International Headache Society

New Targets in the Acute and Preventive Treatment of Migraine

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Conflict of Interest Statement

- German Research Council
- German Ministry of Education and Reserach
- EU
- Böhringer-Ingelheim
- Astra-Zeneca
- Sanofi-Aventis
- Pfizer
- Bayer
- Janssen-Cilag

- Novartis
- Schering
- Eisai
- J&J
- BMS
- Novo Nordisk
- D-Pharm
- MSD
- Paion
- Yamaguchi
- Wyeth
- Solvay
- CoLucid
- Allergan
- Addex

Treating the Acute Migraine Attack

Established

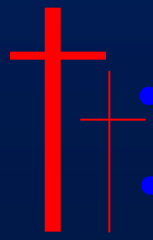
- Triptans
  - tablets
  - melt tablets
  - nasal spray
  - suppositories
  - s.c. injection

Established

- Simple analgesics
- Combination analgesics
- Ergotamine
- (DHE)
- Antiemetics

War of the Triptans

- **Sumatriptan** (Imigran® GlaxoSmithKline)
- **Zolmitriptan** (AscoTop® AstraZeneca)
- **Naratriptan** (Naramig® Glaxo/Schwarz)
- **Rizatriptan** (Maxalt® MSD)
- **Eletriptan** (Relpax® Pfizer)
- **Almotriptan** (Almogran® Allmiral, Bayer)
- **Frovatriptan** (Elan,Berlin Chemie)



- Avitriptan
- Alniditan

New Targets for Treating the Acute Migraine Attack

- CGRP antagonist
- TRV1 antagonist
- EP4 receptor antagonist
- 5-HT-1F agonist
- NO- synthase inhibitor
- Gap-junction inhibitor

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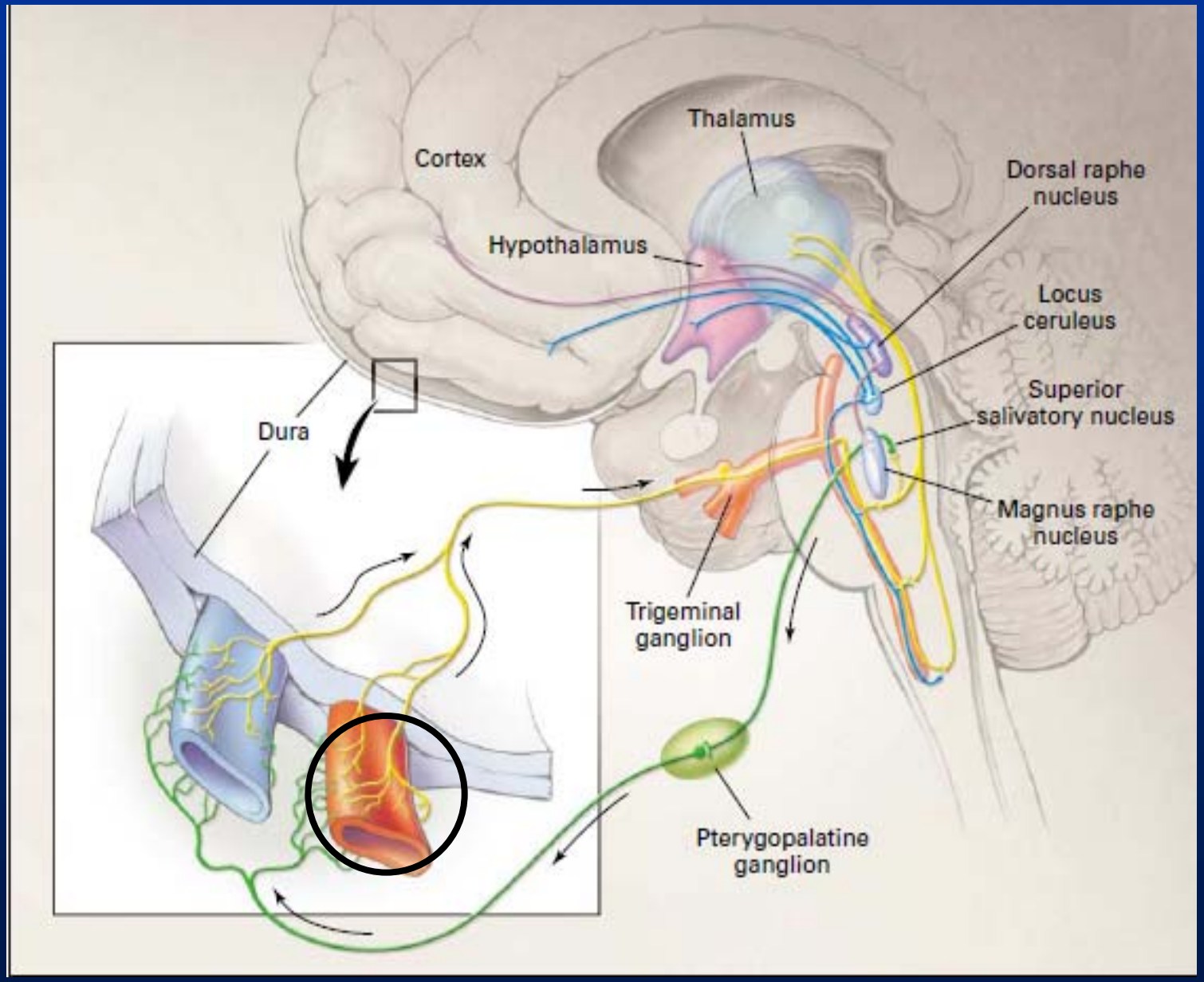
CGRP-antagonists

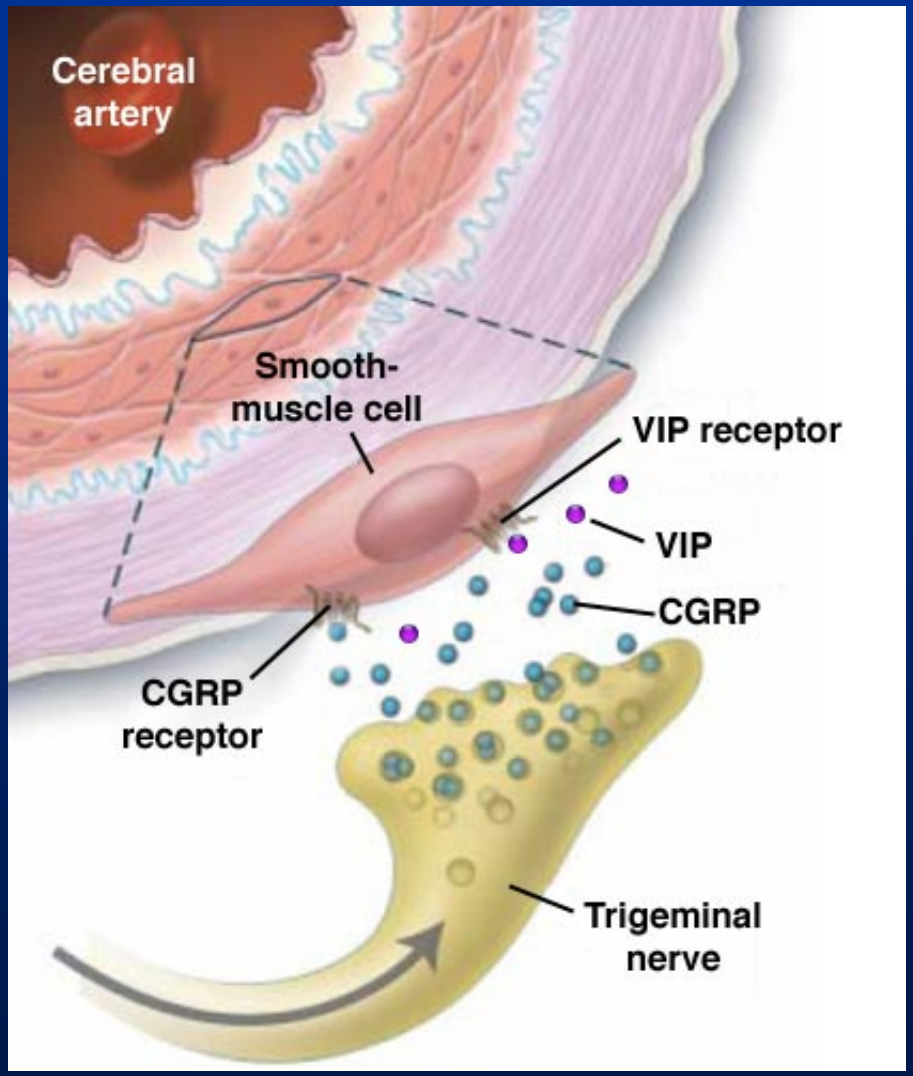
- CGRP is a potent vasodilator
- CGRP levels are increased during migraine attacks
- Triptans lead to a decrease in CGRP levels in venous blood
- CGRP receptors are on cell bodies of the trigeminal ganglion

Goadsby et al, 1990,1991, Zhang et al, 2007



Goadsby et al. NEJM 2002

Vasodilation of Cerebral Vessels



Adapted with permission from Durham PL. *N Engl J Med*. 2004;350:1073–1075.

