blind treatment phase. Key secondary measures included the percentage of patients with ≥50%, ≥75%, and 100% reduction in monthly MHD, reduction in monthly MHD requiring acute migraine treatments, change in the Role Function-Restrictive (RF-R) domain score of the Migraine-Specific Quality of Life Questionnaire (MSQ), and change in the Patient Global Impression of Severity (PGI-S) rating.

Results: Mean number of monthly MHD at baseline was 19.4 and was similar across treatment groups. At the primary endpoint, both GMB doses demonstrated statistically significant difference from placebo in overall mean reduction (least square [LS] mean change) in number of monthly MHD during the 3-month double-blind treatment phase: placebo: −2.74, GMB 120 mg: −4.83, GMB 240 mg: −4.62 (p < .001 for each dose). Statistically significant improvements in MHD for both GMB doses were also observed at each month starting from Month 1. The mean percentages over all 3 months of patients with ≥50% reduction from baseline in MHD were significantly higher for both GMB doses than placebo (p < .001 for both doses). Compared with placebo, patients in the 240 mg GMB group also had significantly higher percentages of patients with ≥75% response rates (p < .001), greater reductions in monthly MHD requiring acute migraine treatment (p < .001), and greater improvement in the MSQ RF-R (p < .001) and PGI-S (p < .001). The 120-mg dose did not separate from placebo on those additional key secondary measures after multiplicity adjustment. There were no clinically meaningful differences between either GMB dose and placebo on any safety parameters except for a higher incidence of injection site reaction (p < .05), injection site erythema (p < .01), and sinusitis (p < .05) in the GMB 240 mg group relative to placebo.

Conclusion: Both doses of GMB were superior to placebo in the reduction in monthly MHD, with significantly higher percentages of patients reducing their monthly MHD by ≥50%. The 240 mg dose was also superior to placebo on most key secondary measures. Both GMB doses appear to be efficacious, safe, and well-tolerated for the preventive treatment of chronic migraine. This study is registered as NCT02614261 at ClinicalTrials.gov.


Migraine Preventive Therapy

PO-01-196

Efficacy and Safety of 2 Dose Regimens of Subcutaneous Fremanezumab (TEV-48125) Versus Placebo for the Preventive Treatment of Chronic Migraine

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Objectives: Fremanezumab, a fully humanized monoclonal antibody targeting the calcitonin gene-related peptide (CGRP) ligand, is a preventive treatment designed to
specifically target a pathophysiologic mechanism of migraine. This study evaluated the efficacy, tolerability and safety of two subcutaneous (SQ) dose regimens of fremanezumab in the preventive treatment of chronic migraine (CM).

**Methods:** This was a 16-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in adults with CM. Patients maintained a daily diary during a 28-day baseline period. Patients were assigned randomly to 1:1:1 ratio to 1 of 3 treatment groups: (1) monthly dosing: an initial dose of 675 mg of fremanezumab followed by 225 mg of fremanezumab at months 2 and 3 (2) quarterly dosing: a single dose of 675 mg of fremanezumab at month 1, followed by placebo injections at months 2 and 3 and (3) monthly administration of matching placebo. The primary efficacy endpoint, the mean change from baseline (28-day run-in period) to the 12-week randomization period in the monthly average number of headache days of at least moderate severity was analyzed using an analysis of covariance method or the Wilcoxon rank sum test.

**Results:** Patients treated with fremanezumab had a significant reduction in the number of monthly headache days of at least moderate severity vs. placebo (−2.5 days) during the 12-week period after 1st dose, for both monthly (−4.6 days; p < 0.0001) and quarterly (−4.3 days; p < 0.0001) dosing regimens. Patients treated with fremanezumab had statistically significant reduction in the number of monthly migraine days during the 12-week period after the 1st dose, for both dosing regimens [monthly (−5.0 days from a baseline of 16.0 days) and quarterly (−4.9 days from a baseline of 16.2 days; p < 0.0001)] vs. placebo (−3.2 days from a baseline of 16.3 days), and during the 4-week period after 1st dose, for both dosing regimens (p < 0.0001). Fremanezumab was also significantly superior to placebo for the following prespecified secondary endpoints; reduction in the number of monthly days of acute headache medication use for both monthly (−4.2 days) and quarterly (−3.7 days) versus placebo (−1.9 days; p < 0.0001). A ≥50% reduction in monthly average number of headache days of at least moderate severity were also statistically significantly improved with both dosing regimens [monthly (40.8%) and quarterly (37.6%); p < 0.0001] as compared to placebo (18.1%); improvement in disability as measured by the 6-item Headache Impact Test (HIT-6) with both dosing regimens [monthly (−6.8; p < 0.0001) and quarterly (−6.4; p = 0.0001)] as compared to placebo (−4.5). The most commonly-reported adverse event in the study was injection site pain, with similar rates in the placebo and active groups.

**Conclusion:** These results confirm the efficacy and favorable tolerability profile of fremanezumab, administered as both monthly and quarterly subcutaneous injections, for the preventive treatment of chronic migraine.


**Migraine Preventive Therapy**

**PO-01-197**

**Phase 3 Studies (EVOLVE-1 & EVOLVE-2) of Galcanezumab in Episodic Migraine: Results of 6-Month Treatment Phase**

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**Objectives:** Galcanezumab, a humanized monoclonal antibody that selectively binds to the calcitonin gene-related peptide, was investigated in two Phase 3 studies (EVOLVE-1 and EVOLVE-2) to determine superiority to placebo in the prevention of migraine headache.

**Methods:** EVOLVE-1 and EVOLVE-2 were double-blind, 6-month studies in patients with episodic migraine (4 to 14 monthly migraine headache days [MHD]) conducted in North America and globally, respectively. Patients were randomized 2:1:1 to monthly subcutaneous injections of placebo, galcanezumab 120 mg or 240 mg. Primary endpoint was overall mean change from baseline in the number of monthly MHD during Months 1–6. Key secondary measures included rates of ≥50%, ≥75%, and 100% reduction in monthly MHD and overall mean change from baseline in monthly MHD with acute migraine treatments, and mean change from baseline over Months 4–6 on the Role Function-Restrictive domain score of the Migraine-Specific Quality of Life Questionnaire (MSQ-RFR) and Patient Global Impression-Severity of Illness (PGI-S).

**Results:** Baseline mean number of monthly MHD was 9.1 for both studies. Both galcanezumab doses demonstrated a statistically significant improvement compared with placebo (both studies p < .001) for overall mean change in monthly MHD (EVOLVE-1: placebo = −2.81; GMB 120 mg = −4.73; GMB 240 mg = −4.57; EVOLVE-2: placebo = −2.28; GMB 120 mg = −4.29; GMB 240 mg = −4.18). Percentage of patients with MHD reductions of
≥50%, ≥75%, or 100% were significantly higher for each galcanezumab dose compared with placebo (both studies p < .001). Patients had a significantly greater overall mean reduction of monthly number of MHD with acute migraine treatment for both galcanezumab doses relative to placebo (both studies p < .001). Mean change in MSQ-RFR and PGI-S ratings were statistically significant for each galcanezumab dose versus placebo (MSQ-RFR: p < .001 and PGI-S: p < .05, in both studies). There were no statistically significant differences between galcanezumab and placebo on the most common treatment-emergent adverse events except for a greater incidence of injection-site pruritus (both studies/doses p < .01) and injection-site reaction (both studies/doses p < .05), and injection-site erythema (p < .05, galcanezumab 240 mg) in EVOLVE-2.

Conclusion: Both doses of galcanezumab met the primary and all key secondary objectives, after adjusting for multiplicity. Treatment effects were similar across galcanezumab doses for efficacy, and safety; however, there was a higher rate of injection-site pruritus and reaction in galcanezumab-treated patients in both studies. EVOLVE-1 and EVOLVE-2 demonstrated that galcanezumab, at either 120 mg or 240 mg monthly, provided clinical benefit and improved function in patients with episodic migraine.

Studies were registered as NCT02614183 and NCT02614196 at ClinicalTrials.gov.


Migraine Preventive Therapy

PO-01-198

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of Erenumab on Exercise Time During a Treadmill Test in Patients with Stable Angina

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Objectives: During myocardial ischemia, cardiac sensory nerves release a number of vasodilatory mediators in addition to calcitonin gene-related peptide (CGRP). To date, the relative importance of the CGRP pathway among the many biochemical changes that occur during myocardial ischemia has not been established. Erenumab, a human anti-CGRP receptor monoclonal antibody, is being developed for preventive treatment of migraine. The primary objective of this study was to evaluate the effect of erenumab compared with placebo on exercise capacity in patients with stable angina as measured by total exercise time (TET) during an exercise treadmill test (ETT).

Methods: This study was a double-blind, placebo-controlled study in patients with stable angina due to documented coronary artery disease. Patients were randomized 1:1 to a single intravenous infusion of erenumab 140 mg or placebo stratified by baseline TET (<7 minutes or 3–7 minutes) defined as the average TET of two qualifying ETTs performed during screening. Following study drug administration, a post-administration ETT was conducted on Day 1. The primary endpoint was the change from baseline in exercise duration as measured by TET with a non-inferiority margin of −90 seconds and was analyzed using an analysis of variance model with treatment, randomization strata (<7 or ≥7 minutes), age (<65, ≥65) and sex as covariates. Secondary efficacy endpoints included time to onset of ≥1 mm ST-segment depression and time to onset of exercise-induced angina during the ETT. Safety follow-up visits occurred every 2–4 weeks for 12 weeks. At the time of primary analysis all patients had a postbaseline ETT and 38 patients (43%) had completed the week 12 visit.

Results: Eighty-nine patients were enrolled in the study. Baseline demographics and disease characteristics were similar between groups. In the erenumab group, the LS mean (SE) change from baseline in TET was −2.9 [14.8]
seconds and in the placebo group it was 8.1 [14.4] seconds. The adjusted mean (90% confidence interval [CI]) treatment difference in change from baseline in TET was −11.0 (−44.9, 22.9) seconds. The TET change from baseline in the erenumab group was non-inferior to that observed in the placebo group, as the lower bound of the CI (−44.9) did not reach the pre-defined non-inferiority margin of −90 seconds, supporting the hypothesis that erenumab does not substantially decrease exercise duration. There was no difference observed between erenumab and placebo groups for the secondary endpoints of time to exercise-induced angina (hazard ratio [90% CI]: 1.11 [0.73, 1.69], p = 0.69) or time to onset of ≥1 mm ST-segment depression (hazard ratio [95% CI]: 1.14 [0.76, 1.69], p = 0.59). Adverse events were reported by 13.6% of erenumab-treated patients and by 27.3% of placebo patients. Maximum changes from baseline in vital signs (systolic blood pressure, diastolic blood pressure and heart rate) during the ETT were similar between the two groups.

Conclusion: Erenumab did not adversely affect exercise time in an at-risk population of patients with stable angina. No new safety concerns were identified. These results suggest that inhibition of the CGRP pathway does not worsen myocardial ischemia and support the hypothesis that other vasodilatory mechanisms and the CGRP pathway are redundant responses in patients with chronic stable angina.

Disclosure of Interest: C. Depre Conflict with: Amgen, Conflict with: Amgen, L. Antalik: None Declared, A. Starling Conflict with: eNeura, Eli Lilly & Company, Amgen, Alder, M. Koren Conflict with: Jacksonville Center for Clinical Research that received research and consulting fees from Amgen, O. Eisele Conflict with: Amgen, Y. Kubo Conflict with: Amgen, R. Lenz Conflict with: Amgen, Conflict with: Amgen, D. Mikol Conflict with: Amgen, Conflict with: Amgen

Migraine Preventive Therapy

PO-01-199

Eptinezumab Infusion Associated with Meaningful Reductions in Daily Migraine Activity on Day 1 and Over Weeks 1 Through 4 in Patients with Frequent Episodic Migraine: Results of the PROMISE-1 (PRevention Of Migraine via Intravenous eptinezumab Safety and Efficacy 1) Trial

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3Clinical Research Institutes, Minneapolis
4Headache Wellness Center, Greensboro
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Objectives: Calcitonin gene-related peptide (CGRP) is associated with the facilitation of pain transmission and neuronal sensitization in both central and peripheral sensory pathways, and is believed to have an important role in migraine pathophysiology. PROMISE-1 is a Phase 3 study to evaluate the efficacy and safety of eptinezumab, an anti-CGRP monoclonal antibody, for the prevention of frequent episodic migraine (FEM). Here we describe the effect of eptinezumab on migraine activity from Day 1 and through Week 4 after an intravenous (IV) infusion.

Methods: Adult patients with 4 to 14 headache days per month, of which 4 or more met ICHD-II criteria for migraine, were randomized to receive eptinezumab 300 mg, 100 mg, 30 mg, or placebo by IV infusion every 12 weeks for 4 total doses. Current analyses use double blind data through Week 24 (2 doses). The primary endpoint was the mean change in monthly migraine days over Days 1–12. Key secondary endpoints evaluated here are the percentage of patients with a migraine (migraine prevalence) on the day after the first infusion (Day 1) and the percentage of patients who had ≥75% reduction in monthly migraine days over Weeks 1–4. An exploratory analysis evaluated the percentage of patients with a migraine on any given day during Weeks 1–4. Statistical significance versus placebo was pre-specified at the two-sided p value <0.05.

Results: 888 patients received study treatment and were included in the efficacy analyses. Baseline migraine days averaged 8.5 days/month across groups. There were highly significant decreases in mean change from baseline in monthly migraine days for Weeks 1–12 in the eptinezumab 300 mg, 100 mg, and 30 mg groups vs the placebo group (−4.3, −3.9, and −4.0 vs −3.2; p = 0.0001, p = 0.0179, and p = 0.0045 respectively). The percentages...
of patients with a migraine on Day 1 decreased by over 50% in the eptinezumab 300 mg and 100 mg groups (53.6% and 51.3%, respectively) and 44.6% in the 30 mg group vs. 20.7% with placebo (p = 0.0087*, p = 0.0167*, and p = 0.074* respectively). These reductions were maintained at similar magnitudes through Week 4 as evidenced by mean daily migraine prevalence by week for Weeks 1–4. Nearly 1/3 of patients in the 300 mg, 100 mg, and 30 mg groups had a ≥75% reduction in migraine days vs. placebo over Weeks 1–4 (31.5%, 30.8%, and 30.0% vs. 20.3%; p = 0.0066, p = 0.0112, and p = 0.017*, respectively). Adverse event rates for eptinezumab were similar to placebo.

*unadjusted

**Conclusion:** In PROMISE-1, eptinezumab demonstrated efficacy for migraine prevention across several measures. Reductions in migraine prevalence of up to 54% were seen as early as Day 1 and maintained at similar levels through Week 4. These results are consistent with the finding that nearly 1/3 of patients given eptinezumab had a ≥75% reduction in migraine days over Weeks 1–4. Adverse event rates were similar to placebo and eptinezumab’s safety profile was consistent with previous studies.

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**Migraine Preventive Therapy**

**PO-01-200**

**Benefit-Risk Assessment of Migraine Prophylaxis Treatments Using Likelihood of Being Helped or Harmed (LHH)**

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**Objectives:** A key measure of successful therapy in migraine is the ability to sustain efficacy. Numerous prophylactic medications are available for this chronic disorder; however most of them have major shortcomings primarily due to variable efficacy and poor tolerability due to side effects. This study aimed to evaluate the benefit-risk of novel CGRP receptor antagonist erenumab, relative to other approved prophylactic migraine therapies

**Methods:** Potential trials for inclusion were identified via a published systematic literature review1 updated up to November 2016 using MEDLINE. As at the time of evaluation erenumab’s complete pivotal trial results were unpublished, clinical study reports were used (NCT02066415, NCT02456740). The ≥50% responder rates and discontinuations due to adverse events were defined as primary efficacy and tolerability variables to generate numbers needed to treat (NNT) and harm (NNH). The LHH as a quantitative benefit-risk measure was computed based on the ratio of NNH/NNT. Sensitivity analyses were conducted using alternative efficacy and tolerability data.