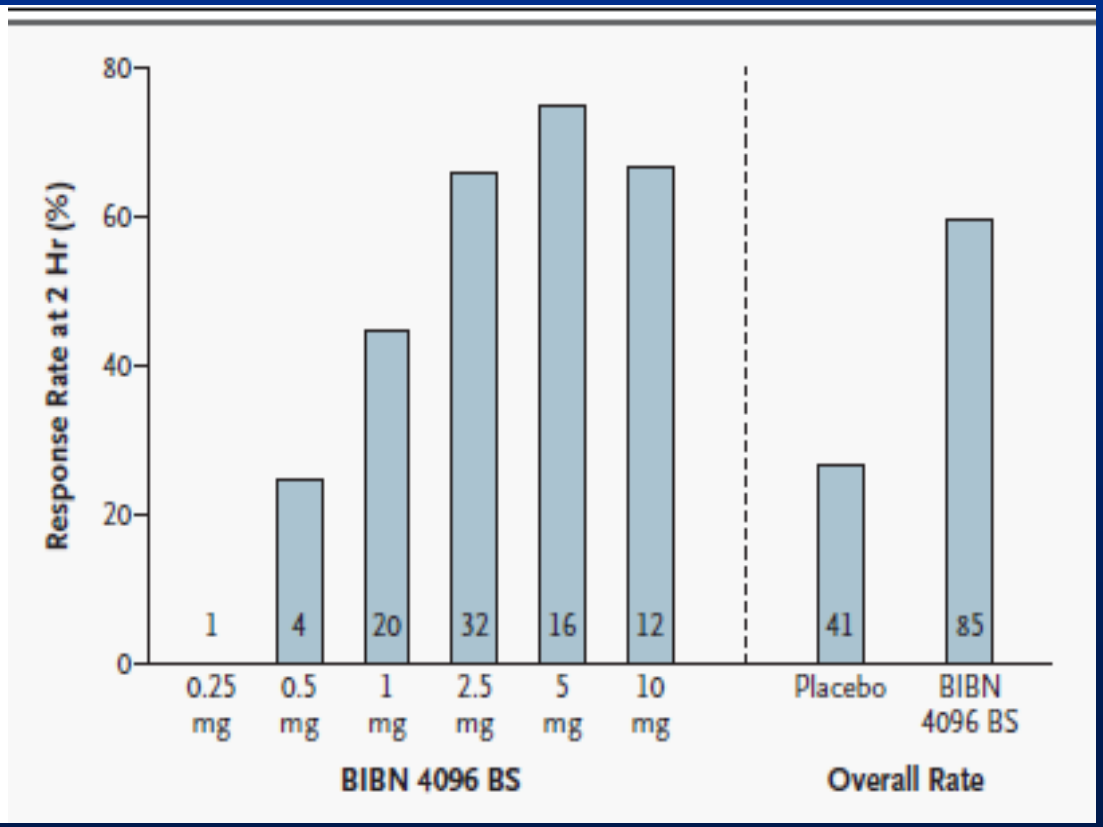
CGRP Antagonists in the Treatment of Acute Migraine Attacks

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Calcitonin Gene–Related Peptide Receptor Antagonist BIBN 4096 BS for the Acute Treatment of Migraine

Jes Olesen, M.D., Hans-Christoph Diener, M.D., Ingo W. Husstedt, M.D., Peter J. Goadsby, M.D., David Hall, Ph.D., Ulrich Meier, Ph.D., Stephane Pollentier, M.D., and Lynna M. Lesko, M.D., for the BIBN 4096 BS Clinical Proof of Concept Study Group



MK-0974 (Telcagepant) for the Treatment of Acute Migraine Attacks

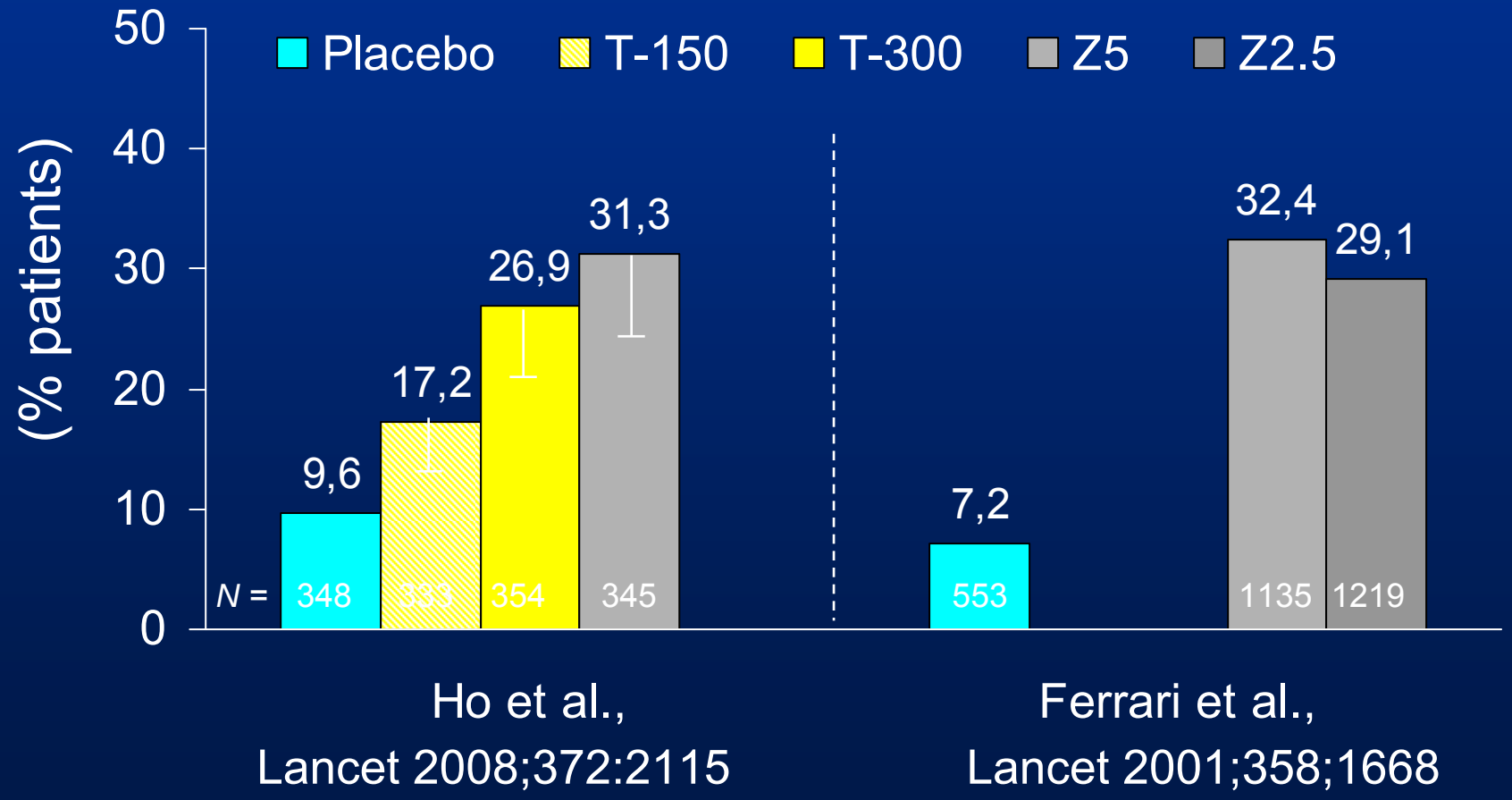
Randomized controlled trial of an oral CGRP receptor antagonist, MK-0974, in acute treatment of migraine

T.W. Ho, MD
L.K. Mannix, MD
X. Fan, PhD
C. Assaid, PhD
C. Furtek, BS
C.J. Jones, MS
C.R. Lines, PhD
A.M. Rapoport, MD
On behalf of the MK-0974 Protocol 004 study group*

Neurology, 2008

CGRP receptor antagonist telcagepant is effective in the treatment of acute migraine

- Double-blind parallel group randomised controlled trial
  - ➢ 2 Hour pain free



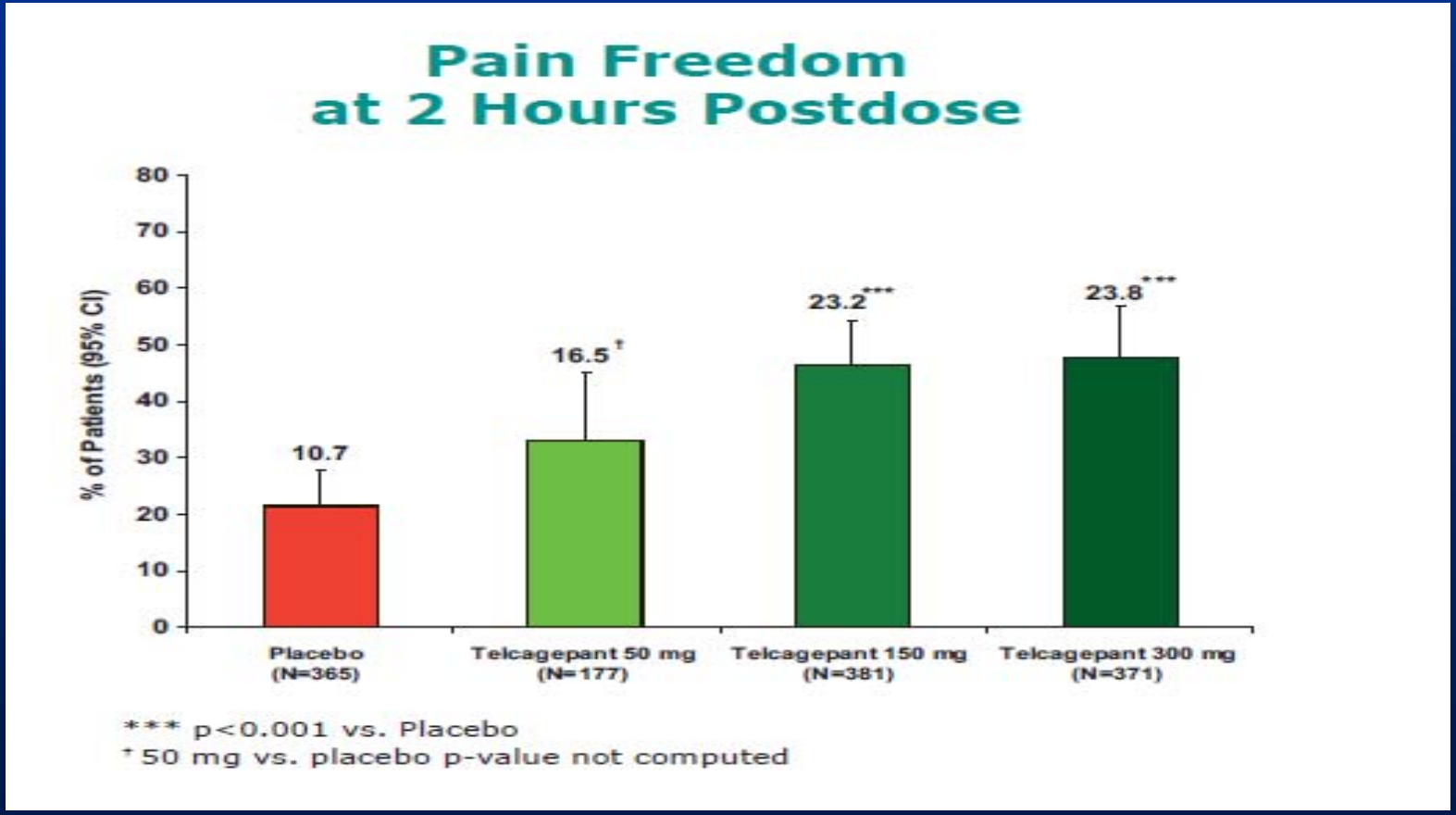
Efficacy and Safety of telcagepant (MK-0974), a Novel Oral CGRP Receptor Antagonist, for Acute Migraine Attacks

Kathryn M. Connor,[1] Robert E. Shapiro,[2] Hans-Christoph Diener,[3] Sylvia Lucas,[4] James Kost,[1] Xiaoyin Fan,[1] Christopher Assaid,[1] Tony W. Ho[1]

[1]Merck Research Laboratories, North Wales, PA, USA, [2]University of Vermont College of Medicine, Burlington, VT, USA, [3]University of Essen, Essen, Germany, [4]University of Washington Medical Center, Seattle, WA, USA

- 1294 patients treated
- 50, 150 and 300 mg telcagepant or placebo
- Randomization 1:2:2:2
- Primary endpoint:
  - Pain free
  - Pain free
  - Improvement of nausea, photo- phonophobia

MK-0974 for the Treatment of Acute Migraine Attacks



Ho et al., Neurology 2009 in press

MK-0974 for the Treatment of Acute Migraine Attacks

- Advantages of CGRP antagonists:
  - No vasoconstrictive properties
  - Treatment in patients with contraindications for triptans
  - Adverse event profile like placebo
- Yet unknown
  - Efficacy in combination with triptans?

Telcagepant

Merck announced in April 2009 that the Company would not file a New Drug Application for telcagepant with the U.S. Food and Drug Administration in 2009 based on findings from a Phase IIa exploratory study in which a small number of patients taking telcagepant twice daily for three months for the prevention of migraine were found to have marked elevations in liver transaminases. The daily dosing regimen in the prevention study was different than the dosing regimen used in Phase III studies in which telcagepant was intermittently administered in one or two doses to treat individual migraine attacks as they occurred.

New Targets for Treating the Acute Migraine Attack

- CGRP antagonist
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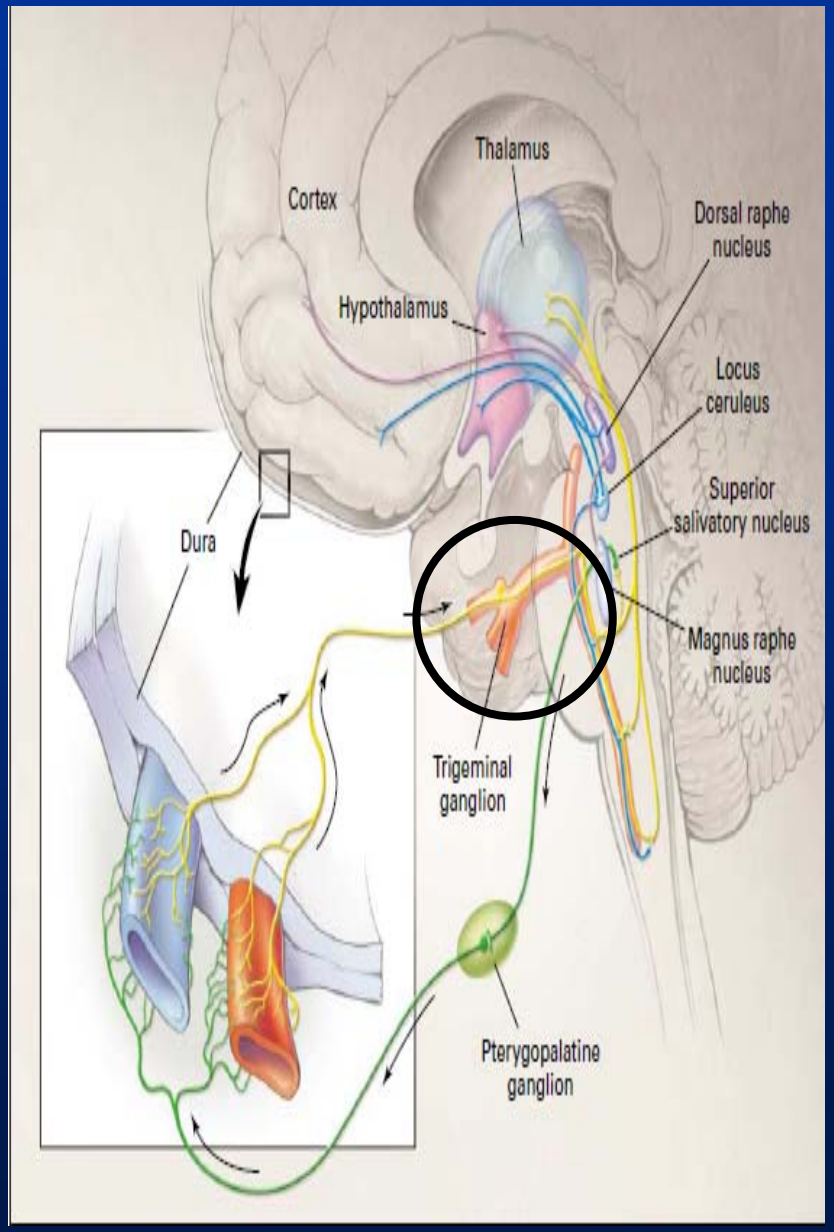
- EP4 receptor antagonist
- 5-HT-1F agonist
- NO- synthase inhibitor
- Gap-Junction inhibitor



Vanilloid receptors on C- or A delta fibres

Trigeminal and dorsal root ganglia

Co-localized with CGRP receptors in the trigeminal ganglion

Ichikawa and Sugimoto, Brain Res 2001, Hou et al, Neuroscience Lett 2002

TRPV1-Antagonists

- ~ 40 different compounds developed for the treatment of pain
- As to now all trials reported negative results
- SB705498 investigated in migraine (2007)
- Results not reported

New Targets for Treating the Acute Migraine Attack

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- 5-HT-1F agonist
- NO- synthase inhibitor
- Gap-Junction inhibitor

EP4 receptor antagonist

- Prostaglandin E receptor 4 antagonists show anti-hyperalgesic effects in animal models of inflammatory pain
- BGC20-1531 under investigation for the treatment of migraine attacks