**Image:**

**Table 1**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Chronic migraine (CM)</th>
<th>Episodic migraine (EM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erenumab 160 mg</td>
<td>Topiramate 100 mg</td>
<td>OnabotulinumtoxinA</td>
</tr>
<tr>
<td>NNT</td>
<td>6</td>
<td>4 and 6</td>
</tr>
<tr>
<td>NNH</td>
<td>4 and 6</td>
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</table>

**Results:** Of 146 articles assessed, 9 RCTs (11 articles) met inclusion/exclusion criteria and were deemed of high quality per the Jadad score. Propranolol, topiramate, and onabotulinumtoxinA (the latter approved for CM only) were retained as comparators as they are approved for migraine prophylaxis and available in the majority of European countries. Table 1 shows an NNT of around 6 in both CM and EM for erenumab. This low NNT is numerically comparable to topiramate and onabotulinumtoxinA and show the strong treatment benefit of erenumab. NNH showed substantial differences among treatments, with higher numbers indicating better tolerability for erenumab. A favorable relative benefit-risk was seen for erenumab with LHHs of 41.7 and 166.7 for CM and EM respectively. In comparison, LHHs were lower in CM for topiramate (1.6 and 3.3) and onabotulinumtoxinA (4.3), and in EM, for topiramate (1.6) and propranolol (2.2). Sensitivity analyses showed...
Methods: This was a 16-week, multicenter, randomized, preventive treatment of episodic migraine (EM). Fremanezumab, a fully humanized monoclonal antibody targeting the calcitonin gene-related peptide (CGRP) ligand, is a preventive treatment designed to specifically target a pathophysiologic mechanism of migraine. This study specifically targeted a pathophysiologic mechanism of migraine; it has proven efficacy in the treatment of migraine. The objective was to evaluate the efficacy, tolerability and safety of two subcutaneous (SQ) dose regimens of fremanezumab in the preventive treatment of migraine compared with other migraine prophylactic treatments available in Europe.

Disclosure of Interest: P. Vo Conflict with: Novartis, S. Wen Conflict with: Novartis, M.-L. Martel Conflict with: Xcenda, D. Mitsikostas Conflict with: 1st Neurology Department, Aegionin Hospital, National and Kapodistrian University of Athens, U. Reuter Conflict with: Department of Neurology, Charité Universitätsmedizin Berlin, J. Klatt Conflict with: Novartis

Migraine Preventive Therapy

PO-01-201

Efficacy and Safety of 2 Dose Regimens of Subcutaneous Administration of Fremanezumab (TEV-48125) Versus Placebo for the Preventive Treatment of Episodic Migraine

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Objectives: Fremanezumab, a fully humanized monoclonal antibody targeting the calcitonin gene-related peptide (CGRP) ligand, is a preventive treatment designed to specifically target a pathophysiologic mechanism of migraine; it has proven efficacy in the treatment of migraine. This study evaluated the efficacy, tolerability and safety of two subcutaneous (SQ) dose regimens of fremanezumab in the preventive treatment of episodic migraine (EM).

Methods: This was a 16-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in adults with EM. Patients maintained a daily diary during a 28-day baseline period. Patients were assigned randomly to a 1:1:1 ratio to one of three treatment groups: (1) monthly dosing with 225 mg of fremanezumab (2) quarterly dosing: a single dose of 675 mg of fremanezumab at month 1, followed by placebo injections at months 2 and 3 and (3) monthly administration of matching placebo. The primary efficacy endpoint, the mean change from baseline (28-day run-in period) to the 12-week randomization period in the monthly average number of migraine days was analyzed using an analysis of covariance method or the Wilcoxon rank sum test.

Results: Patients treated with fremanezumab had a significant reduction in the number of monthly migraine days during the 12-week period vs. placebo (−2.2 days from a baseline of 9.1 days), for both dosing regimens [monthly (−3.7 days from a baseline of 9.2 days) and quarterly (−3.4 days from a baseline of 8.9 days); p < 0.0001], and during the 4-week period after 1st dose, for both dosing regimens (p < 0.0001). Patients treated with fremanezumab had a significant reduction in the number of monthly headache days of at least moderate severity during the 12-week period for both dosing regimens [monthly (−2.9 days) and quarterly (−3.0 days); vs placebo (−1.5 days); p < 0.0001], and during the 4-week period after 1st dose, for both dosing regimens (p < 0.0001). Fremanezumab resulted in a statistically significant reduction in the number of monthly days of acute headache medication use for both [monthly (−3.0 days) and quarterly (−2.9 days); p < 0.0001] versus placebo (−1.6 days). A ≥50% reduction in monthly average number of migraine days was also significantly improved with both dosing regimens [monthly (47.7%) and quarterly (44.4%); p < 0.0001] as compared to placebo (27.9%). Improvement in disability was observed as measured by Migraine Disability Assessment (MIDAS) with monthly (−24.6; p = 0.0021) and quarterly (−23.0; p = 0.0023) as compared to placebo (−17.5). The most commonly-reported adverse event in the study was injection site pain with rates in active groups 4% higher than placebo.

Conclusion: These results confirm the efficacy and favorable tolerability profile of fremanezumab, administered as both monthly and quarterly subcutaneous injections, for the preventive treatment of episodic migraine.


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Migraine Preventive Therapy

PO-01-202

Evaluating Clinically Meaningful Within-Subject Change in Functioning Associated with Migraine Prevention Using the Migraine Physical Function Impact Diary (MPFID)

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Objectives: To establish a clinically meaningful within-patient change (CMWPC) in migraine impact scores as measured by the Migraine Physical Function Impact Diary (MPFID) and to evaluate these CMWPCs in the STRIVE study, a Phase 3 clinical trial of erenumab subjects with episodic migraine (EM).

Methods: MPFID is a 13-item questionnaire that measures the impact of migraine on physical function in the past 24 hours. Monthly MPFID domain scores (Impact on Everyday Activities [EA]; 7 items and Physical Impairment [PI; 5 items]) are based on daily scores averaging across migraine and non-migraine days and range from 0–100 (higher score = greater impact). A Global Impact on Everyday Activities score (G-EA) is generated from a single item. CMWPCs for MPFID were developed using anchor- and distribution-based methods using data pooled across treatment groups from a clinical trial of erenumab for the prevention of migraine (ARISE; NCT02483585) and data from adults with EM who recently initiated or changed their migraine preventive regimen in an observational study. Clinically relevant anchor variables, including ≥30% and ≥50% reduction in monthly migraine days (MMD) and ≥20% and ≥50% reduction in MPFID G-EA score, were used to estimate average within-subject point change from baseline in MPFID domain scores; distribution-based estimates based on variability were considered supportive. These CMWPCs were used to examine the proportion of responders to treatment in a post-hoc analysis of data from the STRIVE study, where adults with EM were randomized 1:1:1 to subcutaneous monthly placebo or erenumab 140 mg or 70 mg for 24 weeks. Cumulative distribution function (CDF) plots were generated to describe % of subjects within each treatment group achieving the range of CMWPCs from baseline in MPFID domain scores.

Results: Using multiple anchors and distribution-based methodology, estimates from the ARISE study and an observational study suggested that CMWPCs starting at 3-point change in MPFID EA and PI domains represented clinically meaningful within-subject change. In the STRIVE study, larger proportions of erenumab-treated subjects than placebo subjects achieved a ≥5-point reduction (pre-specified endpoint) from baseline to mean of weeks 13–24 in PI (140 mg: 42.5%; 70 mg: 39.1% vs placebo: 30.1%, p < 0.05 for both) and EA domain scores (140 mg: 50.3%; 70 mg: 49.0% vs placebo: 34.5%, p < 0.001 for both). Post-hoc analyses as described by CDF curves by treatment groups showed that more subjects in 140 mg and 70 mg erenumab groups compared to placebo had greater reductions in EA and PI domain scores. The erenumab groups had consistently larger proportions of responders compared to placebo starting as low as a 3-point change from baseline score and across a range of CMWPCs.

Conclusion: Reductions starting at 3 points in MPFID domains are representative of CMWPCs. Treatment with erenumab 140 mg and 70 mg in the STRIVE study was related to clinically meaningful reductions in the impact of migraine on physical functioning compared to placebo, based on greater proportions on erenumab experiencing within-subject change of 5 points or more. This supports the utility of MPFID as a marker for migraine clinical benefit and demonstrates the value of erenumab as a preventive therapy to improve functioning in adults with EM.

Web MD. UptoDate, R. Lipton Conflict with: National Institutes of health, the National Headache Foundation, the Migraine Research Fund, Conflict with: Serves as a consultant, serves as an advisory board member, or has received honoraria from Alder, Allergan, American Headache Society, Autonomic Technologies, Boston Scientific, Bristo Myers Squibb, Cognimed, CoLucid, Eli Lilly, eNeura Therapeutics, Merck, Novartis, Pfizer, and Teva, Conflict with: Receipt of royalties: Wolff's Headache, 8th Edition (Oxford University Press, 2009), S. Tepper Conflict with: ATI, Conflict with: Alder, Allergan, Amgen, ATI, Avanir, Teva, Zosana Conflict with: Consultant: Acorda, Alder, Allergan, Amgen, ATI, Avanir, Eli Lilly, Kimberly-Clark, Pernix, Pfizer, Teva, Zosana; Salary: American Headache Society, Conflict with: Advisors board: Allergan, Amgen, ATI, Avanir, BioVision, Dr Reddy’s, Kimberly-Clark, Scion Neurostim, Teva, Pfizer, Conflict with: Receipt of royalties: University of Mississippi Press

Headache Pathophysiology – Imaging and Neurophysiology

PO-01-203
Impaired cholinergic transmission in migraine: a short-latency afferent inhibition (SAI) study

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Objectives: Short-latency afferent inhibition (SAI) is a form of inhibition related to the cholinergic activity in the cerebral cortex. It consists in an electrical stimulation of a peripheral nerve that can suppress motor cortex excitability, as tested by transcranial magnetic stimulation (TMS), when given at a short interstimulus interval (ISI) between 18 and 21 ms. SAI is considered an in-vivo way to study the sensorimotor integration mechanisms, and is influenced by the excitatory effect of acetylcholinergic thalamocortical afferents on the inhibitory GABAergic (typically GABAa) cortical networks.

Methods: We recruited 30 migraine without aura patients (16 between [MO] and 14 during [MI] attacks), and we compared them to a group of 16 healthy volunteers (HV). We first recorded somatosensory evoked potentials N20 latency and N20-P25 peak-to-peak amplitude at the contralateral parietal area. Afterward, SAI was recorded in all study’s participants as follows: after a conditioning single pulse delivered on the median nerve at the wrist, a TMS pulse was delivered with ISIs derived from the latency of N20 plus 2 to 8 ms in steps of 2 ms and in random order. Five stimuli were delivered at each ISI. We calculated the SAI slope of the linear regression between the unconditioned motor evoked potential (MEP) amplitude and the 4-conditioned MEPs as a measure of cortical excitability.

Results: Compared with HV, SAI was significantly reduced in MO, but enhanced in MI patients (slope HV = +11.2, MO = +242, MI = −129). In both HV and MO groups, but not in MI, the SAI slope positively correlated with the SSEP N20-P25.

Conclusion: The reduction of SAI in MO patients and its enhancement in MI patients suggests a decrease and an increase respectively in facilitatory thalamocortical cholinergic activity on GABAergic network activity in the motor cortex. Since from the correlation analysis emerges that slope of SAI normally correlates with the parietal response in MO, but not in MI, we argue that more dysfunctional sensorimotor integrative mechanisms might characterize migraineurs during an attack.

Disclosure of Interest: None Declared

Headache Pathophysiology – Imaging and Neurophysiology

PO-01-204
Cognitive function performance of migraine in auditory evented-related potential and functional magnetic resonance imaging

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Objectives: Migraine is a common and painful condition that affects many people, predominantly from young adulthood to middle age; the years of maximum work and family commitments. Although treatment guidelines were proposed for acute and preventive treatment of migraine, the pathogenesis of migraine was still uncertain. Recent studies showed learning disabilities and attention deficits disorder in children and adolescents with migraine and
adult migraine patients often reported cognitive complaints, especially regarding attention and memory. Cognitive function change in migraine patients was highly suspected. Because the migraine without aura (MoA) patients are more common, we selected MoA patients as experimental group. We hope to compare the difference of brain physiologic & cognitive function change between MoA patients and normal people by these non-invasive electrophysiologic & neuroimaging techniques [auditory event-related potential (ERP) and functional magnetic resonance imaging (fMRI)] and cognitive assessment [Mini-Mental State Examination (MMSE) and Wechsler Memory Scale-Third Edition (WES-III)]. This study showed some cognitive impairment in MoA patients, especial over recall memory and working memory. These cognitive change could be compatible with some findings in these electrophysiologic & neuroimaging techniques.

Methods: Nineteen migraine subjects (M/F = 5/14, age = 42 ± 10 y/o) and thirteen healthy controls (M/F = 5/8, age = 32 ± 9 y/o) who had no history of neurological disease participated in this study. All participants received MMSE (Folstein et al., 1975) & WES-III (Larrabee, 1999) mental tests and auditory ERP & fMRI examinations. The auditory ERP and fMRI examination were performed during the ictal phase of the MoA patients. We used an auditory oddball paradigm to analyze target processing using event-related potentials and measured latency and amplitude of P300 target stimulus in P3, Pz and P4 three sites. We also compared the functional connectivity in resting-state fMRI (rsfMRI) between controls and MoA patients and analyzed the data according to Stanford University laboratory. All imaging data were acquired from a 3.0T MR scanner (Skyra, Siemens, Erlangen, Germany).

Results: Our results showed MoA patients have some cognitive impairment in the total score & recall score in MMSE and index scores & percentiles of working memory in WMS-III. More prolonged distal latency and reduced amplitude P300 target stimulus in the MoA patients. There was decreased functional connectivity in rsfMRI in the basal ganglion, higher visual and primary visual networks of MoA patients.

Conclusion: These results suggested that patients with migraine might present a higher risk of cognitive impairment and the auditory ERP & rsfMRI data provided an evidence of the cognitive dysfunction in these patients.

Disclosure of Interest: None Declared

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

PO-02-149

Infusion of calcitonin gene-related peptide provokes cluster headache attacks

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2Department of Systems Neuroscience, University Medical Center Eppendorf, Hamburg, Germany

Objectives: To investigate whether calcitonin gene-related peptide (CGRP) provokes cluster headache attacks.

Methods: We randomly allocated 32 cluster headache patients (3 groups: 9 active phase episodic cluster headache, 9 remission phase episodic cluster headache, and 14 chronic cluster headache patients) to receive intravenous infusion of 1.5 μg/min CGRP or placebo over 20 min on two study days separated by at least 7 days. Headache characteristics including cephalic autonomic symptoms were recorded. The primary end-point was difference in incidence of cluster headache attacks within 90 min by CGRP compared with placebo.

Results: CGRP induced cluster headache attacks in 8/9 patients compared to 1/9 after placebo in active phase (P = 0.046). None of the patients in remission phase reported attacks either after CGRP or placebo (P > 0.999). Seven out of 14 patients chronic cluster headache reported attacks after CGRP and none of the patients reported attacks after placebo (P = 0.023). Chronic cluster headache patients who developed attacks had a higher attack burden the month before provocation than those who did not develop attacks.

Conclusion: CGRP provokes cluster attacks in episodic cluster headache in active phase but not in remission. Periodicity or attack burden may influence the incidence of CGRP induced attacks in chronic cluster headache. We suggest that attack induction only during active phase may reflect the hypothalamic control of cluster headache. Our data also cautiously suggest efficacy of CGRP antagonism in the treatment of cluster headache.

Disclosure of Interest: A. L. Vollesen: None Declared, A. Snoer: None Declared, R. P. Beske: None Declared, S. Guo: None Declared, J. Hoffmann Conflict with: Allergan, Autonomic Technologies Inc. (ATI), Chordate Medical AB, Novartis and Teva, Conflict with: Speaking honoraria from Allergan, Novartis and Teva, R. H. Jensen Conflict with: Lectures for Pfizer, Berlin-Chemie, Norspan, Merck and Autonomic Technologies and is a member of the advisory panel of Allergan, Autonomic Technologies Inc. (ATI), Chordate Medical AB, Novartis and Teva

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boards of Autonomic Technologies, Medotech and ElectroCore, M. Ashina Conflict with: Alder, Allergan, Amgen, ATI and Eli Lilly. Conflict with: Speaking/teaching fees, honoraria Alder, Allergan, Amgen, ATI and Eli Lilly.

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

PO-02-150

Chronic cluster headache is associated with traumatic head injury and familial cluster headache

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Objectives: We wish to describe the clinical differences between the chronic (cCH) and episodic (eCH) form of cluster headache (CH) and the association with familial CH and traumatic head injury (THI).

Methods: Patients from the Danish Cluster Headache survey aged 18–65 years, diagnosed with CH according to ICHD-II, completed questionnaires and structured interviews. Familial CH was defined as either one or more 1st or 2nd degree relative with CH.

Results: 400 patients (cCH: 154 and eCH: 246) and 200 headache-free controls participated. cCH patients reported longer attack duration with treatment (47 min vs. 34 min, p < 0.05), more attacks per day (4.07 vs 3.33, p < 0.01) than in eCH patients) and autonomic symptoms as ptosis (60 % vs 48 %, p < 0.05) and eyelid edema (34 % vs 23 %, p < 0.05) were also more frequently reported in cCH than eCH.

A history of CH within the family was more frequent among patients than controls (16.75 % vs 2.5 %, p < 0.0001), and in addition more frequent among cCH than eCH (23 % vs 13 %, p < 0.05). THI was also more frequent in patients vs controls (43 % vs 25 %, p < 0.0001) and was reported more often in cCH patients than in eCH (53 % vs 38 %, p < 0.01). THI was not more frequent among sporadic CH than familial CH (43 % vs 46 %, p = 0.68)

Conclusion: Not only the duration of the remission period differ between cCH and eCH patients, but cCH patients also experience more frequent and longer lasting attacks compared with eCH patients. Despite our expectation, THI was not more frequent in sporadic CH than in familial CH, and this may indicate that THI is not at risk factor for developing CH. Further, familial CH is more frequently reported in cCH than in eCH which could point to differences in heritability and genetic load.

Consequently, it is pivotal for future genetic studies to address the difference between the two phenotypes.

Disclosure of Interest: None Declared

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

PO-02-151

Epidemiologic study of cluster headache prevalence in a medium-size city of brazil

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Objectives: To determine the prevalence of cluster headache (CH) in Barbacena, a medium size city in the State of Minas Gerais, Brazil.

Methods: The total population of Barbacena, totals 126.284 inhabitants and Family Health Strategy Program covers 84.610 of them. In order to identify patients with cluster headache, 36.145 of these were screened following which a questionnaire was collected by 181 health agents, distributed among the 28 health posts belonging to the Family Health Strategy network. The completed questionnaires were selected based on the clinical criteria established by the International Headache Society, and those patients (aged 18 year of age or over) with a possible CH diagnosis were later assessed by a headache specialist. This is an observational, cross-sectional study.

Results: In all, 15 patients were diagnosed as having CH, comprising a prevalence of 0.0414%; or 41.4/100,000 inhabitants.

Conclusion: Cluster Headache prevalence in Barbacena is lower than that observed in many locations worldwide.

Disclosure of Interest: None Declared

Epidemiology

PO-02-152

Exploring insulin resistance in migraine: a population-based study

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Objectives: An association between migraine and insulin resistance (IR) has been reported in some studies but data are conflicting. This study aimed to assess IR according to migraine type in the general population.

Methods: Among the 751 participants to the NESCaV population survey, 116 were migraineurs without aura (MO) and 79 were migraineurs with aura (MA). Diagnosis of migraine was based on the ef-ID migraine questionnaire. All participants had a clinical examination, a general blood test and filled-out a self-administered questionnaire. The homeostatic model assessment of IR (HOMA-IR), b-cell function (HOMA-B) and the quantitative insulin sensitivity check index (QUICKI) were used to calculate IR. Data were analyzed by weighted regression procedures and reported as means with 95% confidence interval (95%CI).

Results: After adjusting for stratification (gender, age, district) and other factors (smoking, physical inactivity, arterial hypertension, dyslipidemia, body mass index, antidiabetics and corticosteroids treatment), MA subjects presented lower fasting blood glucose levels than non-migraineurs and MO subjects: 5.05 (95%CI: 4.83–5.29) vs. 5.26 (5.01–5.51) vs. 5.31 mmol/L (5.03–5.61), respectively (p = 0.018). A significant difference in HOMA-B was observed between MA subjects, non-migraineurs and MO subjects: 111 (95%CI: 92–134) vs. 95 (80–111) vs. 95 (76–117), respectively (p = 0.037). No difference was observed for insulin (p = 0.60), HOMA-IR (p = 0.83) and QUICKI (p = 0.71).

Conclusion: This population-based study demonstrated a decrease in fasting blood glucose levels and an increase of HOMA-B scores in MA subjects. These findings highlight the importance of a systematic exploration of glucose metabolism especially in MA subjects, already known to be more exposed to cardiovascular diseases.

Disclosure of Interest: None Declared

Headache and Gender

PO-02-153

Untangling the burden of menstrual migraine from headache day frequency: Results from the 2017 Migraine in America Symptoms and Treatment (MAST) Study

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Objectives: Among women of child-bearing potential who have migraine, the International Classification of Headache Disorders characterizes pure menstrual migraine (PMM), menstrually related migraine (MRM) and non-menstrual migraine (NMM). The objective of this study was to assess the relative frequency and burden of migraine in a population sample of women representing these 3 migraine subtypes.

Methods: Survey data were obtained from a general US population sample of women with migraine from the 2017 Migraine in America Symptoms and Treatment (MAST) Study. The survey collected sociodemographic features, headache characteristics, time since most recent menstruation, use of exogenous hormones and data on the relation of headache to the menstrual cycle. Eligible women were <55 years old, met ICHD criteria for migraine and reported at least one period in the last 12 months. Modified ICHD-3 beta diagnostic criteria were used via a validated questionnaire to screen women for migraine and to classify them as PMM, MRM or NMM. The burden of migraine was assessed using the Migraine Disability Assessment Scale (MIDAS: cut point 310, moderate-to-severe disability) and a 4-item measure of anxiety and depression (Patient Health Questionnaire, PHQ-4: cut point of 6, moderate-to-severe depressive and anxious symptomology). Allodynia was assessed using the 12-item Allodynia Symptom Checklist, (ASC-12: cut point of 3, presence of cutaneous allodynia). In order to assess the burden of menstrually related attacks independent of headache frequency, binary logistic regression contrasted women who met criteria for PMM and MRM with a NMM reference group. Covariates included headache day frequency, highest headache intensity, age, race, BMI and the use of exogenous hormones.

Results: Among 9,953 women meeting criteria for migraine, 6,269 met the additional inclusion criteria for the analysis (mean age 34.7, 74.8% Caucasian). Women were classified as PMM (n = 271, 4.3%), MRM (n = 2,374, 37.9%) or NMM (n = 3,624, 57.8%) based on their retrospective self-report of timing for migraine headache attacks in the prior 3 months. Women with PMM were somewhat older (Chi 51.5, p < .001) and more likely to be married (Chi 17.0, p < .001). A higher proportion of the MRM group had high disability, psychological symptomatology, attack–related allodynia symptoms, and higher average monthly headache day frequency (PMM 2.8 days, MRM 4.7 days and NMM 3.5 days). After adjusting for covariates, PMM and NMM did not differ in the aforementioned outcomes. In comparison with the NMM group, the MRM group had higher odds of moderate-to-severe disability (OR 1.30, CI 1.15, 1.47) and higher odds of ictal allodynia (OR 1.28, CI 1.15, 1.43). There were no differences in psychological symptomology (OR 1.04, CI 0.92, 1.19).

Conclusion: MRM was diagnosed in 38% of our sample. Independent of overall headache frequency, these women
were more likely to have moderate-to-severe headache-related disability and more likely to report attack-related allodynia than women with NMM or PMM. The greater burden in MRM may reflect biological differences among these subgroups. While the underlying factors that contribute to higher disability and allodynia in the MRM group requires further investigation, these findings confirm a need for more effective methods to reduce the burden of MRM.

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Headache and Gender

PO-02-154

Etiological beliefs and experiences of gender suffering with headaches at the University Hospital Teaching Center of Yaounde(UHTCY)

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Objectives: To describe the etiological beliefs of headaches according to gender and how these headaches are treated.

Methods: This descriptive and qualitative study was conducted from September 25th to December 12th, 2016 at the University Hospital Center of Yaounde. The study population consisted of 12 patients and spouses of five patients. Data was collected on the etiological beliefs of sufferers, self-esteem and relationship with relatives. An interview guide and a sound recorder were used for data collection. The analysis consists in gathering information according to the objectives.

Results: Patients ages varied from 3 to 68 years old. Etiological factors reported by patients included: aging (1/12); diabetes(1/12); spinal diseases(1/12); hormonal...
changes in women(7/12) child birth(4/12) and mysticism(8/12). Three children between the ages 3 to 11 years did not mention any etiological factor. Relationships with relatives have been destabilized with the husband for one woman and with the family in-laws for another one. Other relationships have been more bonding as partners turn to be more affectionate.

**Conclusion:** Most of the sufferer mentioned the etiological factors listed above. Some have gone into depression because of a destabilized relationship with the family. Sensitization on early medical consultation and treatment could be of great importance.

**Disclosure of Interest:** None Declared

### Headache Classification

**PO-02-155**

**Incorrect patient perception of the number of Headache types they have**

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**Objectives:** Most patients who think they have several headache types, actually have only migraine. Many patients report several headache types with varying symptoms and carry multiple headache diagnoses. This often results in excessive testing and inappropriate treatments. The objective of this work is to determine how often a patient’s perception of the number of different types of headache they have is accurate.

**Methods:** We reviewed 3118 reports generated by a validated on-line questionnaire from BonTriage with responses tied to ICHD 3 beta diagnostic criteria. Patients were asked how many distinct headache types they had, and then were queried in detail about each type. We then used ICHD diagnostic criteria to form clinical impressions. A rule-based engine was then used to generate these diagnoses.

**Results:** 3118 patient histories were collected and analyzed. Of these, 1622 reported 1 headache type, 1020 reported 2, and 476 reported more than 2. Migraine was a frequent diagnosis. Many patients with one type of migraine and other headaches there were similar to tension-type headache had only the diagnosis of chronic migraine.

**Conclusion:** It appears from this study that patient’s perception of multiple headache types is accurate only 29% of the time. When more than one headache type is reported, the most common headaches represented are migraine or chronic migraine or migraine with head trauma.

Chronic migraine is also seen. This study suggests that further education regarding the natural history of migraine and how it presents is an important educational element often lacking in the management of migraine.

**Disclosure of Interest:** None Declared

### Headache Classification

**PO-02-156**

**Chronic Secondary Headache in Children: A Case Report**

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**Objectives:** Headache is a common reason for pediatric patients to seek medical care. Headaches can result from any of a number of causes, including genetic predisposition, trauma, an intracranial mass, a metabolic or vascular disease, or sinusitis. Recognition that pediatric headaches can result from primary and secondary causes is crucial to their treatment.

**Methods:** Male 8-years old with severe headache. Throbbing pain felt in his face (around the eyes, cheeks and forehead), both sides affected with right more dominant. The pain get worsen in the morning, when moving his head, strain or bend down, and when experience extreme changes in temperature. The pain was almost daily in the last five months and last for 15–45 minutes during attack, followed by pain free between attacks. He also had chronic rhinitis since couple years ago. Physical and neurological examinations were normal. Numeric Rating Scale (NRS) was 10 during acute attacks. He was referred from primary healthcare service and ever treated with paracetamol, ibuprofen but no reduction either in intensity or frequency of pain. The head X-Ray and CT-Scan resulted normal condition, but the head MRI showed bilateral sphenoidalis sinusitis and ethmoidalis sinusitis. Then he was given a combination of paracetamol, decongestant and broad spectrum antibiotics for sinusitis.
Results: Patients had remission of cluster headache period within 7 days of treatment with combinations of paracetamol with tramadol as abortive treatments, decongestant and amoxicillin with clavulanic acid 50 mg/kg/day three daily for 10 days as initial treatment. There were no attacks anymore. NRS reduce until zero. Sinus headaches are an uncommon type of headache caused by inflamed sinuses (sinusitis). Sinus headache typically occurs in the area of the sinuses in the area of the cheeks (maxillary sinus), bridge of the nose (ethmoid sinus), or above the eyes (frontal sinus). Less often it may refer pain to the top or back of the head (sphenoid sinus). Sinus headache may occur on one side or both sides of the head and the neck is typically not involved. The symptoms are frequently worsened by bending over or coughing (as with migraine), and examination of the facial area may reveal local tenderness, redness, swelling, and possibly the presence of clear or discolored nasal discharge. Sinus disease can happen to people who suffer from migraine or to those who do not and may lead to increased migraine activity in migraine sufferers, often confusing the diagnosis. Upon determining that a headache’s origin is a sinus infection, short-term antibiotics (typically less than 2 weeks) and decongestants (several days only) may be prescribed. Allergic sinusitis may respond to simple antihistamine and steroid-based nasal sprays. A chronic sinus infection may require weeks of therapy, various antibiotic regimens, or the judicious use of supportive steroid preparations. Sometimes nasal surgery is indicated to correct underlying anatomical factors.

Conclusion: The initial presentation of sinus infection is so similar to migraine that it is often mistakenly diagnosed and treated like just another headache. However, despite overlapping symptoms, differences between the two entities can be distinguished through a careful evaluation.

Disclosure of Interest: None Declared

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Headache Education for Clinicians and Patients

PO-02-157

The Prevalence and Characteristics of Cranial Autonomic Symptoms (CAS) in Migraine Patients with or without Aura

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Objectives: Cranial autonomic symptoms (CAS) include a broad spectrum of symptoms such as conjunctival injection, lacrimation, nasal congestion, eyelid oedema, forehead or facial sweating, miosis, ptosis and facial flushing which all are key features of trigeminal autonomic cephalalgias (TACs). However, CAS may also present with migraine attacks. Based on the literature, compared with TACs patients, these symptoms are more bilateral, less severe, often unrelated to the headache side and less dependent to headache attack in migraine patients. It has been also reported that CAS can occur in 27% to 73% of migrainures. In this study we aimed to explore the prevalence and characteristics of CAS in migraine with and without aura.

Methods: This retrospective study was conducted on patients with migraine diagnosis referred to a private headache clinic in Tehran between January 2011 to January 2015. Migraine diagnosis was based on the latest international headache society criteria (ICHD III). Medical records, status of CAS and other non-autonomic parameters of patients with migraine (with or without aura) were recorded. Data analysis was performed using SPSS19.

Results: Of 657 patients (aged 38.78 ± 14.15 years), 68.6% were female, and 60.1% had episodic migraine. Regarding headache characteristics, in 40.6% of patients it was unilateral. The mean frequency and intensity of headache were 7.83 ± 1.71 and 13.28 ± 8.48 days, respectively. The prevalence of CAS was as follows: conjunctival injection (28.9%), lacrimation (24.4%), nasal congestion (15.2%), ear fullness (15.2%), rhinorhea (11%), eyelid oedema (10.2%), forehead or facial sweating (4.9%), flushing (4.1%), ptosis (2.1%) and miosis (0.9%). 64.2% of patients had at least one CA symptom. Presence of CAS was significantly higher in migrainers with aura (80.6%) than those without aura (61.4%, (p = 0.00)). However, CAS did not differ between patients with unilateral and bilateral headaches. Tearing and nasal congestion were also significantly more prevalent in patients with more severe
and frequent headaches (17.3%, 15.0%, 25.2% and 17.0%, respectively $p < 0.05$) than others.