Nakoa et al. J Pharmacol Exp Ther 2007, Maubach et al. Br J Pharmacol 2009

New Targets for Treating the Acute Migraine Attack

- CGRP antagonist
- TRV1 antagonist
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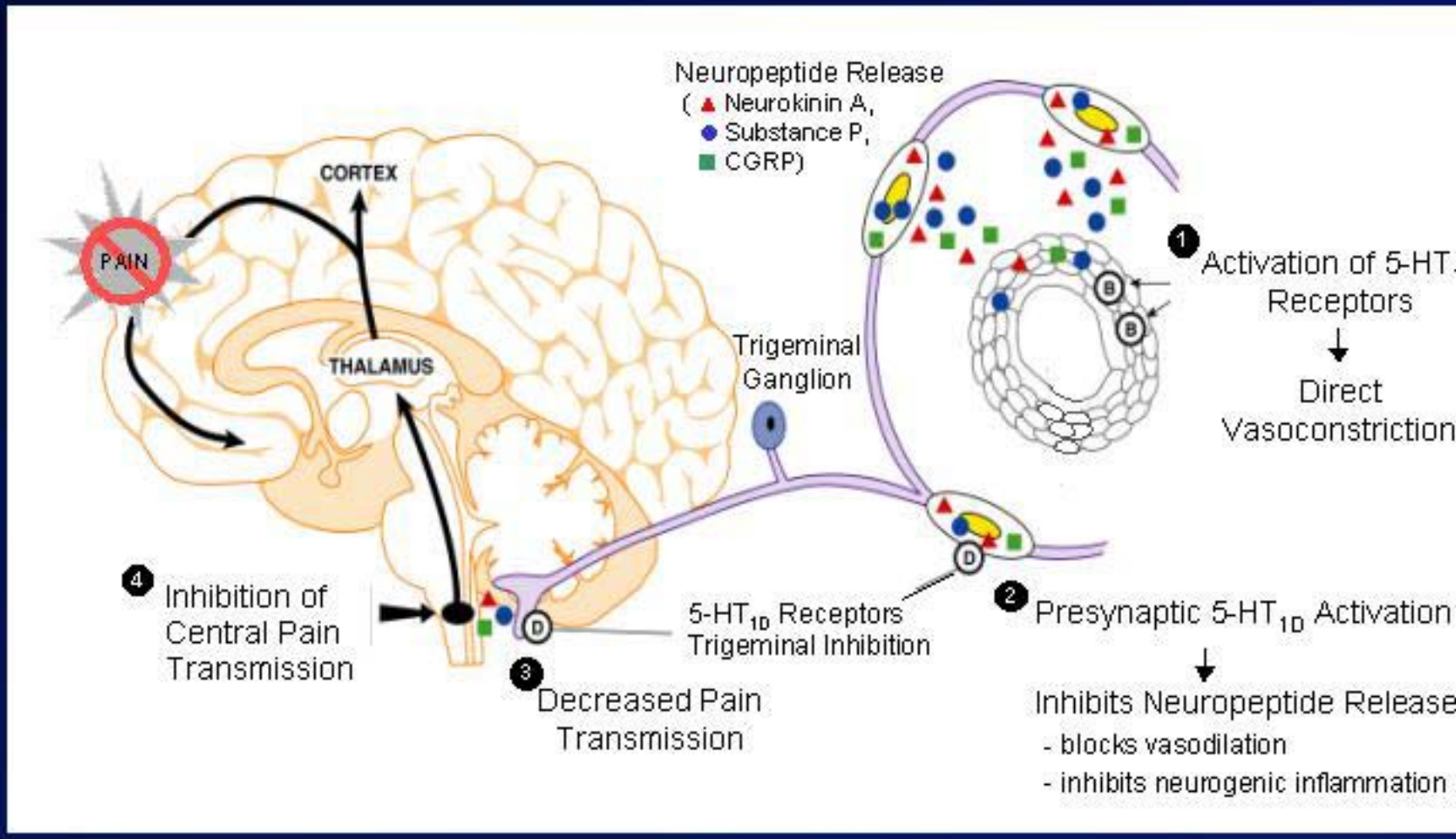
- 5-HT-1F agonist
- NO- synthase inhibitor
- Gap-junction inhibitor

5-HT-1F Agonist

- All triptans are agonists at the 5-HT 1B 1D and 1F receptor
- 5-HT-1F receptors in the trigeminal nucleus and trigeminal ganglion
- Activation of 1F receptors has no vascular effects

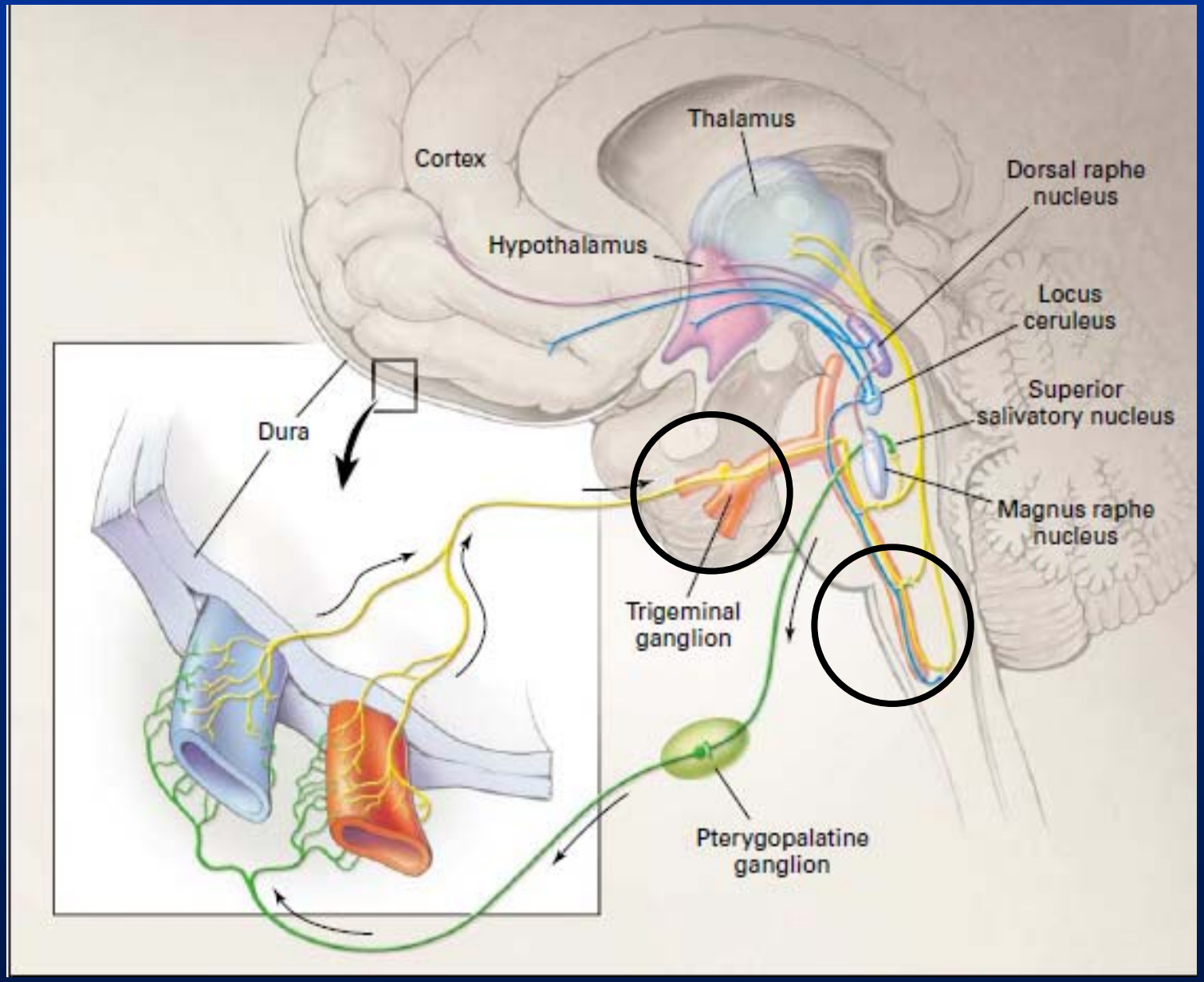
Pascual et al., Europ J Pharmacol 1996, Bouchelet et al.,Mol Pharmacol 1996

Acute Anti-migraine Targets



(Adapted from Hargreaves, Shepheard 1999)

5-HT-1F

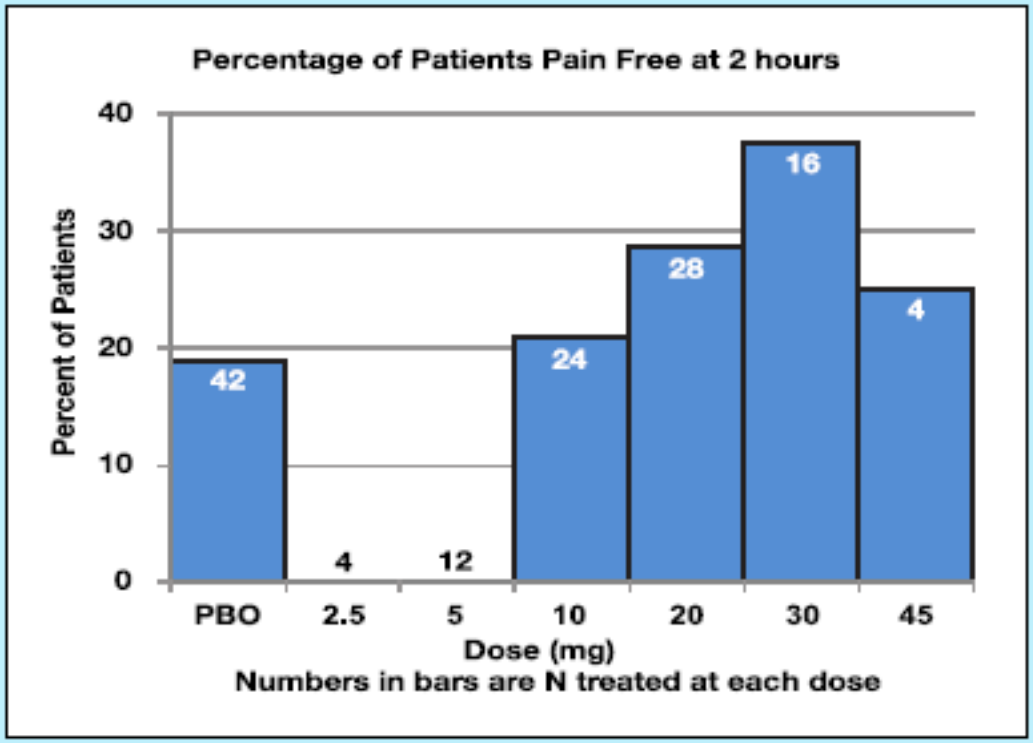

Thalamus
Cortex
Dorsal raphe nucleus
Hypothalamus
Locus ceruleus
Superior salivatory nucleus
Dura
Magnus raphe nucleus
Trigeminal ganglion
Pterygopalatine ganglion

International Headache Society

COL-144: A SELECTIVE 5-HT$_{1F}$ AGONIST FOR THE TREATMENT OF MIGRAINE ATTACKS

Uwe Reuter[1], Alison Pilgrim[2], Hans-Christoph Diener[3], Markus Färkkilä[4] and Michel Ferrari[5]
for the European COL-144 Investigators

Figure 4 – Pain Free



EHMTIC London 2008

Selective seratonin 1F (5-HT$_{1F}$) receptor agonist LY334370 for acute migraine: a randomised controlled trial

D J Goldstein, K I Roon, W W Offen, N M Ramadan, L A Phebus, K W Johnson, J M Schaus, M D Ferrari

- 5-HT-1F agonists are effective in the treatment of acute migraine attacks
- No vasoconstrictive properties
- Could be used in patients with vascular diseases and contraindications for triptans

New Targets for Treating the Acute Migraine Attack

- CGRP antagonist
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- EP4 receptor antagonist
- 5-HT-1F agonist
- NO- synthase inhibitor
- Gap-junction inhibitor

Nitric Oxide Production Blockade

- NO donor nitroglycerin triggers migraine attacks
- NOS inhibition has been shown to abort migraine
- GW 274150 and GW 273629 have been studied
- NOS inhibitors lower blood pressure

Olesen et al, 1995, Lassen et al, 1997

New Targets for Treating the Acute Migraine Attack

- CGRP antagonist
- TRV1 antagonist
- EP4 receptor antagonist
- 5-HT-1F agonist
- NO- synthase inhibitor
- Gap-junction blocker

Gap-junction blocker

- Tonabersat (SB-2200453) inhibits
  - Cortical spreading depression (CSD)
  - CSD-induced nitric-oxide release
  - Cerebral vasodilatation

Read et al 1999, Smith et al. 2000

Cephalalgia
An International Journal of Headache
International Headache Society

Efficacy and safety of tonabersat, a gap-junction modulator, in the acute treatment of migraine: a double-blind, parallel-group, randomized study

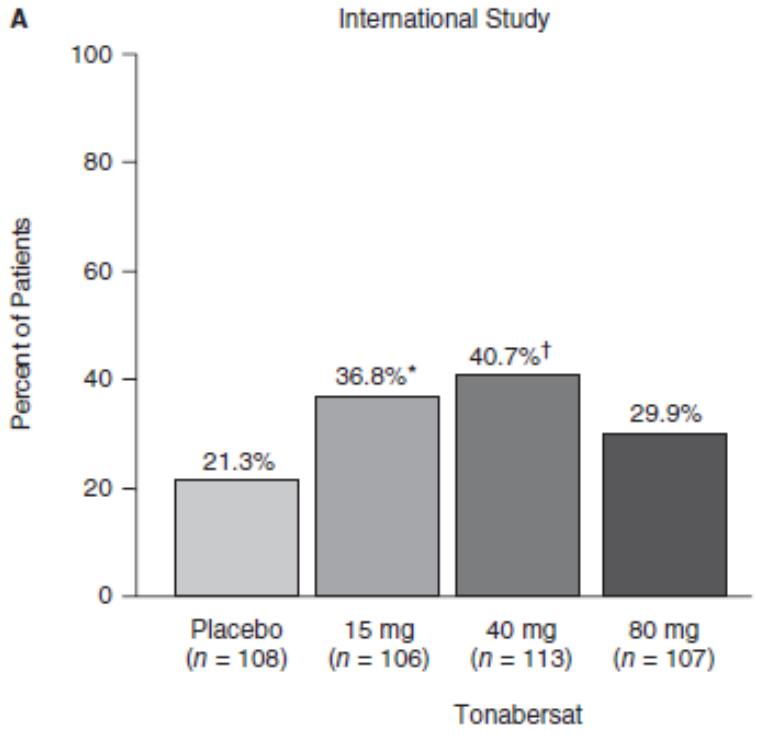
CGH Dahlöf[1], AW Hauge[2] & J Olesen[2]

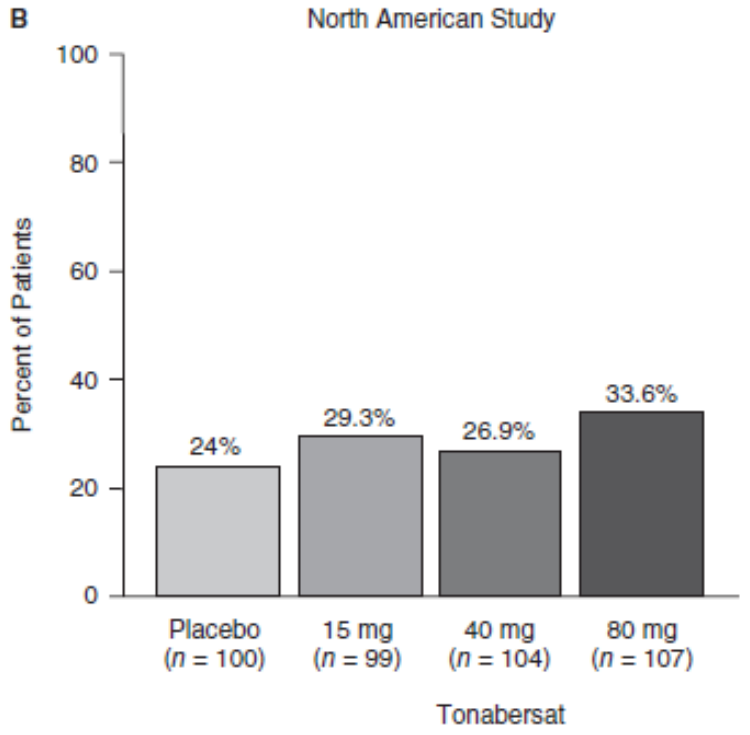
- 591 patients with migraine
- Tonabersat 20 mg, 40 mg, sumatriptan 50 mg, placebo
- Tonabersat not superior to placebo

Cephalalgia
An International Journal of Headache
International Headache Society

Tonabersat, a gap-junction modulator: efficacy and safety in two randomized, placebo-controlled, dose-ranging studies of acute migraine

SD Silberstein[1], J Schoenen[2], H Göbel[3], HC Diener[4], AH Elkind[5], JA Klapper[6] & RA Howard[7]