**Conclusion:** Due to high prevalence of CAS in our study, these symptoms might not be a specific characteristic of TACs, especially for differentiation of hemicrania continua that share some common characteristics with chronic migraine. Also, these findings may raise a question about the possible distinctive therapeutic approaches in migraine with and without autonomic features. Our findings further confirm the idea of involvement of trigeminal autonomic reflex in the migraine headaches. Furthermore, the presence of CAS might be a sign of migraine progression. Larger prospective studies are suggested for more precise results.

**Disclosure of Interest:** None Declared

**Headache Epidemiology, Outcomes and Burden**

**PO-02-159**

**Characteristics and diagnoses of acute headache in pregnant women—a retrospective cross-sectional study**

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**Objectives:** Acute headache is one of the most frequent neurological symptoms in pregnant women. Early diagnosis of underlying secondary conditions has a major influence on patient outcome, especially in emergency settings. However, at the time being no well-established guideline for diagnostic evaluation of acute headache during pregnancy exists. We aimed to characterize acute headache in pregnant women in a European urban population concerning demographic, clinical, and diagnostic features, and to determine predictors of secondary headache.

**Methods:** We analysed retrospectively the data of 151 pregnant women who received neurological consultation due to acute headache between 2010 and 2016 at the Charité hospital in Berlin, Germany. To assess risk factors for secondary headache in these patients we compared multiple anamnestic and clinical features of the primary and secondary headache group. Subgroup proportions were compared using chi-squared test. Logistic regression was used to assess the correlation between clinical features with a $p$ value $\leq 0.02$ in univariate analyses as independent variables and the dependant variable being the final diagnosis secondary headache.

**Results:** Patients had a mean age of 30.1 (IQR 10.0) years, a mean gestational age of 22.2 ($\pm 10.1$) weeks and 2.1 ($\pm 1.7$) pregnancies. 57.6% of the patients were diagnosed with primary headache, most common migraine with aura (41.3%), migraine without aura (33.3%) and tension type headache (21.8%). Within secondary headaches, the most common aetiologies were infections (29.7%) and hypertensive disorders (22.0%). The primary and secondary headache group were similar in most anamnestic and clinical features. In univariate analysis, secondary headaches were associated with complications during current pregnancy (28.1 vs. 12.6%, $p = 0.017$), history of secondary headache disorders (14.1 vs. 3.4%, $p = 0.017$), progressive pain dynamic (37.2 vs. 19.3%, $p = 0.046$), seizures (4.7 vs. 0.0%, $p = 0.041$), abnormal internal examination (15.9 vs. 4.8%, $p = 0.025$), elevated blood pressure (31.7 vs. 8.4%, $p < 0.001$), fever (14.1 vs. 1.1%, $p = 0.002$) and abnormal neurological examination (35.9 vs. 11.5%, $p < 0.001$). In multivariate logistic regression, history of secondary headache disorders [OR 6.6; 95% CI 1.3–33.1], elevated blood pressure [OR 7.2; 95% CI 2.3–22.6], fever [OR 12.1; 95% CI 1.3–111.0] and abnormal neurological examination [OR 9.9; 95% CI 2.7–36.3] represented independent predictors for secondary headache. Regarding additional diagnostic procedures, blood tests were conducted in 94.7% of the cases, urine analysis in 57%, lumbar puncture in 13.2% and neuroimaging in 50.3%. Abnormal thrombocytes, GOT, GPT and CRP, proteinuria, as well pathologic results of lumbar puncture and/or neuroimaging were associated with secondary headache.

**Conclusion:** Secondary headache disorders are common during pregnancy, occurring in one third of acute headache cases receiving neurological consultation. Most anamnestic and clinical features may not allow a clear distinction between primary and secondary headaches. Clinicians should pay particular attention in presence of secondary headache history, elevated blood pressure, fever and abnormal findings in the neurological examination. These symptoms can be considered as predictors for secondary headache in pregnant women. However, attack features alone cannot adequately discriminate between primary and secondary headache. Additional diagnostic investigations, including laboratory tests and neuroimaging, are essential for the diagnostic process.

**Disclosure of Interest:** None Declared
Predictors of Allodynia in Persons with Migraine: Results from the 2017 Migraine in America Symptoms and Treatment (MAST) Study

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Objectives: Prior work has identified associations between cutaneous allodynia, increased migraine day frequency and inadequate acute treatment response. The objectives of this study were to 1) estimate rates of allodynia in migraineurs who met ICHD-3beta medication overuse (MO) criteria vs. those who did not (nonMO), and 2) determine the influence of headache day frequency and other relevant covariates on the presence of allodynia.

Methods: Participants in the MAST Study were recruited from a nationwide online research panel. Stratified random sampling identified a representative cohort of individuals aged ≥18. A validated migraine diagnostic screen using modified ICHD-3β criteria identified individuals with migraine. Those averaging at least 1 headache day per month over the previous 3 months who reported the use of acute migraine medication(s) were eligible to participate. The presence of cutaneous allodynia on days with headache was identified using the Allodynia Symptom Checklist (ASC-12, score ≥3). ICHD-3β criteria were used to identify MO and nonMO respondents based on monthly usage frequency of acute medications. Binary logistic regression modeling included the following covariates: monthly headache frequency category (1–4, 5–9, 10–14, ≥15 days/month), a pain intensity measure (0–10 intensity rating), the migraine symptom severity score (MSSS) sum, sociodemographics (age, gender, race, income, BMI, smoking) and depression and anxiety symptomology (PHQ-4, sum score ≥6). Allodynia was treated as a dichotomous outcome. Covariates were added to the model in a hierarchical manner and retained if significant. Odds ratios (OR) and 95% confidence intervals (CI) are provided for models and Chi-square tests (p < .05) for group comparisons.

Results: N = 117,150 individuals responded to an email survey invitation about health issues; 95,821 surveys were usable and matched US Census on sex, age, and income. A total of 14,396 acute medication users met inclusion criteria. Mean age was 43.4 years, 73.1% were women, 81.5% were Caucasian, 70.8% were employed full- or part-time and 40.1% met criteria for allodynia. 50% of MO respondents met criteria for allodynia vs 37.5% of nonMO respondents (p < .001). The unadjusted logistic model (OR 1.68, CI 1.55, 1.83) indicated that MO respondents were 68% more likely to report cutaneous allodynia vs. nonMO respondents. The OR was attenuated somewhat with the addition of PHQ/psychological symptomology to the model (OR 1.55, CI 1.42, 1.69), and was attenuated further with the addition of headache frequency and intensity covariates (OR 1.15, CI 1.04, 1.27) but retained significance (p = 0.006). Modeling results also found being female was associated with increased odds of having allodynia (OR 1.71, CI 1.57, 1.87), as was being Caucasian (OR 1.16, CI 1.05, 1.27). The presence of PHQ/psychological symptomology (OR 1.83, CI 1.68, 2.00), having frequent (≥15 days/month) headache (OR 1.41, CI 1.23, 1.61 vs. 1–4 headache days/month reference group), increasing MSSS (1.17, CI 1.15, 1.19) and pain intensity (OR 1.11, CI 1.08, 1.14) were also associated with greater odds of having cutaneous allodynia.

Conclusion: Attack-related cutaneous allodynia is associated with medication overuse even when relevant covariates (headache frequency, headache intensity, sociodemographics and psychological symptomology) are accounted for. This finding supports the clinical approach of minimizing the overuse of acute medications. Other factors associated with the presence of allodynia included symptoms of depression and anxiety, headache frequency, headache intensity and being female.

Objectives: Hemiplegic migraine (HM) is a rare type of migraine with aura with a unique genetic etiology, pathophysiology and a distinct and defining clinical characteristic of motor weakness. HM exists in either a familial (FHM) or sporadic (SHM) form depending on the presence of a family history. Due to the rarity of HM, there is a paucity of data regarding the spectrum of the HM phenotype. The objective of this study was to conduct an online survey in order to better understand the variability in the symptomatology of HM attacks, the use of medications to treat or prevent HM attacks and to explore the burden of the disorder in patients with HM.

Methods: A detailed questionnaire was developed to obtain self-reported data from patients who experience HM symptoms. The patient questionnaire was hosted online and comprised 45 questions investigating demographic information, aura symptoms, HM attacks, other migraine attacks, family history, comorbidities and medication use. Free text boxes were included throughout the questionnaire to collect qualitative data from patients regarding the impact of HM symptoms on their lives. Patients were also asked if their diagnoses came from a physician and the specialty of the physician. Online patient responses were screened for study eligibility using the 3rd International Classification of Headache Disorders (ICHD-3 beta) diagnostic criteria for HM, with individual follow-up by email or telephone interview where necessary. 380 patients who met the ICHD-3 beta criteria for HM were enrolled into the study for this analysis, however, the study is still open and collecting additional patient responses. The patient survey protocol and questionnaire were approved by an independent institutional review board (Veritas).

Results: Patients reported the onset of HM attacks between 2–65 years of age with 56% reporting an onset at ≤30 years of age. Attacks including motor weakness occurred at least once a month in 76% of patients and 69% reported that motor weakness occurred in every attack. The duration of motor weakness during an attack...
was variable and ranged from minutes to days, typically lasting up to 2 hours in 37% of the patients, however, 12% of patients reported motor weakness persisting more than 72 hours. 67% of the respondents had been diagnosed by a physician, of which 86% were either a neurologist or headache specialist. Frequently reported consequences of HM in patients’ lives included impacts on eating and drinking, driving, working and self-care in addition to significant physical, social and emotional impacts. 51% of patients reported they are currently taking a preventive medication, the most common of which was topiramate, while amitriptyline, verapamil and propranolol were the next most frequently used. Only 13 to 34% of patients are currently on or continuing to take any of these reported medications, suggesting a 66 to 87% rate of treatment failure.

Conclusion: HM is a highly variable and often severely debilitating disorder. Many patients who experience hemiplegic migraine symptoms have difficulty in obtaining a diagnosis from a knowledgeable medical practitioner. There is no current standard of care for this condition and current therapies appear to have a high failure rate.


Headache Epidemiology, Outcomes and Burden

PO-02-162

Inpatient Detoxification in Medication Overuse Headache – 32 Years Experience in 807 Patients

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Objectives: About 2–3% of the general population and 11–70% of chronic headache patients suffer from medication overuse headache (MOH). Definitions according to the IHS, overused substances, as well as the management of MOH has changed over time and recently, inpatient detoxification is only recommended to patients with complicated MOH. To the best of our knowledge, no systematically collected data is available on how the above mentioned changes affected clinical characteristics of MOH patients, who are hospitalized for inpatient detoxification. The aim of our study was therefore to evaluate changes over time in clinical characteristics of these patients.

Methods: We retrospectively collected data of all MOH patients, who were admitted to the Neurological Department of the General Hospital of Vienna from 01-01-1984 to 31-12-2015. We created three periods ranging from 1984–1993 (P1), 1994–2003 (P2), and from 2004–2015 (P3). Demographic and clinical characteristics were obtained from the medical reports and changes between periods were analyzed. We categorized overused medications as simple analgesics, combination analgesics, opioids, ergotamines, triptans, and tranquilizers.

<table>
<thead>
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<tbody>
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<td>Tranquilizers</td>
<td>5.6</td>
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<td>3.2</td>
<td>&lt;0.001</td>
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</table>

Results: Within 32 years, a total of 807 patients accounted for 935 hospital admissions (78% women, 22%men, mean age 46.4 ± 12.2): 199 admissions in P1, 360 in P2 and 376 in P3. Underlying headache diagnoses were migraine, tension type headache, and other headaches in 50.6%, 44%, and 5.4%, respectively. Migraine was found in 42.7% and tension type headache in 50% of admissions in P1 and in 53.2% and 35.1% in P3, respectively (p = 0.017). Median time since first manifestation of the underlying headache disorder changed from 20 years in P1 to 16 years in P3 (p < 0.001). Median time since first manifestation of MOH changed from three years in P1 to two years in P3 (p < 0.001). In P1 the majority of admissions for inpatient detoxification was due to ergotamine-overuse, while in P3 it was due to overuse of simple-analgesics. Ergotamine overuse decreased and triptan overuse increased significantly during the study period (p < 0.001) (see table 1). The median cumulative number of single-dose administrations decreased from 120 per month in P1 to 90 in P3 (p = 0.001).

Conclusion: Clinical characteristics of MOH patients changed over 32 years. Nowadays, patients predominantly suffer from migraine, have a shorter history of migraine and MOH before start of inpatient detoxification, and the cumulative number of single-dose administrations is lower. As expected, the overuse of ergotamines decreased,
whereas triptan overuse increased during the study period.

**Disclosure of Interest:** None Declared

**Headache Epidemiology, Outcomes and Burden**

**PO-02-163**

**THE DIAGNOSTIC AND THERAPEUTIC JOURNEY OF PATIENTS PRIOR TO REVIEW IN HEADACHE CLINIC**

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**Objectives:** Headache is a common medical problem that causes great morbidity; worldwide, migraine on its own is the cause of 1.3% of all years of life lost to disability. Referrals for headaches account for up to one-third of new specialist neurology appointment in the United Kingdom even though GPs only refer 2–3% of patients consulting for headaches to neurologists. There are numerous, easily accessible guidelines aimed at all healthcare professionals who care for patients with headaches, however, it is known that a minority of migraine patients use specific anti-migraine drugs, and medication overuse is consistently underdiagnosed. There also continues to be a significant delay in diagnosis and access to treatment for patients with trigeminal autonomic cephalalgias. Given the issues outlined above, our objective was to review the past diagnoses, investigations and management of 526 patients referred to a tertiary headache clinic in London.

**Methods:** A retrospective audit was conducted of new headache referrals to one neurologist between June 2006 and June 2016. Data was collected from the electronic patient records system.

**Results:** 526 patients were included in the audit, 69.5% were female. There were 845 diagnoses within the cohort; 224 of episodic migraine, 196 of chronic migraine, and 194 patients were identified as having medication overuse. 76 patients (14.4%) had a diagnosis of trigeminal autonomic cephalalgia, 39 of cluster headache, 12 of SUNCT/SUNA, 19 and 8 of paroxysmal hemicrania (PH) and heimcrania continua (HC), respectively. 49.8% of patients had 2 or more diagnoses. Regarding the patients with migraine, 123 of the patients with chronic migraine also had a diagnosis of medication overuse. 82% of migraine patients had tried a preventative agent, and 83% had seen at least one neurologist previously. Only 34.3% of referral letters mentioned discussion with patient about medication overuse. The most frequently used medication was amitriptyline in this cohort. 44% had tried propranolol before, at an average dose of 109 mg (standard deviation 76.4 mg), with only 6.6% still being on it at the time of review; 30.6% found it ineffective and 26.5% ceased it secondary to intolerability.

41% tried topiramate, at an average dose of 127.9 mg (standard deviation 95.7 mg). 59% of patients had a MRI prior to review and 73% of them were normal. Analgesia withdrawal was suggested to 55% of patients, and topiramate and propranolol were the most frequently prescribed medications at their first consultation. Of the 39 patients with cluster headaches, 70% had tried verapamil, at an average dose of 618 mg, and 5% had tried lithium. Acute treatment was prescribed to 75%. Of the 21 patients with HC or PH, only 8 had previously tried indomethacin. Of the 14 patients with SUNCT/SUNA, 6 tried each of pregabalin and lamotrigine, at an average dose of approximately 300 mg each.

**Conclusion:** Our audit shows that the prevalence of medication overuse, in a population that has seen both primary and secondary physicians is high, and first-line, evidence based treatments are most frequently trialled, but at sub-optimal doses and imaging remains a frequent investigation, that is usually normal.

**Disclosure of Interest:** None Declared

**Headache Epidemiology, Outcomes and Burden**

**PO-02-164**

**An analysis of headache attack occurrence on days of the week and hours of the day using the MigrnX mobile system**

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**Objectives:** To use novel data from the MigrnX mobile system to characterize the distribution of reported migraine attacks by day of the week and hour of the day.