Summary: New Targets for Treating the Acute Migraine Attack

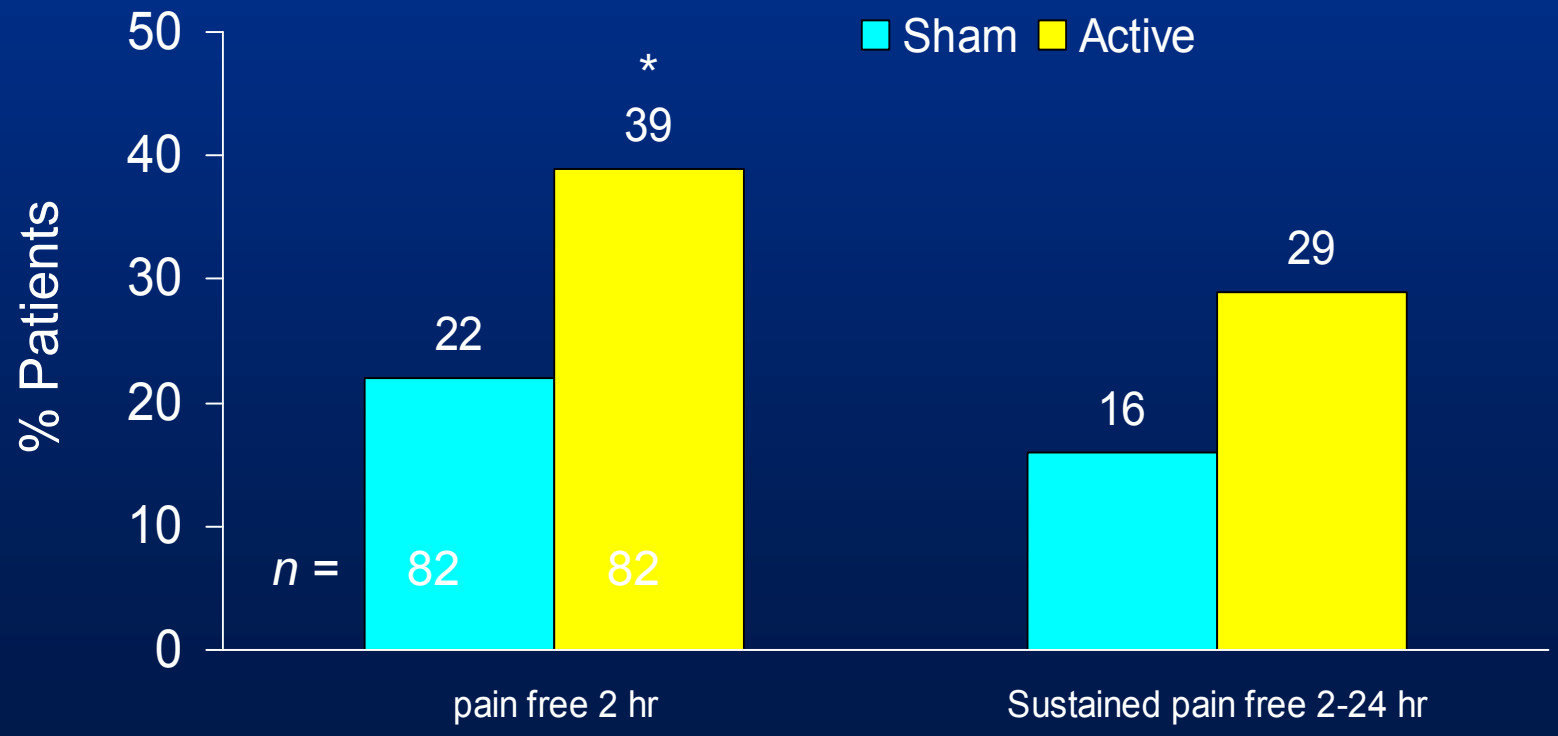
- CGRP antagonist
- TRV1 antagonist
- EP4 receptor antagonist
- 5-HT-1F agonist
- NO- synthase inhibitors
- Gap-Junction inhibitor

Transcranial Magnetic Stimulation for the Treatment of Migraine Aura

Philip R. Holland, San Francisco, CA, Carol T. Schembri, Joe P. Fredrick, Sunnyvale, CA, Peter J. Goadsby, San Francisco, CA

Transcranial magnetic stimulation for Migraine

- Randomised double-blind placebo controlled study
- *Include*: 30% aura episodes, aura leads to headache 90%
- *Exclude*: Prolonged aura, MOH
- TMS- 0.9T for 180 μs; Sham- click and vibrate
- *Primary endpoint:* 2 hr pain free plus non-inferiority for nausea/photo/phono
- *Blinding*: Thought they got active, 67% Sham and 72% active



(Lipton *et al*., AHS Late-breaking abstract)

New Targets in the Acute and Preventive Treatment of Migraine

Hans-Christoph Diener

Department of Neurology and Headache Center

University Hospital Essen

Germany

Migraine Prophylaxis

Good Evidence

- Betablockers
- Flunarizine*
- Valproic acid*
- Topiramate
- (Amitriptyline)*

Poor evidence*

- Magnesium ?
- Vitamine B2 (Riboflavin)?
- Butterburr
- NSAIDs
- Gabapentin
- SSNRIs

New Targets for Migraine Prevention

- Carisbamate
- Tonabersat
- Telmisartan
- Botulinum toxin
- PFO closure
- Neurostimulation

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Carisbamate

- Effective in human partial seizures
- Fewer cognitive side effects compared to topiramate
- Mode of action unknown

Evaluation of Carisbamate for the Treatment of Migraine in a Randomized, Double-Blind Trial

Roger K. Cady, MD; Ninan Mathew, MD; Hans-Christoph Diener, MD; Peter Hu, PhD; Magali Haas, MD, PhD; Gerald P. Novak, MD, on behalf of the Study Group

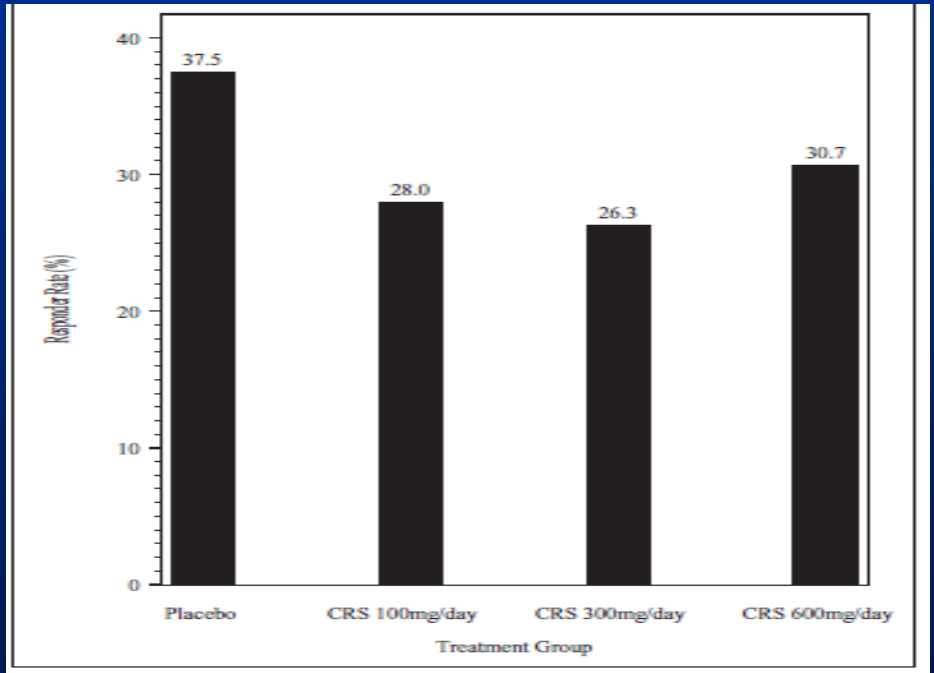
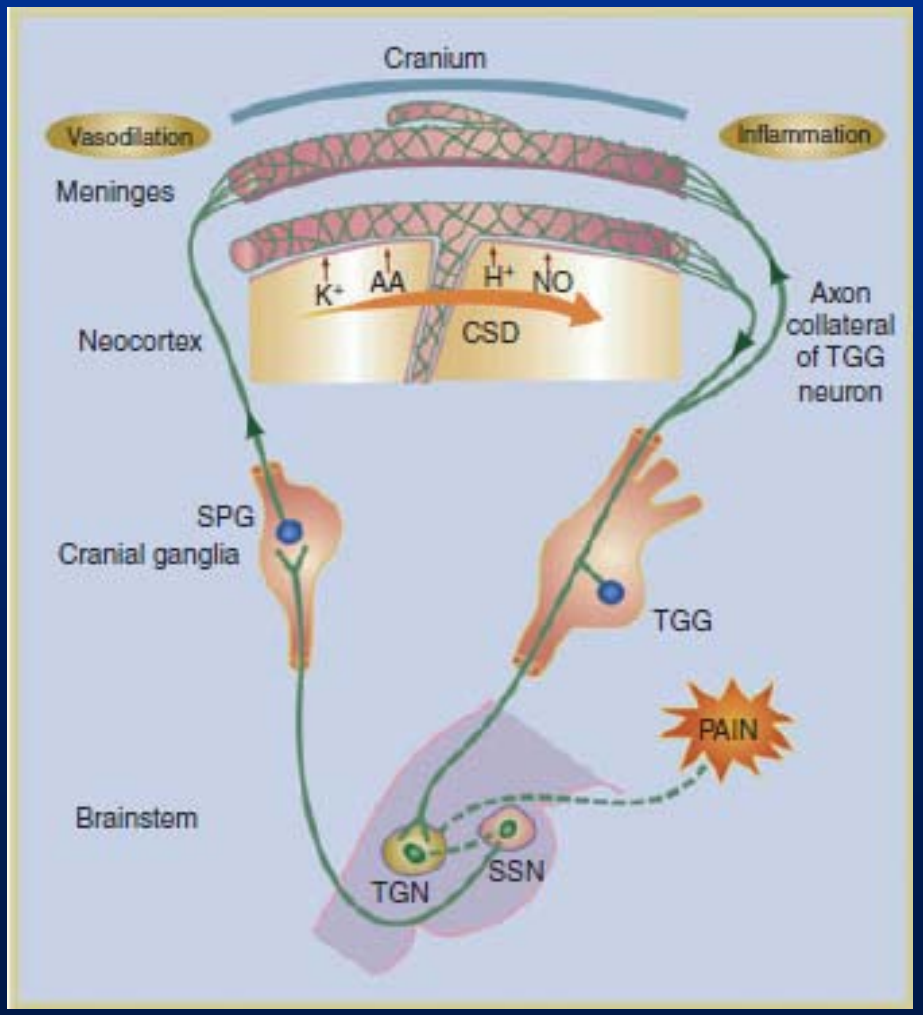