**Methods:** An IRB approved study was conducted in a Carolinas Health System, Northeast Neurology practice using the MigrnX mobile (Android and iOS) tool (copyright SensorRx) to collect real time data from patients regarding migraine attacks. MigrnX records and shares actionable data for providers (e.g., migraine attack occurrence, pain intensity, associated symptoms, and medication usage) in a 5 touch format requiring less than 15 seconds of user time. MigrnX also uses embedded smart phone sensors to automatically record ancillary data associated with headache (e.g., date, time, weather, light, sound, etc.) which can be used to correlate and predict headache patterns via machine learning. Patients were diagnosed with migraine by a neurologist using ICHD-3beta criteria. We

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used descriptive statistics to characterize the patterns of migraine occurrence by day of the week and hour of the day and tested for deviation from the expected random distribution using a Chi-square test over a 90-day window.

**Results:** We report data from 111 patients meeting ICHD-3beta criteria for migraine (median age 42, age range 24–62). Most were Caucasian (80%) and female (76%). They entered 1,056 migraine attacks in a 90-day window. Over 90 days, the mean number of migraine attacks was 9.6, median 5, SD 11.8. The lowest frequency was 1 attack (N = 24, 21.6%) and the highest was 59 (N = 1, 0.9%). The modal number of migraine attacks per month was 1 (N = 31, 27.9%), ranging from 0 (N = 24, 21.6%) to 20 (N = 1, 0.9%). Migraine occurrence by day differed from the predicted random occurrence (p < 0.001). Attacks were most common on Wednesdays (17.3%) and Tuesdays (16.8%) and least common on Saturdays (9.5%). Attacks were most frequently reported between noon to 10 pm. The most frequent time of day for migraine attacks was 4–6 pm (13.8%) followed by 8–10 pm (13.5%). Attacks were least frequently reported between 6–8 am (1.4%). (See Table).

**Conclusion:** This analysis of the MigrnX diary system reveals important information about the distribution of attacks in persons with migraine. We found that migraine attack occurrence peaked midweek and later in the day with a low on Saturdays as well earlier in the day. The availability of large-scale, real-time patient reports as provided by MigrnX should find broad application in both research and patient care.

**Disclosure of Interest:** G. McLendon: None Declared, D. Buse Conflict with: Allergan, Avanir, Amgen, and Dr. Reddy’s Laboratories, Conflict with: Eli Lilly, Conflict with: Montefiore Medical Center, which in the past 12 months, has received research support funded by Allergan, Alder, Avanir, CoLucid, Dr. Reddy’s Laboratories, and Labrys via grants to the National Headache Foundation and/or Montefiore Medical Center, Conflict with: Editorial board of Current Pain and Headache Reports, the Journal of Headache and Pain, Pain Medicine News, and Pain Pathways magazine, J. Zhao: None Declared, R. Bodner Conflict with: Shareholder in Sensorxx, Conflict with: Sensorxx, Inc, A. Dzedza: None Declared, R. Lipton Conflict with: eNeura Therapeutics, Conflict with: NIH, Conflict with: Alder, Allergan, American Headache Society, Amgen, Autonomic Technologies, Avanir, Biohaven Inc, Boston Scientific, Colucid, Dr. Reddy’s, Electrocore, Eli Lilly, eNeura Therapeutics, Glaxo, Merck, GlaxoSmithKlein, Pfizer, Teva, Vedanta, Conflict with: Served on the editorial board of Neurology and as senior advisor to Headache. Received support from the Migraine Research Foundation and the National Headache Foundation. He has reviewed for the NIA and NINDS. Receives royalties from Wolff’s Headache, 8th Edition, Oxford Press University, 2009 and Informa

**Headache Epidemiology, Outcomes and Burden**

**PO-02-165**

Awareness of migraine in Neo-Latin countries: a study in 12 headache centers located over 7 countries

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7 Padua University, Padua, Italy
8 FAME/FUNJOB and FHEMIG, Barbacena, Brazil
9 National Headache Center – Republic of Moldova, Chisinau city, Moldova, Republic of
10 Hospital Universitario, Monterrey, Mexico
11 Policlinico Universitario, Palermo, Italy
12 Hospital DIPRECA, Santiago, Chile
13 Hospital Maciel, Montevideo, Uruguay
14 Clínica Neurológica Batatais, Batatais, Brazil
15 University of Pavia, Pavia, Italy
Objectives: To assess the awareness of migraine (M) and previous diagnostic and therapeutic paths in naive migraineurs visited by a headache specialists in several neo-latin countries.

Methods: This is a multicentre study conducted in parallel in 12 headache centers located over 7 neo-latin speaking countries and coordinated by Mondino Institute, Pavia, Italy. Each center recruited up to 100 consecutive M patients (pts) aged 18 to 75 years who had been referred for a first visit. After receiving diagnosis of M, pts answered questions about 1) the type of headache they thought to suffer from; 2) their perceptions of the cause of M; 3) the previous diagnosis received by health professionals; and 4) previous visits/investigations/treatments for M.

Results: 1161 pts were enrolled. Only 326 pts (28%) knew that they suffered from M, while 72% pts did not. 64% of pts simply called their M headache. Other common names were cervical pain (4%, mostly in Italy), tension-type headache (3%, mostly in Mexico, Chile and Uruguay), sinusitis (1%).

Factors associated with the awareness of M were: a high education level (p = <0.001), positive family history of M (p = 0.032), duration of the attack (p = 0.002), pain localised to the lateral head (p = 0.007), throbbing quality of pain (p = 0.007), presence of vomiting (p = 0.014) and presence of phonophobia (p = 0.011).

Mexico had the highest rate of M awareness (51%) followed by Chile (39%), Argentina (34%), Brazil (30%), Italy (25%), Moldova (17%) and Uruguay (12%). 5% of pts was aware that the cause of attacks was M predisposition, 50% of the patients attributed their headache to one of M triggers, while in Brazil and Argentina about 12% of pts causally related their M to anxiety, depression and other psychological problems.

All our pts had previously visited by a GP for M, but only 8% of them diagnosed it as M. The majority of pts (80%) has been visited by at least one specialist for their M, but only 35% of them formulated the correct diagnosis.

High rates of migraine diagnosis were observed in Moldova (53%), Argentina (68%) and Uruguay (52%), but a minority of pts in these countries was aware to suffer from M: 17%, 34% and 11% respectively.

50% of pts were prescribed a X-ray and/or CT and/or MRI of the cervical spine. 76% of pts underwent to imaging of brain and/or cervical spine that exposed them to radiation. 28% of patients had previously received a symptomatic migraine specific medication and 29% had received at least one migraine preventative medication.

Conclusion: Although M is the 3rd most common pathology worldwide and the 7th for disability, there is poor awareness of it among pts even after consultation with at least one physician. These findings speak in favor of the importance of educating doctors and patients in the field of M in order to reduce its burden worldwide.

This work was developed by the Italian Linguistic Group of IHS and supported by Mondino Institute (grant of the Italian Ministry of Health RC 2013–2015).

Disclosure of Interest: None Declared

Headache Pathophysiology – Basic Science

PO-02-167

VEGF-dependent signaling between dural endothelial cells and dural afferents: a potential neurovascular mechanism contributing to migraine headache.

Blaine Jacobs1,*, Yesenia Morales1, Jasper Kuhn1, Theodore Price1 and Gregory Dussor1

1University of Texas at Dallas, Richardson, United States

Objectives: Historically, cranial vasodilation was considered the major contributing event in the pathophysiology of migraine. However, recent reports indicate little to no dilation of cranial blood vessels during spontaneous migraine. The reverse is also true; blood vessel dilation does not always produce migraine. A recent meta-analysis of 375,000 individuals identified 38 loci for migraine, the majority of which corresponded to genes associated with vascular disease and regulation of vascular tone. These opposing data highlight the unclear role of cranial blood vessels in migraine pathophysiology. One potential unifying hypothesis however is that the cells which comprise dural blood vessels (e.g. endothelial cells) contribute to migraine pathology independent of changes in vascular tone. Therefore, the purpose of this study was to determine the contribution of endothelial cell-specific signaling via Vascular Endothelial Growth Factor (VEGF) to dural afferent activation and headache.

Methods: Mouse dura mater was dissociated and dural endothelial cells were sorted using biotinylated PECAM-1 (CD-31) antibody and Dynabeads M-280 streptavidin-coated magnetic beads. Dural endothelial cells were subsequently cultured after bead-based purification. Once 80–90% confluent, cells were serum starved overnight, and then treated with Interleukin-6 (IL-6) for 24 h. The endothelial cells were washed and the conditioned media (CM) collected for 5 h at 37 °C. Next, the dural endothelial cell CM was concentrated and probed for VEGF (1:200; sc-507) via western blot. Additionally, primary cultures of trigeminal ganglion (TG) were stimulated with recombinant human VEGF and changes in intracellular calcium levels assessed via Fura-2. Using a pre-clinical migraine model, recombinant human VEGF or endothelial cell CM was injected supradurally and the referred mechanical sensitivity of the periorbital region of the face assessed using withdrawal thresholds to von Frey filaments.

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**Results:** There was a significant increase in VEGF release from primary cultures of dural endothelial cells stimulated with IL-6 (80 ng/ml) for 24 h compared to control. Correspondingly, 41% of TG neurons in culture respond to [5 nM] VEGF with an average percent increase in intracellular calcium (from baseline to peak response) of 45.9% ± 39 (average % increase ± SD). A subsequent KCl [50mM] exposure after VEGF increased intracellular calcium in these cells by 70.9% ± 56; N = 39 TG neurons. Using a preclinical migraine model we found that supradural injection of VEGF [50 pmols] significantly increased mechanical allodynia in the periorbital region of the face compared to heat inactivated VEGF (95°C for 5 min) also applied to the dura (N = 6, 2-way ANOVA, Bonferroni post-hoc, ***, p < 0.0001). Additionally, supradural injection of endothelial cell CM significantly increased mechanical allodynia in the periorbital region of the face compared to the vehicle (DMEM) (N = 4, 2-way ANOVA, Bonferroni post-hoc, ***, p < 0.001).

**Conclusion:** These findings show that VEGF is released by dural endothelial cells, it activates trigeminal ganglion neurons, and it causes headache behaviors when applied to the dura mater. Since dural endothelial cells directly contact the circulating blood in the lumen, they may release VEGF in response to various immunological stimuli present in the blood including IL-6, a cytokine previously shown to be elevated in jugular blood of migraine patients during attacks. Thus, the pain of migraine may occur due to signaling events between vascular endothelial cells and dural afferent neurons, without a requirement for dilation of cranial vessels.

**Disclosure of Interest:** None Declared

**Headache Pathophysiology – Basic Science

PO-02-168

Abnormal response of the systemic circulation to nitroglycerin in migraine

Willebrordus P. Van Oosterhout1,*, Guus G. Schoonman2,3, Dirk P. Saaf1, Michel D. Ferrari1 and Gert J. Van Dijk1

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2Neurology, Elizabeth TweeSteden Hospital, Tilburg/Waalwijk
3Neurology, LUMC, Leiden
4Neurology, St. Franciscus Gasthuis, Rotterdam, Netherlands

**Objectives:** Migraine and vasovagal syncope are associated epidemiologically and may share part of their pathophysiology too. Vasovagal syncope can be provoked through systemic vasodilatation using nitroglycerin, which can also be used to provoke a migraine attack, through as yet impartially known mechanisms. Here, we report on the effects and responses of the systemic cardiovascular system on a vasodilatory influence in migraine and matched controls.

**Methods:** Sixteen female migraine without aura patients and ten age- and gender matched controls were included. Nitroglycerin (0.5 µg kg⁻¹ min⁻¹) was administered intravenously to provoke a migraine attack. Subjects lay in the supine position, and finger photoplethysmography was used to measure mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), stroke volume (SV) and total peripheral resistance (TPR) continuously in periods before infusion (for 10 min), during it (for 20 min) and directly afterwards (for 10 min). Per block and 1-minute averages were used in generalized estimating equations models.

**Figure 1.** Cardiovascular responses during the course of nitroglycerin infusion in migraineurs and controls. Time-series analysis showed that the minute-to-minute response to nitroglycerin differed between migraineurs and controls for several cardiovascular parameters (during nitroglycerin infusion; grey area).

**Results:** The per block analysis comparing averages during nitroglycerin infusion with baseline showed increases in HR (p < 0.001; both groups), and decreases in CO (p < 0.001; both groups), MAP (p = 0.002; migraine) and SV (p < 0.001; migraine, p = 0.03; controls), which were confirmed by the time-series analysis using 1-minute averages (all p < 0.001). The per block average TPR during infusion was higher than at baseline (p = 0.006; migraine), with the 1-minute showing a decrease after an initial migraine specific increase. There were also differences in the other parameters between the groups (1-minute average analysis: p < 0.001 for group*time interaction): CO and SV decreased faster and more prolonged in the migraine group. MAP showed an initial migraine-specific increase, but then a decrease over time. HR increased more in the migraine group (Figure 1).

**Conclusion:** Nitroglycerin induced overall decreases in SV, CO and MAP, suggesting increased venous pooling, and the increases in HR and TPR represent compensation.
attempts. The larger decreases of SV and CO in migraine suggest that nitroglycerin induced more venous pooling in the migraine group. MAP was similar between groups at the start, increased initially in the migraine group at nitroglycerin infusion and then decreased. This suggests an initial ample compensatory increase in MAP in the migraine group, that ultimately was no longer sufficient. Overall, this points to an abnormal susceptibility towards vasodilation of the systemic circulation in migraine.

Disclosure of Interest: None Declared

Headache Pathophysiology – Basic Science

PO-02-169

Transcriptomic Profiling of Trigeminal Nucleus Caudalis and Spinal Cord Dorsal Horn

Rikke Elgaard Christensen¹*, Lisette J. A. Kogelmann¹, Thomas F. Hansen¹, Inger Jansen-Olesen¹ and Jes Olesen¹

¹Danish Headache Center, Glostrup, Denmark

Objectives: The somatosensory system can be divided into the trigeminal pathway and the spinothalamic pathway. Even though the two systems are homologous in terms of function, differences in nociceptive signalling and gene expression must exist, as several signalling substances cause headache but not peripheral pain. Furthermore, migraine can be treated with highly specific drugs that do not have an effect on other types of pain. Recently, RNA-Sequencing has been used to characterise transcriptomes from trigeminal and dorsal root ganglia. However, the tissues where the signal is relayed to secondary afferents are largely unstudied. Thus, we aimed at investigating the transcriptomes from laminae I-V of the trigeminal nucleus caudalis (TNC) and laminae I-V from the dorsal horn of the thoracic part of the spinal cord (SDH).

Methods: Six 10-week-old male Wistar rats were anaesthetised, transcardially perfused, and brain stem and thoracic spinal cord were removed and flash frozen. Laminae I-V of the TNC and SDH were microdissected with a laser capture microdissection microscope. Purified RNA was sequenced on the [Illumina HiSeq 2500] platform. Differentially expressed (DE) genes were detected using DESeq2 and called to be DE when the false discovery rate was below 0.05 and their log2 expression in at least one of the tissues was >3.6. Pathway enrichment analysis was performed with the R-package GOseq using the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway database. P-values were adjusted for multiple comparisons by the Benjamini & Hochberg method.

Results: We found 3,591 genes to be DE; 1,696 were higher expressed in TNC and 1,895 were lower expressed in TNC compared to SDH. There was no difference between ratios of cell-specific markers between the two tissues, thus difference in cell type distribution is not causing differential expression. We describe the differential gene expression of relevant ion channels and G-protein coupled receptors, such as Mas-related G protein-coupled receptors, serotonin receptors, pituitary adenylate cyclase activating polypeptide-38 and vasoactive intestinal polypeptide, calcitonin gene-related peptide and histamine, and their receptors.

Pathway analysis showed 13 overrepresented pathways among the genes higher expressed in TNC and 11 overrepresented pathways among the genes lower expressed in TNC compared to SDH. Two of the most interesting findings were the differences in gene expression in the GABAergic pathway (KEGG pathway 04727) and the cGMP signalling pathway (KEGG pathway 04022). Furthermore, we characterised the expression of 36 of the 41 migraine-associated loci found by GWAS. Below a table of some of the significantly DE migraine-relevant genes is included.