Fig 3.—Responder rate (ITT population). *P* values are vs placebo: *P* = .2 for CRS 100 mg/day (n = 82) and CRS 300 mg/day (n = 80); *P* = .3 for CRS 600 mg/day (n = 75). For placebo, n = 80. Pairwise comparisons made using generalized Cochran-Mantel-Haenszel test, stratified by pooled analysis center (CRS = carisbamate).

New Targets for Migraine Prevention

- Carisbamate
- Tonabersat
- Telmisartan
- Botulinum toxin
- PFO closure
- Neurostimulation



Moskowitz, Iadecola

Effects of tonabersat on migraine with aura: a randomised, double-blind, placebo-controlled crossover study

Anne W Hauge, Mohammed S Asghar, Henrik W Schytz, Karl Christensen, Jes Olesen

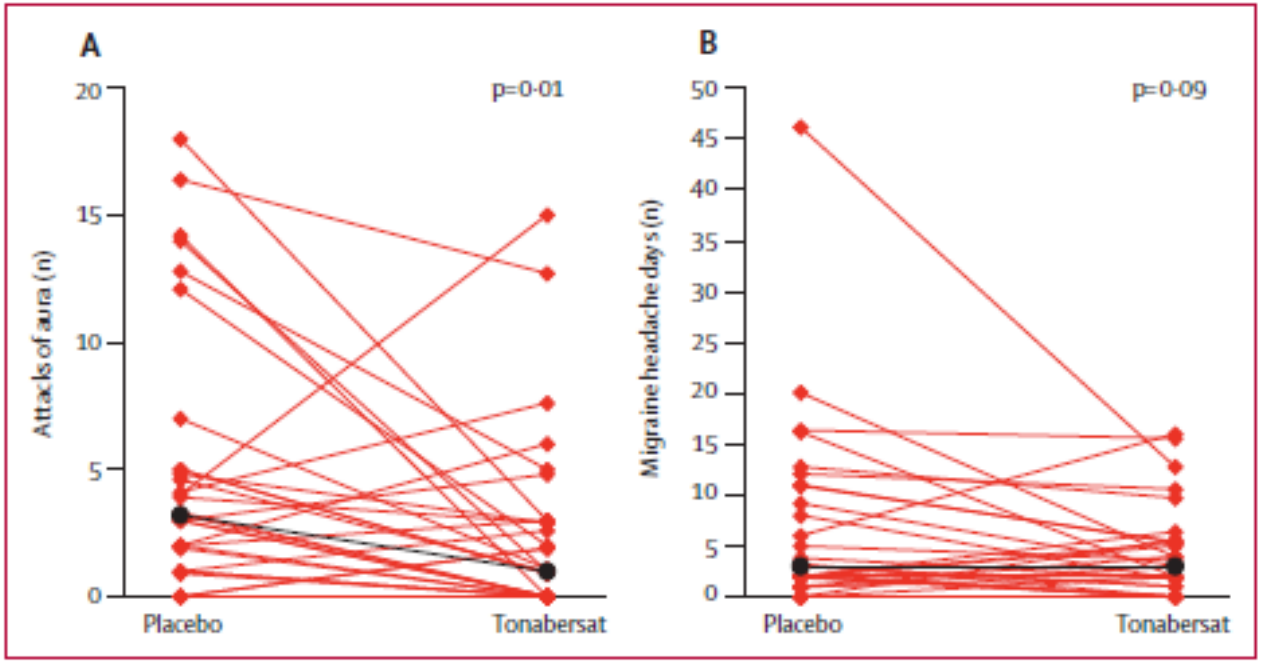


Figure 3: **Primary variables during placebo and tonabersat treatment**
(A) Attacks of aura and (B) migraine headache days during 12 weeks' treatment with placebo versus 12 weeks' treatment with tonabersat. Red lines show individual patients and black lines show the medians of the two treatment groups (tonabersat–placebo and placebo–tonabersat).

New Targets for Migraine Prevention

- Carisbamate
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- Neurostimulation

Cephalalgia
An International Journal of Headache
International Headache Society
doi:10.1111/j.1468-2982.2008.01825.x

Telmisartan in migraine prophylaxis: a randomized, placebo-controlled trial

HC Diener[1], A Gendolla[1], A Feuersenger[2], S Evers[3], A Straube[4], H Schumacher[5] & G Davidai[6], on behalf of the Study Group*

Table 5 Analysis of migraine days

	Telmisartan	Placebo	*P*-value*
n	40	44	
Baseline, mean (S.D.)	6.18 (2.89)	7.59 (3.66)	
End of study, mean (S.D.)	4.53 (3.41)	6.45 (4.47)	
Change from baseline (Wilcoxon), mean (S.D.)	−1.65 (3.46)	−1.14 (3.78)	0.7388
% change from baseline (ANCOVA*), mean (95% CI)	−38% (−49%, −24%)	−15% (−30%, 5%)	0.0262

*Adjusted for baseline and centre, data log-transformed.

S.D., standard deviation; CI, confidence interval.

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- Neurostimulation

Botulinum Toxin Type A Prophylactic Treatment of Episodic Migraine: A Randomized, Double-Blind, Placebo-Controlled Exploratory Study

Sheena K. Aurora, MD; Marek Gawel, MB, BCh, FRCPC; Jan L. Brandes, MD; Suriani Pokta, PhD; Amanda M. VanDenburgh, PhD; for the BOTOX North American Episodic Migraine Study Group