Conclusion: We describe differential expression of several genes believed to be involved in pain signalling. Also, the GABAergic and cGMP pathways showed different signalling between tissues. Thus, many genes are expressed differently in TNC and SDH in naive rats. Further analysis of these findings may lead to increased understanding of migraine mechanisms and to novel drug targets.

Disclosure of Interest: None Declared

Table  Significantly DE migraine-relevant genes. Asterisk denotes the value and tissue with highest expression. TNC: Trigeminal nucleus caudalis, SDH: spinal cord dorsal horn

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<th>SDH (log2)</th>
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**Migraine Acute Therapy**

**PO-02-170**

Double blind trial of sumatriptan for cilostazol induced headache in migraine without aura patients. Intracellular VS extracellular mechanisms

Katrine Falkenberg¹,*, Jes Olesen¹, Messoud Ashina¹, Song Guo¹ and Bara A Dunga¹

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**Objectives:** There remains a great need for more effective anti-migraine drugs with fewer side-effects. A human model to test new drugs is needed, but still not developed. This is the third attempt in a series, aiming to develop such a model. To validate whether cilostazol could be used as a model in migraine patients, we tested the effect of sumatriptan on the induced headache and hypothesized that sumatriptan would reduce the headache score.

**Methods:** 200 mg of cilostazol was given on two separate days to 30 patients with migraine without aura. The patients treated the induced headache in a double-blind cross-over design with 50 mg of sumatriptan and placebo. Headache intensity and accompanying symptoms were registered in a questionnaire until 12 hours after intake. To verify the sensitivity of the patient material, as many as possible (15) participants also treated their spontaneous attacks in a double-blind cross-over design with sumatriptan and placebo and filled out the same questionnaire.

**Results:** Cilostazol induced headache with some migraine characteristics in all participants on both study days and 77% fulfilled criteria for a migraine-like attack on one or both provocation days. There was no reduction in headache score 2 h after any of the two treatments (P=0.0002) indicating some effect of sumatriptan. At 4 h after treatment, the difference in median headache score was significant (P=0.003). The participants subsequently treated spontaneous migraine attacks with sumatriptan double blindly. The difference between placebo and sumatriptan was not significant at 2 h (P=0.26), but was highly significant 4 h after intake (P=0.006) due to a significant decrease in headache score after sumatriptan (P=0.003).

**Conclusion:** Cilostazol induced a headache indistinguishable from spontaneous migraine attacks but spontaneous attacks responded better than cilostazol induced attacks to sumatriptan. The low efficacy on cilostazol induced migraine has bearings upon the mechanisms of migraine and the mechanisms of action of sumatriptan. Sumatriptan acts via 5-HT₁B/D/F receptors in the cell membrane which are coupled to G-proteins that inhibit adenylate cyclase and thereby decrease intracellular cyclic adenosine monophosphate (cAMP) concentration. Cilostazol works directly intracellularly by inhibiting Phosphodiesterase 3 (PDE3) which breaks down cAMP and hence causes intracellular cAMP accumulation. Sumatriptan and cilostazol thus have opposing effects on cAMP-level. We also know from previous studies of NO donors that work directly intracellularly that they don’t respond to sumatriptan. On the basis of these studies we propose that cilostazol- and perhaps NO based models will respond to new drugs that act intracellularly or directly on ion channels responsible for intracellular signaling. But these models will not respond to drugs acting extracellularly e.g. CGRP receptor antagonists. The attacks induced by cilostazol are identical to spontaneous attacks and will therefore be highly valuable in the investigation of the pathophysiological mechanisms behind migraine, e.g. via imaging.

**Disclosure of Interest:** None Declared

**Migraine Acute Therapy**

**PO-02-171**

Use of Most Bothersome Symptom as a Co-Primary Endpoint in an Acute Treatment of Migraine Trial

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**Objectives:** In October 2014, the FDA issued a Guidance Document for Acute Migraine Treatment. In the FDA document, the use of subject-identified migraine-associated most bothersome symptom (MBS) in addition to pain is recommended as a co-primary efficacy endpoint. Recently, this approach was utilized in a multi-center, dose-ranging efficacy and safety trial of a novel intracutaneous formulation of zolmitriptan (M207), and herein we report the results with this novel endpoint.

**Methods:** The subject’s MBS (photophobia(PT), phonophobia(PN), or nausea (N)) was ascertained at screening. Subjects were asked to select the associated symptom that was most bothersome and “present most of the time” during a migraine attack. Subsequently, subjects who qualified could only treat a migraine with study drug when the previously-selected MBS was present. For qualifying
subjects, treatment assignment was stratified via MBS, and subjects were assigned to placebo or one of three doses of M207 (1:1:1:1). Results for placebo and M207 3.8 mg are presented here.

Table  Number (%) of Subjects Pain Free and MBS Free at 2 Hours

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>M207 3.8 mg</th>
<th>Treatment Difference (M207-Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>N 77</td>
<td>82</td>
<td>27.2%</td>
</tr>
<tr>
<td></td>
<td>Pain Free</td>
<td>11 (14.3%)</td>
<td>34 (41.5%)</td>
</tr>
<tr>
<td></td>
<td>MBS Free</td>
<td>33 (42.9%)</td>
<td>56 (68.3%)</td>
</tr>
<tr>
<td>Photophobia as MBS</td>
<td>N 37</td>
<td>42</td>
<td>31.6%</td>
</tr>
<tr>
<td></td>
<td>Pain Free</td>
<td>13 (13.5%)</td>
<td>15 (35.7%)</td>
</tr>
<tr>
<td></td>
<td>MBS Free</td>
<td>28 (35.1%)</td>
<td>66 (77.5%)</td>
</tr>
<tr>
<td></td>
<td>N 21</td>
<td>22</td>
<td>39.8%</td>
</tr>
<tr>
<td>Photophobia as MBS</td>
<td>Pain Free</td>
<td>3 (14.3%)</td>
<td>9 (40.9%)</td>
</tr>
<tr>
<td></td>
<td>MBS Free</td>
<td>19 (42.9%)</td>
<td>12 (26.6%)</td>
</tr>
<tr>
<td></td>
<td>N 19</td>
<td>18</td>
<td>96.8%</td>
</tr>
<tr>
<td>Nausea</td>
<td>MBS Free</td>
<td>11 (57.9%)</td>
<td>16 (88.9%)</td>
</tr>
</tbody>
</table>

Results: 365 subjects were randomized; 321 treated with study drug (n = 244 for M207 and 77 for placebo) and had at least one post-treatment symptom assessment and comprised the modified intent to treat population. The most commonly reported MBS was PT (50.5%), followed by PN (26.8%), and N (22.7%). The 2-hour pain free rate was higher in the M207 3.8 mg group compared to the placebo group, 41.5% vs 14.3%, as was the 2-hour MBS freedom rate, 68.3% vs 42.9% (p < 0.001 for both, CMH test). Co-primary efficacy results as a function of their selected MBS are shown above.

In an additional post-hoc analysis, the percentage of subjects who were both pain free and MBS free at 2 hours following M207 3.8 mg was 42.2%, and somewhat similar percentages were seen when categorized by MBS (PT 33.3%, PN 40.9% and N 55.6%).

Conclusion: Approximately 50% of subjects selected photophobia as their MBS. Those who selected nausea showed the largest treatment effect. Subjects who selected photophobia as their MBS had the smallest therapeutic gain for MBS freedom. MBS as a co-primary endpoint is a viable and patient-centered alternative to utilizing four co-primary endpoints in acute treatment of migraine trials and is worthy of discussion in future IHS clinical trial guidelines.


Migraine Acute Therapy

PO-02-172
Lasmiditan inhibits CGRP release in the mouse trigeminovascular system.

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Objectives: Migraine pathophysiology is associated with activation of the trigeminovascular system, CGRP release and cranial vasodilatation. Triptans are 5-HT1B/1D/(1F) receptor agonists with vasoconstrictive effects that inhibit trigeminal CGRP release presynaptically, but they are contraindicated in patients with cardiovascular disease. In contrast, lasmiditan is a selective 5-HT1F receptor agonist devoid of vasoconstrictor properties. The present study investigated the modulation of trigeminal CGRP release by lasmiditan and sumatriptan.

Methods: The effects of sumatriptan and lasmiditan (both 30 μM) were investigated on KCl-induced CGRP release from isolated preparations of dura mater, trigeminal ganglion (TG) and trigeminal nucleus caudalis (TNC) from mice. The release of CGRP was measured by enzyme-linked immunoassay. Experiments were approved by the Erasmus University Medical Center’s institutional ethics committee, in accordance with National Institute of Health guidelines.

Results: In contrast to vehicle, sumatriptan significantly inhibited (p < 0.05) CGRP release by 49% in the dura mater (n = 8), 48% in the TG (n = 9), and 75% in the TNC (n = 7). Interestingly, lasmiditan also inhibited (p < 0.05) CGRP release by 47% in the dura mater (n = 8), 59% in the TG (n = 9), and 70% in the TNC (n = 5).

Conclusion: Based on our results, the clinical efficacy observed with lasmiditan and sumatriptan may be due to inhibition of CGRP release from peripheral and central...
trigeminal nerve terminals. In mice, the 5-HT receptor subtypes activated by lasmiditan at the concentration evaluated could be 5-HT_{1F} or 5-HT_{1A}. However, prior publications would support that the release of CGRP is most likely mediated by the 5-HT_{1F} receptor, not 5-HT_{1A}. Since activation of 5-HT_{1F} receptors is not associated with vasoconstriction, this may represent a therapeutic advantage over the vasoactive triptans.


**Migraine Acute Therapy**

**PO-02-173**

In vitro characterization of agonist binding and functional activity at a panel of serotonin receptor subtypes for lasmiditan, triptans and other 5-HT receptor ligands and activity relationships for contraction of human isolated coronary artery


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**Objectives:** Ergot alkaloids and triptans (5-HT_{1B/1D} receptor agonists) are well-established antimigraine drugs, but their use is contraindicated in patients with coronary artery disease. In contrast, lasmiditan is a selective 5-HT_{1F} receptor agonist devoid of coronary vasoconstrictive properties. We investigated the binding and functional agonist pharmacological properties of individual anti-migraine drugs (ergotamine, sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan, frovatriptan, donitriptan, avitriptan, alniditan, lasmiditan, LY334370, LY344864, 5-HT and 5-carboxamidotryptamine on a panel of human 5-HT receptors.

**Methods:** In vitro radiolabelled competition and second messenger activity assays were performed using membrane preparations from CHO cells transfected with gene constructs for human orthologs of 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}, 5-HT_{2A}, 5-HT_{2B} and 5-HT_{7} receptors. We related radioligand binding affinity and second messenger activation to the contractile potency of these compounds in human isolated coronary arteries as determined earlier by our group or from other publications (for almotriptan and frovatriptan).

**Results:** The potency of these compounds to inhibit forskolin-induced cAMP increase was positively correlated to their potency to contract the human isolated coronary artery in case of the 5-HT_{1B} receptor, and was negatively correlated for the 5-HT_{1F} receptor.

**Conclusion:** Our results indicate that, as expected, 5-HT_{1B} receptor-induced inhibition of cAMP responses, directly correlates to human coronary artery contraction. Furthermore, the negative correlation between the human coronary artery contraction and activation of 5-HT_{1F} receptors seems a cardiovascular safety advantage over 5-HT_{1B} receptor agonists; future studies should elucidate the underlying mechanism. Finally, our results confirm that lasmiditan is a selective 5-HT_{1F} receptor agonist devoid of vasoconstrictive properties.


**Migraine Acute Therapy**

**PO-02-174**

A Double-Blind, Placebo-Controlled, Study Evaluating the Efficacy of DFN-02 (Nasal Spray of Sumatriptan 10 mg + Permeation Enhancer) in Migraine With or Without Aura

Sagar Munjal and Elimor Brand-Schieber

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**Objectives:** DFN-02 is a sumatriptan 10 mg intranasal spray containing 1-O-n-dodecyl-β-D-maltopyranoside 0.2% (DDM), a permeation enhancer. DFN-02 is being
developed for the treatment of acute migraine with or without aura. The safety and efficacy of sumatriptan are well established. Following DFN-02 intranasal administration, sumatriptan plasma concentration peaked 5 minutes faster than subcutaneously injected 4 mg and 6 mg Imitrex®. This pharmacokinetic profile of DFN-02 may provide improved therapeutic effect via the nasal route. This study was conducted to primarily compare headache pain freedom response between DFN-02 and placebo at 2 hours postdose in acute migraine with moderate to severe pre- dose pain.

**Methods:** Subjects were randomized in a double-blinded fashion to treat one migraine attack (DB1) with DFN-02 or placebo within one hour of experiencing moderate (Grade 2) or severe (Grade 3) headache pain; the primary endpoint was the proportion of subjects with pain freedom (Grade 0) at 2 hours postdose compared between DFN-02 and placebo. Subjects were then re-randomized to receive DFN-02 or placebo to treat a migraine attack at any headache pain level. Subjects reported data in real-time eDiary. Safety was evaluated throughout the study.

**Results:** There were 107 subjects randomized, 93 had data in DB1, 86 continued, and 75 completed DB2. The study met its primary endpoint: in DB1, 43.8% of patients (n = 21/48) taking DFN-02 were pain-free at 2 hours compared with 22.5% taking placebo (p = 0.044). DFN-02 was also superior to placebo in alleviating the most bothersome symptom (MBS) (70.7% versus 39.5% MBS free; p = 0.007). After taking DFN-02, 38.9% of subjects (n = 14/36) were pain-free from 2–24 hours versus 13.8% (n = 4/29) on placebo (p = 0.029). DFN-02 reduced migraine-associated symptoms (i.e. nausea/photophobia/phonophobia; p = 0.026/0.005/0.004) and disability at 2 hours (p < 0.001). For DB2 trends were similar, however, fewer endpoints reached statistical significance, possibly due to a high placebo response. There were no discontinuations due to adverse events (AEs) and no reported serious AEs during the study. Overall DFN-02 was well tolerated.

**Conclusion:** The DFN-02 (sumatriptan 10 mg + DDM) treatment group had statistically significant higher proportion of subjects who had their moderate to severe migraine pain reduced to none (pain freedom) and symptom relief (including their most bothersome) at 2 hours postdose, compared with placebo. This novel product may provide an effective noninvasive option for the acute treatment of migraine.

**Disclosure of Interest:** S. Munjal Conflict with: Dr. Reddy’s Laboratories, Conflict with: Owns stock in Dr. Reddy’s Laboratories, E. Brand-Schieber Conflict with: Dr. Reddy’s Laboratories, Conflict with: Owns stock in Dr. Reddy’s Laboratories

### Migraine Acute Therapy

#### **PO-02-175**

**Experience with Delayed Treatment of Migraine and Morning Migraine Treatment Using Intracutaneous Zolmitriptan (M207)**

Pete Schmidt¹, Whitney Halladay¹, Jean Engels¹ and Alan Rapoport²

¹Zosano Pharma, Fremont
²Ronald Reagan UCLA Medical Center, Los Angeles, United States

**Objectives:** Migraineurs are typically instructed to treat migraine attacks with triptans early or when pain is still mild, as current data suggest that triptans are less effective when used late in a migraine attack. In practice, this becomes challenging, as patients often treat late for many reasons, including certainty that they are having a migraine attack and not a tension-type headache.

A new adhesive dermally-applied microarray (ADAM) system of zolmitriptan delivery (M207) recently demonstrated efficacy in a phase 2b/3 trial in episodic migraine. Subjects in this trial were instructed not to treat until their headache pain was moderate or severe and thus treatment was often delayed in relation to the onset of the headache. We sought to analyze the effects of delayed time-to-treatment on the efficacy of ADAM zolmitriptan.

**Methods:** A Cochran-Mantel-Haenszel test controlling for baseline randomization stratification by most bothersome symptom other than pain (MBS) was performed to compare M207 3.8 mg to placebo for each of the co-primary endpoints (pain freedom and freedom from MBS, both at 2 hours). A subject’s MBS was defined as the symptom other than pain that is present during the majority of migraine attacks and was most bothersome to the subject. This could be either photophobia, phonophobia or nausea. We performed post-hoc analyses for the subgroup of subjects who awoke with their migraine versus those who did not, and also for those who treated more than 2 hours after headache onset versus those who treated in under 2 hours.

**Results:** Approximately 51% of patients reported waking up with headache pain already present at moderate to severe intensity. The mean time to migraine treatment after subject-estimated headache onset in all groups was 4.96 hours and the median was 1.79 hours. 33.3% and 69.4% of the M207 subjects treating ≥2 hours achieved the co-primary endpoints (pain freedom and freedom from MBS), respectively, compared with 10.3% and 41.0% receiving placebo. In those treating <2 hours, 46.5% and 65.1% receiving active treatment achieved the co-primary endpoints, compared with 19.4% and 47.2% receiving placebo.

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In subjects who awoke with moderate to severe headache pain, 44.4% and 72.2% of subjects receiving active treatment achieved the co-primary endpoints, versus 15.9% and 38.6% of subjects receiving placebo. All comparisons achieved statistical significance (nominal p-values less than 0.05), with the exception of MBS freedom in those treating in <2 hours (p = 0.0899).

**Conclusion:** Therapeutic gain with M207 for the co-primary endpoints was nearly the same for subjects who treated in <2 hours, as compared to those who treated ≥2 hours after migraine onset. Consistent with these findings, M207 also provided a significant therapeutic gain i(28.5%) in those who woke up with migraine (i.e. morning migraine).

**Disclosure of Interest:** P. Schmidt Conflict with: Zosano Pharma, W. Halladay Conflict with: Zosano Pharma, J. Engels Conflict with: Zosano Pharma, A. Rapoport Conflict with: Zosano Pharma

**Migraine Acute Therapy**

**PO-02-176**

**Migraine Treatment Patterns and Opioid Use Among Chronic and Episodic Migraine Patients Identified by a Clinician-Administered Semi-Structured Diagnostic Interview**

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3 Jefferson Headache Center, Philadelphia
4 Vedanta Research, Chapel Hill
5 DaVita Medical Group, El Segundo
6 Stanford University School of Medicine, Stanford
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8 Headache Center; Department of Neurology, Albert Einstein College of Medicine; Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, United States

**Objectives:** Chronic migraine (CM) remains suboptimally treated. Opioids have been used for acute treatment of migraine, but are not recommended for regular use due to the risks of medication overuse, tolerance, dependence, and opioid hyperalgesia. The objectives of this study were to describe migraine treatment patterns and opioid use in CM and episodic migraine (EM) patients.

**Methods:** An observational study using retrospective claims data and survey data was conducted in a large medical group. Eligible patients were ≥18 years old, had ≥12 months of continuous medical and pharmacy enrollment prior to the screening date, and had ≥1 medical claim with a migraine diagnosis (ICD-9/10 code of 346.xx/G43.xxx) in the 12 months prior to the screening date. A Semi-Structured Diagnostic Interview (SSDI) administered by a trained clinician was used to determine if a patient had CM (≥15 headache days/month) or EM (<15 headache days/month). The SSDI included 31 questions related to headache symptoms, frequency, disability, medication use, and diagnosis. Acute treatment of migraine, preventive treatment of migraine, opioid use, and baseline characteristics were assessed for CM and EM patients based on claims data collected in the 12 months prior to the screening date. Results were summarized using descriptive analyses.

**Results:** Of the 192 patients included, 129 had CM and 63 had EM. The CM cohort had a mean age of 49.4 years (SD = 12.6) and was 93.8% female. The EM cohort had a mean age of 48.9 years (SD = 15.4), and was 82.5% female. In relation to migraine treatment patterns, 67.4% of CM patients and 55.6% of EM patients had ≥1 claim for both acute and preventive medications. 53.5% of CM patients and 36.5% of EM patients also had ≥1 opioid claim (p < 0.05); the mean number of opioid claims was 4.0 (SD = 7.1) among all CM patients and 2.8 (SD = 8.2) among all EM patients. Additionally, 33.3% of CM patients and 15.9% of EM patients had ≥3 opioid claims. The mean Deyo-Charlson Comorbidity Index scores were 0.3 (SD = 0.7) for the CM cohort and 0.2 (SD = 0.5) for the EM cohort. Furthermore, 13.2% of CM patients and 7.9% of EM patients had a diagnosis for a pain disorder other than migraine (e.g. psychogenic pain, central pain syndrome, chronic pain syndrome).

**Conclusion:** Approximately two-thirds of patients with CM filled prescriptions for both acute and preventive medications in the past year. The majority of patients with CM and about a third of patients with EM also received an opioid prescription in the same time period. Treatment patterns, including opioid use, in CM patients indicate opportunities for better management through improved care.

**Disclosure of Interest:** J. Yu Conflict with: Allergan plc, Conflict with: Allergan plc, J. Pavlovic Conflict with: Allergan plc, the American Headache Society, S. Silberstein Conflict with: Allergan, Inc.; Amgen; Cumberland Pharmaceuticals, Inc.; ElectroCore Medical, Inc.; Labrys Biologics; Eli Lilly and Company; Merz Pharmaceuticals; and Troy Healthcare, Conflict with: Alder Biopharmaceuticals; Allergan, Inc.; Amgen; Avanir Pharmaceuticals, Inc.; eNeura; ElectroCore Medical, LLC; Labrys Biologics; Medscape, LLC; Medtronic, Inc.; Neuralieve; NINDS; Pfizer, Inc. and Teva Pharmaceuticals, M. Reed Conflict with: Vedanta

**Migraine Acute Therapy**

**PO-02-177**

Higher Treatment Satisfaction and Reduced Functional Disability in Subjects with Acute Migraine Treated with DFN-02 (Sumatriptan 10 mg + 0.2 % DDM) Compared with Placebo

Elimor Brand-Schieber1,* and Sagar Munjal2

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2Clinical Development and Medical Affairs, Promius Pharma, a subsidiary of Dr. Reddy’s Laboratories, Princeton, United States

**Objectives:** The majority of migraine sufferers report dissatisfaction with their migraine medication. This study evaluated treatment satisfaction and functional disability in acute migraine patients who use DFN-02 10 mg (sumatriptan 10 mg +0.2% DDM, a permeation enhancer).

**Methods:** Subjects were randomized in a double-blinded fashion to treat one migraine attack (DB1) with DFN-02 or placebo within one hour of experiencing moderate or severe headache pain; the primary endpoint was the proportion of subjects with pain freedom at 2 h postdose. Subjects were then re-randomized to receive DFN-02 or placebo to treat a migraine attack at any level of headache pain (DB2). Subjects reported data in real-time in an eDiary. Safety was evaluated throughout the study. Among secondary endpoints, treatment satisfaction was assessed using a validated Patient Perception of Migraine Questionnaire-Revised (PPMQ-R). At baseline, subjects evaluated their usual migraine medication and at 24 h postdose, they evaluated the study medication. The PPMQ-R Global Satisfaction item alone was used at 2 h postdose. Functional disability was evaluated using a 4-point scale (0 = no disability, 1 = mild, 2 = moderate, 3 = severe) at predose and 2 h and 24 h postdose.

**Results:** In subjects acutely treating a migraine with moderate to severe predose headache pain in DB1, mean scores for functional disability significantly improved (p < 0.001) for DFN-02 at 2 h postdose (−1.2) (n = 48) compared with placebo (−0.6) (n = 39). No differences in disability were observed between treatments at 24 h postdose. For the PPMQ-R subscales, comparing DFN-02 treatment (n = 36) to the subjects’ usual migraine treatment (n = 48), the Total PPMQ-R score at 24 h postdose was significantly higher for DFN-02 (62.16 for usual migraine treatment versus 74.56 for DFN-02; p = 0.012). Similarly, the Overall Satisfaction item was significantly better (p = 0.013) for DFN-02 at 2 h postdose (n = 48) compared with usual migraine medication assessed at baseline (n = 48).

Subjects treated with DFN-02 (n = 37) had significantly higher satisfaction compared with placebo (n = 30) for the Efficacy subscale (mean score 65.23 versus 42.53; p = 0.016) and the Function subscale (mean score 68.92 versus 42.08; p = 0.001), but no significant difference was observed for Ease-of-use subscale (mean score 78.83 versus 85.28; p = 0.520) at 24 h postdose. The Total Score (Efficacy + Function + Ease of use) was significantly better for DFN-02 compared with placebo (mean score 70.99 versus 56.63; p = 0.016). The Global items: Medication Effectiveness and Overall Satisfaction were significantly better for DFN-02 at 24 h (p = 0.027 and p = 0.019, respectively). Moreover, the Overall Satisfaction item was significantly better for DFN-02 than placebo at 2 h postdose (p = 0.003). The placebo treatment had a significantly lower Tolerability subscale (94.83) than DFN-02 (88.51) at 24 h postdose (p = 0.026), however, the Global Side Effects item, was not significantly different between the treatment groups (p = 0.383). Results from DB2 show similar trends overall but few comparisons reached statistical significance, possibly due to a high placebo effect.

**Conclusion:** Subjects using DFN-02, an intranasal spray of sumatriptan 10 mg +DDM, to acutely treat a migraine attack at moderate to severe headache pain levels reported clinically and statistically significant greater satisfaction with medication effectiveness and had lower disability compared with placebo and greater satisfaction compared with their usual migraine medication. These data demonstrate that DFN-02 has the potential to reduce disability and to improve migraine treatment experience compared with usual migraine medication.

**Disclosure of Interest:** E. Brand-Schieber Conflict with: Dr. Reddy’s Laboratories, Conflict with: Owns stock in
**Migraine Acute Therapy**

**PO-02-178**

A review of pharmacokinetic variability of single doses of oral triptans with some possible clinical implications

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**Objectives:** Wide interindividual variability in plasma concentrations of sumatriptan after oral administration was observed in the first pharmacokinetic studies of the drug. Later, 2 pharmacokinetic studies in migraine patients indicated that both the speed of absorption and the levels of plasma concentrations of an oral triptan could be important for the clinical response to these drugs. In clinical practice, when treating migraine patients with oral triptans, it would often be useful to know the extent of oral variability potential of these drugs when trying to tailor a triptan to a patient. The aim of this review is therefore to provide treating physician with this information based on published pharmacokinetic studies on the oral triptans.

**Methods:** PubMed and Web of Science concentration were searched with the terms “name of a triptan” and “oral pharmacokinetics”. I included in the review pharmacokinetic studies presenting the following quantitative parameters for variability of $C_{\text{max}}$ (maximum plasma concentration) and $T_{\text{max}}$ (time to maximum concentration): mean, SD (standard deviation) or CV (coefficient of variation). If not presented in the paper the CV was calculated as SD/mean. The distribution of the CVs for $C_{\text{max}}$ for each drug is presented as either lower or higher than 40%. For $T_{\text{max}}$ the range for CVs for each drug is presented.

**Results:** A total of 43 pharmacokinetic studies on single dose, oral administration of 5 triptans were retrieved (none for naratriptan and frovatriptan): 12 studies with rizatriptan (5 – 10 mg), 9 studies with almotriptan (12.5 – 25 mg), 4 studies with eletriptan (30 – 80 mg), 9 studies with sumatriptan (25 – 300 mg), and 4 studies with zolmitriptan (2.5 – 10 mg). I found no studies with variability data for naratriptan and frovatriptan. CVs for $C_{\text{max}}$ in studies with the 5 triptans was distributed as follows: rizatriptan, $<40\% = 5$, $>40\% = 7$; almotriptan, $<40\% = 9$, $>40\% = 0$; eletriptan, $<40\% = 0$, $>40\% = 4$; sumatriptan, $<40\% = 7$, $>40\% = 2$; zolmitriptan, $<40\% = 3$, $>40\% = 1$.

The ranges for CVs for $T_{\text{max}}$ were: rizatriptan $= 27\% – 87\%$; almotriptan $= 28\% – 65\%$; sumatriptan $= 26\% – 58\%$. For eletriptan the CVs were 59% and 64% in 2 studies.

Two additional studies investigated oral absorption of a triptan both during and outside migraine attacks. There was no difference in mean $C_{\text{max}}$ but the CV ratios (during attacks/outside attacks) were: 95%/59% (rizatriptan 5 mg), 65%/40% (sumatriptan 25 mg), 76%/39% (sumatriptan 50 mg), and 52%/41% (sumatriptan 100 mg).

**Conclusion:** A CV $> 40\%$ is generally regarded as indicating a high degree of variability in the item reported; and the present review thus indicates moderate/high variability of the early oral absorption of several triptans. Almotriptan is probably an exception with smaller variability.

The variability observed in this review with fasting subjects could be higher during migraine attacks as indicated by an increased CV ratio for $C_{\text{max}}$ for migraine attacks versus outside attacks in 4 cases.

When treating a migraine attack with a triptan the physician should be aware that the dose administered can in reality “be equivalent to both lower or higher doses” than the declared dose of the tablet because of the pharmacokinetic variability. There can be no firm recommendations of how to deal with this problem; but a rational use of the trial and error method will probably benefit the patients.

**Disclosure of Interest:** None Declared

**Migraine Preventive Therapy**

**PO-02-180**

Phase 3 Study (SPARTAN) of Lasmiditan Compared to Placebo for Acute Treatment of Migraine

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**Objectives:** To compare efficacy on headache pain and the patient-centric measure of most bothersome symptom (MBS; nausea, phonophobia, or photophobia) at 2 hours post-dose and safety following treatment with lasmiditan 200 mg, 100 mg, 50 mg, or placebo.

**Methods:** In this randomized, double-blind, placebo-controlled study, patients with at least moderate disability (Migraine Disability Assessment Score ≥ 11) were randomized 1:1:1:1 to a first dose of lasmiditan treatment (200 mg, 100 mg, or 50 mg) or placebo (ClinicalTrials.gov number NCT02605174). Patients were asked to take the first dose within 4 hours of onset of a migraine attack...
If needed, patients took a randomly assigned second dose of either their previously assigned lasmiditan dose or placebo for rescue or recurrence of migraine (2 to 24 hours post-initial dose); patients randomized to placebo received placebo as the second dose. The primary analyses compared the proportions of patients (modified intent-to-treat population [mITT]) in the lasmiditan 200-mg group with the placebo group who were headache pain-free and who were MBS-free at 2 hours post-first dose. Comparisons were made via logistic regression with terms for treatment group and background migraine preventative use. Lasmiditan 100 mg and 50 mg were also compared to placebo and safety was assessed by treatment-emergent adverse events.

**Results:** Results will be provided once data become available to include the following:
- Primary Efficacy Analyses: treatment comparison between lasmiditan 200 mg and placebo for patients who are headache pain-free and patients who are MBS-free at 2 hours post-first dose.
- Secondary Efficacy Analyses: treatment comparison between lasmiditan 100 mg and 50 mg with placebo for patients who are headache pain-free and patients who are MBS-free at 2 hours post-first dose.
- Safety Results

**Conclusion:** Conclusions will be provided once data become available.

(12.8% vs. 7.3% p = 0.056) was slightly higher, but marginally significant.

**Conclusion:** Results demonstrated a statistically significant increase in HRU in terms of HCPs, neurologists, psychiatrists, and ED visits for migraine patients compared with non-migraine controls. To help reduce the burden of migraine on the European healthcare system better treatment options for migraineurs should be investigated.

**Disclosure of Interest:** P. Vo Conflict with: Novartis, A. Biliou Conflict with: Novartis, J. Fang Conflict with: Novartis, A. Laflamme Conflict with: Novartis, S. Gupta Conflict with: Kantar Health

**Migraine Preventive Therapy**

**PO-02-182**

**The Effects of Aerobic Exercise on migraine headache intensity**

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**Objectives:** For people with migraine, exercise is often suggested to health promotion and disease prevention. Recently the role of exercise in the management of migraine is considered, but there are no guidelines in the literature regarding how patients with migraine should be instructed to exercise. The aim of this study was to evaluate the influence of an aerobic exercise on migraine intensity.

**Methods:** In this study 50 untrained patients were recruited and randomized to two groups. The intervention group (n = 25) participated in aerobic exercise program 3 times per week during 8 weeks, for 45–60 minutes with intensity between 50% to 65% of maximal heart rate. Control group only received common medical treatment without change. Borg’s Rate of Perceived Exertion scale (RPE scale, 6–20) was used to set the training intensity. Each training session included a 15-minute warm-up period (intensity: RPE scale, 11–13). the intensity of migraine headache was measured at the baseline and after intervention with VAS (Visual Analog Scale).

**Results:** The intensity of migraine headache reduced significantly in exercise group (1.95 ± 0.8) compared to control group (0.81 ± 1). (P = 0.00)

**Conclusion:** Incorporating exercise into common headache treatments may be a useful approach to managing migraine headache symptoms. According to our study aerobic exercise with moderate intensity can reduce intensity of migraine headache. Future study is recommended to evaluate the efficacy of other types of exercise with different intensity in migraine headache management.

**Disclosure of Interest:** None Declared

**Migraine Preventive Therapy**

**PO-02-183**

**Multi-species probiotic mixture can attenuate the severity of episodic migraine- a double blind randomized controlled trial**

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**Objectives:** Migraine is a recurrent disorder with a lifetime prevalence of 13% in men and 33% in women. Pro-inflammatory cytokines can act on the nociceptors of the trigeminal nerve, causing migraine. A strong trigger of pro-inflammatory immune responses is the leakage of lipopolysaccharides from the intestinal lumen into the circulation. Probiotics are able to improve the intestinal barrier defense mechanism and stimulate the production of tight junctional protein mucins. These effects limit small intestinal permeability and suppress inflammation. Therefore probiotics supplementation can have beneficial effect in migraineurs. In current double blind, placebo-controlled trial, we investigated the effect of a probiotic supplementation containing 14 bacterial strains as an adjuvant therapy on severity and incidence of episodic migraine.

**Methods:** 50 migraineurs, 35 female and 15 male (mean age of 38.74 ± 7.5 Y) were recruited and randomly assigned to placebo and probiotic group (two capsules/d for 8 weeks). Probiotic supplement (Bio-Kult-protexin: 2 × (10)⁹ CFU/capsule) contained 14 bacterial strains included Bacillus subtilis PXN 21, Bifidobacterium bifidum PXN 23, Bifidobacterium breve PXN 25, Bifidobacterium infantis PXN 27, Bifidobacterium longum PXN 30,
Lactobacillus acidophilus PXN 35, Lactob. delbrueckii ssp. bulgaricus PXN 39, Lactob. casei PXN 37, Lactob. plantarum PXN 47, Lactob. rhamnosus PXN 54, Lactob. helveticus PXN 45, Lactob. salivarius PXN 57, Lactococcus lactis ssp. lactis PXN 63, Streptococcus thermophilus PXN 66. Episodic migraine was diagnosed by neurologist according to ICHD III beta criteria. Demographic characteristics, medications, precedent medical history of gastrointestinal disorders, anthropometric measurements, and Migraine disability assessment scale (MIDAS) were documented at baseline visit and at the end of the study. During the intervention, all patients were instructed to record frequency, intensity (10-point scale), and duration of migraine attacks, as well as used analgesics.

Results: Eight weeks of probiotic consumption resulted in significant reduction of the frequency (from 7 ± 3 to 4 ± 3 days/week), intensity (7 ± 2 to 5 ± 1), and duration (7.25 ± 3.7 to 7.02 ± 3.7 hours/day) of attacks (P = 0.001, 0.000, 0.004 respectively). In placebo group, the intensity and frequency of attacks did not changed significantly. Probiotic supplementation also significantly affect MIDAS and analgesics consumption (p < 0.001). The mean reduction of the frequency, intensity, MDAS, and analgesics consumption was significantly greater in probiotic group compared to placebo (P = 0.001, 0.007, 0.000, and 0.007 respectively). The differences remained significant after adjusting for confounding factors.

Conclusion: In patients with episodic migraine, adding probiotic to current prophylactic medication might beneficially affect headache control.

Disclosure of Interest: None Declared

Migraine Preventive Therapy

PO-02-184

Real-world patient perspective on the burden and impact of migraine

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Objectives: Migraine is a prevalent condition affecting about 11% of the adult population. It has debilitating symptoms and affects patient functioning. The present study was undertaken to understand the full burden and impact of migraine in everyday life from the patient’s point of view.

Methods: This cross-sectional study was conducted using Online Bulletin Boards (OBB). This interface was developed for online survey, discussions and interactions led by a trained facilitator over a period of 4 consecutive days. Adults with chronic and episodic migraine aged between 25 and 60 years old were recruited to participate in 6 OBBs established in Germany, Italy and USA (2 per country). Participants were blinded to each other and agreed to partake for at least 30 minutes each day in the OBBs, where they were asked to respond to specific questions on migraine and to provide their perspective on statements and other participants’ blinded responses. All responses were aggregated by country and qualitatively analyzed.

Results: A total of 60 migraine patients participated in this pilot phase of a large global study (20 per country). About half (47%, n = 28) reported having been diagnosed with migraine, either by a general practitioner (GP) or neurologist within the year following the date of their 1st symptoms. Table 1 summarizes the 3 most common migraine attack triggers, symptoms, and coping mechanisms reported by patients. All respondents reported important limitations resulting from migraines in private, professional and social aspects of life, mainly the disruption of daily routines, significant strain on personal relationships, difficulty caring for children, and missed days of work, deadlines, or social events. Anxiety and frustration were most frequently reported as emotional consequences of migraine in private/social life (92% and 72%) and work (97% and 88%). 87% of patients (n = 52) had seen a physician for migraine management but many (85%, n = 51) did...
not consult regularly, especially if their diagnosis had occurred long ago. Two thirds (n = 38/63%) of respondents reported getting functional and emotional support from family and friends, but wished for improved understanding/compassion from others and more efficacious medications.

Conclusion: This study highlights the substantial functional and emotional burden migraine exerts on individuals, as well as the significant unmet needs that remain for these patients despite currently available care and treatment options.


Migraine Preventive Therapy

PO-02-185

Burden and impact of migraine: a caregiver's perspective

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Objectives: Migraine has far-reaching impacts on the family and relatives of individuals with migraine and only limited evidence is available to describe this reality. In an effort to better understand the full burden and impact of migraine, this study sought to describe the effect of migraine from the caregiver’s perspective.

Methods: This cross-sectional study was conducted as a feasibility assessment for a global migraine survey, using Online Bulletin Boards (OBB). This interface was developed for online survey, discussions and interactions led by a trained facilitator over a period of 4 consecutive days. Caregivers aged 25 years or older who were caring for an adult migraine patient in their household were recruited to participate in 3 OBBs established in Germany, Italy and USA (1 per country). The participants were blinded to each other and agreed to partake for at least 30 minutes each day in the OBBs, where they were presented and asked to respond to specific questions on migraine and provide their perspectives on statements and other participants’ blinded responses. All responses and inputs were aggregated by country and qualitatively analyzed.

Results: A total of 30 caregivers participated in this pilot phase of a large global study (10 per country). All caregivers reported that they were highly involved in the management of migraine and that they spent an average of 15 hours per month supporting their family member suffering from migraine. Stress, exhaustion and feeling overwhelmed with the amount of work resulting from their caregiving activities were reported by 83% (n = 25/30) of respondents. They described themselves as powerless witnesses of the frequent and intense suffering of their loved ones and wanting to be helpful while knowing the limits of what they could do. 60% (n = 18/30) of caregivers reported a worsening of personal relationships over time due to migraines. Regardless of whether they were employed, unemployed or retired, 83% of caregivers (n = 25/30) reported that their caregiver role affected their lives due to the significant changes it imposed on their own daily routines and schedules. This thereby affected private life, social engagements, relationships, and professional obligations, including having fear of losing employment. Most caregivers (87%, n = 26/30) reported ambivalent feelings, being torn between commitment, self-sacrifice and resentment, but all agreed that migraine patients were thankful for their help and assistance.

Conclusion: Caregiving has a major impact on the lives of close relatives supporting migraine patients. This study highlights how the burden of migraine extends beyond the patients, with substantial functional and emotional impacts of the disease on caregivers as well. This pilot also confirmed the unique opportunity that this type of study and interface provides for insights into the caregivers’ experience and unmet needs in the current treatments available to migraine patients.

Disclosure of Interest: E. Ruiz de la Torre: None Declared, P. Martelletti Conflict with: Department of Clinical and Molecular Medicine, Sapienza University of
PO-02-186

Outcome of Inpatient Management of Refractory New Daily Persistent Headache

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Objectives: New Daily Persistent Headache (NDPH) is one of the chronic refractory headache conditions and there is limited evidence about its treatment. NDPH causes a severe burden and impairs the functioning of patients that suffer from it. Objective is to determine the outcome of comprehensive inpatient treatment of patients diagnosed with refractory NDPH, mainly whether there is an acute improvement in pain scale when comparing admission to discharge headache assessment.

Methods: This is a retrospective chart review of 73 patients who underwent comprehensive inpatient treatment program which included pharmacological, psychological and ancillary therapy for NDPH. All patients had previously failed multi-approach outpatient treatment and some had failed inpatient treatment as well. Records were reviewed of patients admitted between January 2015 and December 2016. All patients satisfied the ICHD-3 diagnostic criteria for NDPH. At least a 3-point improvement in pain score at discharge was considered clinically significant.

Results: The headache pain rating on a 0–10 pain scale was at a mean of 7.2 at admission and 3.1 on discharge (P < .00001). The majority (55/73, 75.3%) of patients had clinically significant improvement in their pain score and (33/73, 45.2%) had 5 or more points improvement. The average length of stay was 8.4 days. Out of 73 patients, 60 had migraine phenotype, 4 had tension type and 9 patients had both. Age range was between 18 and 73 with mean of 36.7 years. The bulk of the patients 63% were female and 37% males accounted for remaining 37%. The average time since headache onset was 2.5 years. Medication overuse at the time of admission was seen in 29 patients and 50% of them overused opiates. Intravenous Dihydroergotamine (DHE) was the mainstay pharmacological treatment (64/73, 87.7%) patients received. There were minimal known non serious adverse events. The average total DHE dosage during the hospital stay was 10.5 mg which was given in doses ranging from 0.5 to 1 mg per predefined protocol. The majority of the remaining patients received IV sodium valproate or other IV medications mentioned below. All patients were provided with as needed non-opiate IV medications based on their pain level. These medications included NSAID, muscle relaxants and neuroleptics.

Conclusion: Comprehensive inpatient treatment significantly improves pain score in patients with refractory NDPH who had previously not responded to different outpatient therapies. IV DHE therapy with predefined protocol may be considered as current standard for refractory NDPH. Controlled trials may confirm this and further studies may provide a better picture of managing this refractory primary headache syndrome.

Disclosure of Interest: None Declared

Other Secondary Headache Disorders

PO-02-187

Highly positive effect on health care costs and productivity after treatment of medication-overuse headache – results from the multicenter COMOESTAS project

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Objectives: To estimate direct and indirect headache-related healthcare costs from baseline to 6 months after treatment of MOH patients.

Methods: This prospective longitudinal study was a part of the COMOESTAS project. Patients with MOH were included from four European and two Latin American headache centers. Costs of acute medication, costs of health care services, and measurement of productivity were calculated before and after MOH treatment.

Results: A total of 475 patients (71%) completed the treatment and were followed up after 6 months. Direct healthcare costs were significantly reduced by 52% (P < 0.001) for the total study population. Significant reductions were seen in both number of consumed tablets with 71% (P < 0.001) and number of visits to physicians with 43 % (P < 0.001). Fifty percent of patients reduced their number of consumed tablets >80%. Productivity loss (absenteeism from work and reduction of productivity...
50% during the workday due to headache) were reduced by 21% and 34% respectively (P < 0.001).

Conclusion: Globally standardized treatment of MOH significantly reduced the direct healthcare costs and increased productivity. This emphasizes the urgent need for awareness and treatment of MOH.

Disclosure of Interest: None Declared

Other Secondary Headache Disorders

PO-02-188

“Pure” detoxification for medication-overuse headache is the most effective treatment: A randomized controlled trial with 6- and 12-month follow-up

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Objectives: There is lack of evidence on how acute headache medication should be reduced during detoxification for medication-overuse headache (MOH). The aim of this study was to compare the effect of a two-month complete stop of all acute headache medication with a restricted intake in MOH patients.

Methods: MOH-patients were included in a prospective, open-label study and randomized to a 2-months outpatient detoxification program with either A) no acute headache medication or B) acute headache medication restricted to two days/week. Both groups received education on MOH and headache in general and were followed up at 2, 6 and 12 month.

Results: We included 72 patients. Of these 59 succeeded in detoxification, 58 (81%) were followed-up at 6 months and 53 (74%) at 12 months. Patients in program A had a significantly higher reduction in the primary efficacy parameter headache frequency (25 to 13 days/month; 46%) at 6-months follow-up than patients in program B (25 to 19 days/month; 22%) (p = 0.005). After 12 months, headache frequency was reduced by 45% to 13.8 days/month in Program A, and by 31% to 17.0 days/month in Program B (p = 0.14).

Significantly more patients in program A reverted to episodic headache at 6-month (70% vs. 42%, p = 0.04) and 12-month follow-up (74% vs. 42%, p = 0.02).

The number of patients with chronic migraine was decreased from 15 to 1 in program A and from 17 to 8 in program B (p = 0.02).

There were no differences in drop-out rates between the two groups.

Conclusion: Detoxification without any acute medication for two months was more effective than detoxification with restricted intake of analgesics in reducing headache frequency, in converting MOH to episodic headache and particularly in reducing the number of patients with chronic migraine.


Other Secondary Headache Disorders

PO-02-189

Prevalence of Migraine in Patients with Idiopathic Intracranial Hypertension (IIH) in Comparison to the general population

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Objectives: Idiopathic intracranial hypertension (IIH) is a neurological disorder that is characterized by increased intracranial pressure (ICP) accompanied by a small or normal sized ventricles of the brain. The main presenting symptom of IIH is headache that usually is severe. IIH may lead to visual and hearing impairment or even loss of vision. The initial treatment would be medical and conservative. However, some patients may even need surgical intervention to divert CSF flow to decrease the intracranial pressure. On the other hand it seems that migraine headache is common among IIH patients and sometimes it is misdiagnosed as the headache of IIH and might lead to inappropriate management. In the present study, the prevalence of migraine in IIH patients is explored in comparison with the normal population.

Methods: In this case-control study, the presence of migraine in 108 IIH patients was evaluated in comparison to 103 non-IIH subjects. The diagnosis of IIH and migraine was done according to the diagnosis criteria of high opening CSF pressure (>25–40cmH2O) and (ICHD III beta) criteria. In order to collect the required information, all subjects were interviewed by a trained medical student. A checklist for migraine diagnosis was filled. Demographic data was collected. IIH patient’s medical documents were explored and variables such as age, BMI (Body Mass Index), Cerebro-Spinal Fluid pressure, presence or absence of
Papilledema were studied. Data analysis was done using Stata software, Version 11.

**Results:** 211 subjects (86.7% female) with mean age of 38.04 ± 12.19 and mean BMI of 28.12 ± 4.93 kg/m² were studied. In the IIH patients 93 cases (81.6%) had papilledema and the mean CSF pressure was 32.10 cm H₂O (Range: 26 cm H₂O to 65 cm H₂O). There were 70 (64.8%) and 22 (21.4%) migraine patients in case and control groups respectively which the difference was found significant (P-value < 0.001). In 26 of 70 (24.1%) migraine cases in IIH group the disorder was diagnosed after developing IIH. The risk of affecting by migraine in IIH patients was 6.17 times greater than the non-IIH group (95% CI = 3.56–14.36 p < 0.01).

**Conclusion:** According to the higher probability of migraine and even the possibility of developing new onset migraine in IIH patients, taking precise headache history in the follow up period is necessary. This consideration prevents misdiagnosis of migraine headache as the recurrence of IIH or uncontrolled IIH and its inappropriate management.

**Disclosure of Interest:** None Declared
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