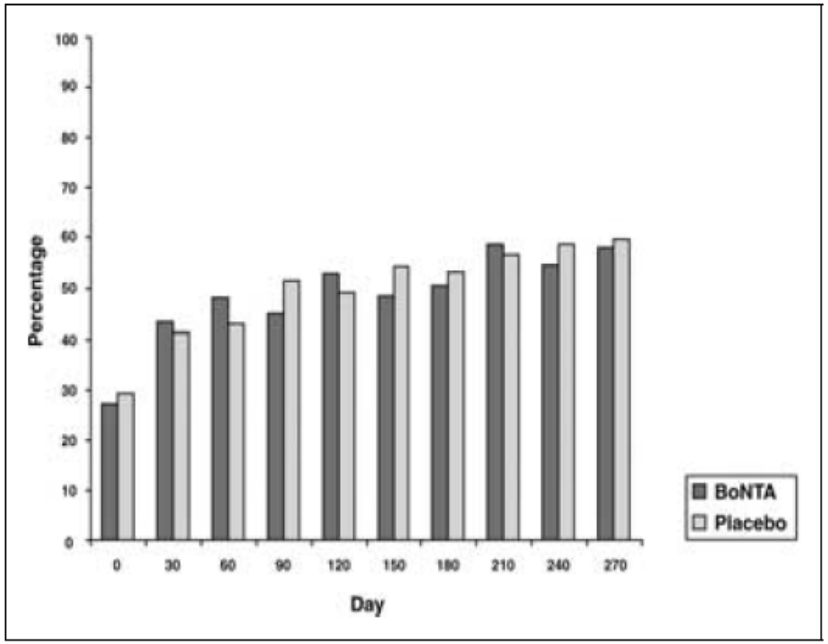


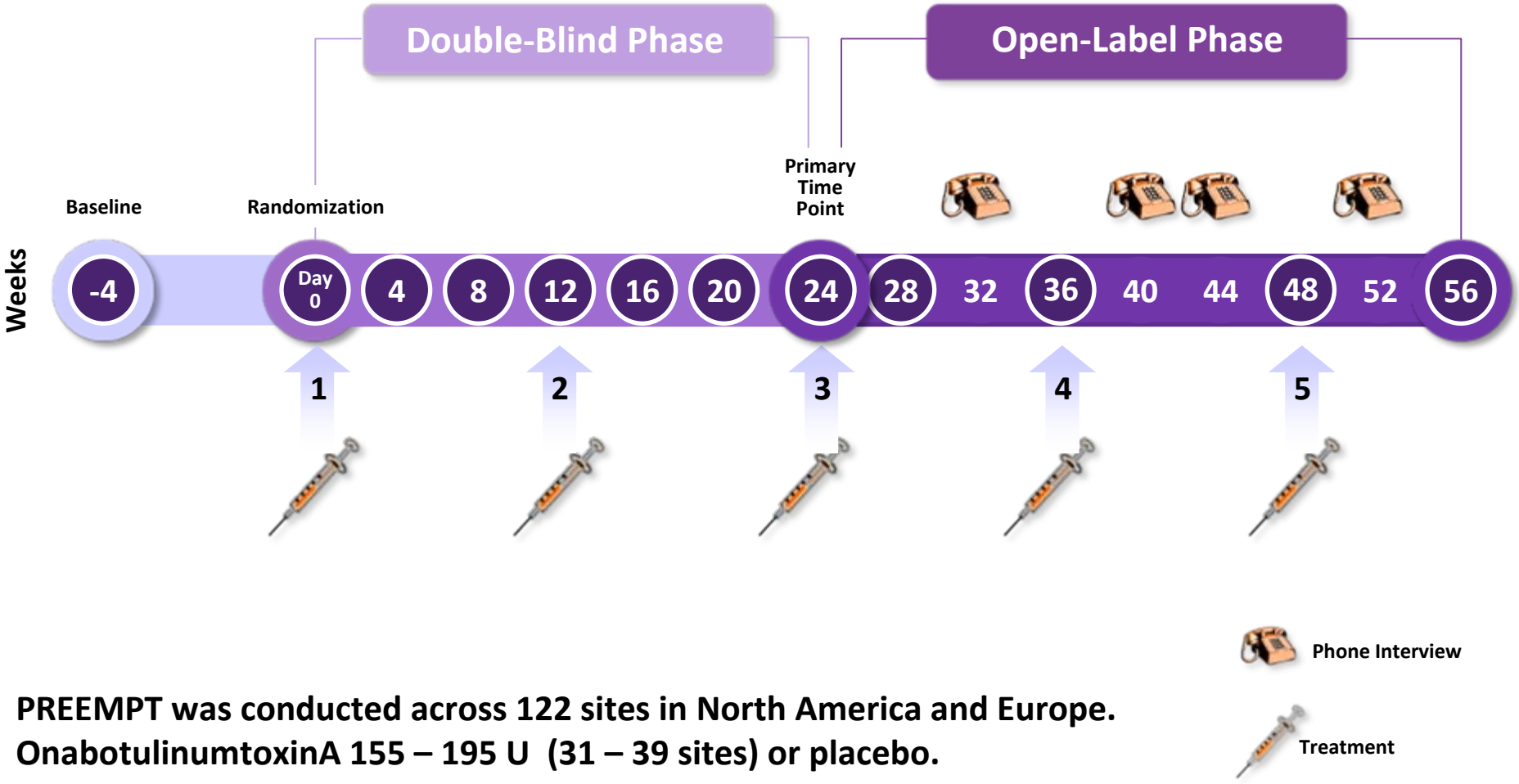
Fig 2.—Percentage of patients with a decrease from baseline of ≥50% of migraine headache episodes of any severity per 30-day period (pooled data).

Onabotulinumtoxin A for treatment of chronic migraine: double-blind, randomized, placebo-controlled PREEMPT trials

Dodick DW, Aurora, SK, Turkel CC, DeGryse RE, Silberstein SD, Lipton RB, Diener HC, Brin MF on behalf of PREEMPT Chronic Migraine Study Group

Study Design

PREEMPT
PHASE III RESEARCH EVALUATING MIGRAINE PROPHYLAXIS THERAPY WITH BOTULINUM TOXIN TYPE A



PREEMPT was conducted across 122 sites in North America and Europe.
OnabotulinumtoxinA 155 – 195 U (31 – 39 sites) or placebo.

Baseline Demographics

PREEMPT
PHASE III RESEARCH EVALUATING MIGRAINE PROPHYLAXIS THERAPY WITH BOTULINUM TOXIN TYPE A

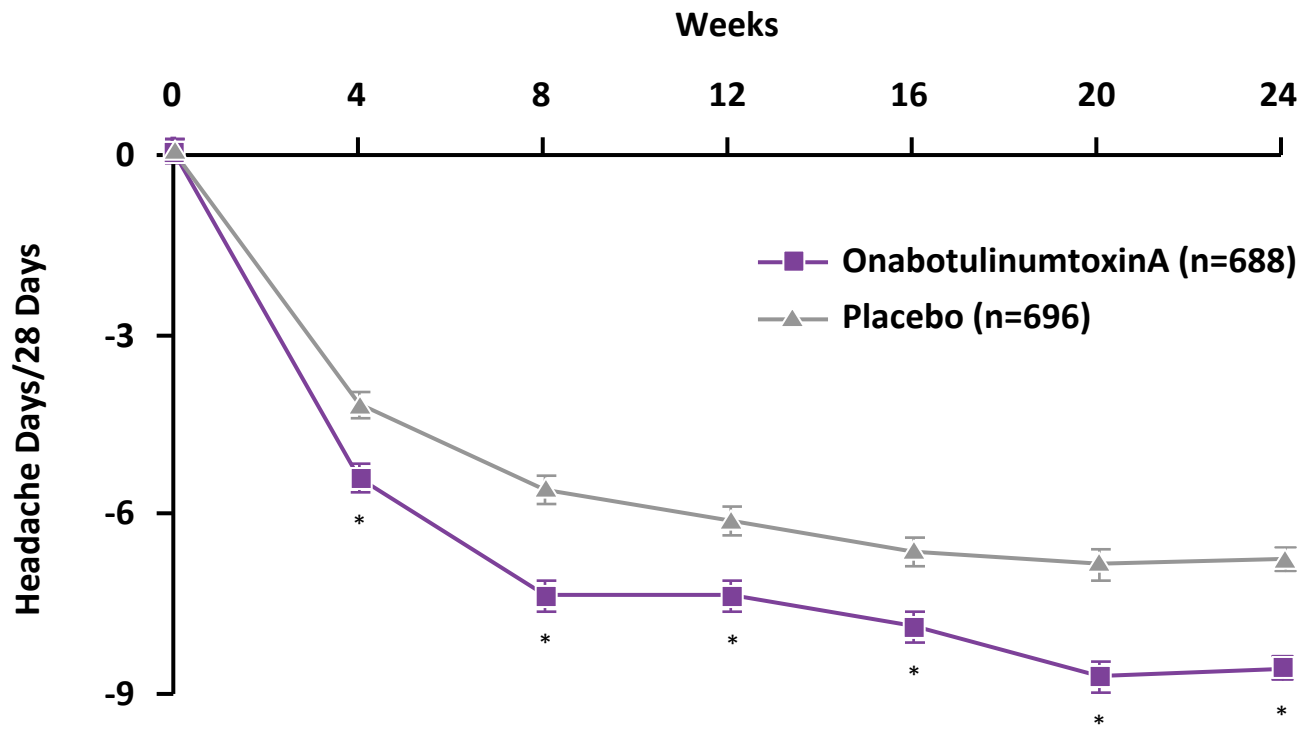
	OnabotA (n=688)	Placebo (n=696)	p value
Mean age, years	41.1	41.5	0.579
Female, %	87.6	85.2	0.185
Caucasian, %	89.7	90.5	0.602
Mean HA days (SD)	19.9 (3.68)	19.8 (3.68)	0.498
Mean migraine days (SD)*	19.1 (3.99)	18.9 (4.05)	0.328
Mean moderate/severe HA days (SD)	18.1 (4.12)	18.0 (4.25)	0.705
Mean cumulative hours of HA occurring on HA days (SD)	295.93 (116.88)	281.22 (114.74)	0.021
Mean HIT-6 score	65.5	65.4	0.638
% with severe (≥60) HIT-6 score	93.5	92.7	0.565
Mean HA episodes (SD)	12.2 (5.25)	13.0 (5.5)	0.004
Mean migraine episodes (SD)*	11.4 (5.02)	12.2 (5.42)	0.004
% overusing acute head pain medication†	64.8	66.1	0.450

onabotA = onabotulinumtoxinA; HA = headache; HIT = Headache Impact Test.
*ICHD-II 1.1 (migraine without aura), 1.2 (migraine with aura), 1.6 (probable migraine).[1] †Patients must have taken acute pain HA medication at least twice per week in any week with ≥5 diary days and ≥10-15 days (depending on medication category) during the baseline period.

1. The International Classification of Headache Disorders: 2nd ed. *Cephalalgia.* 2004;24(suppl 1):24-36.

Mean Change From Baseline in Frequency of Headache Days

PREEMPT
PHASE III RESEARCH EVALUATING MIGRAINE PROPHYLAXIS THERAPY WITH BOTULINUM TOXIN TYPE A



*p<0.001.
Mean ± standard error.

New Targets for Migraine Prevention

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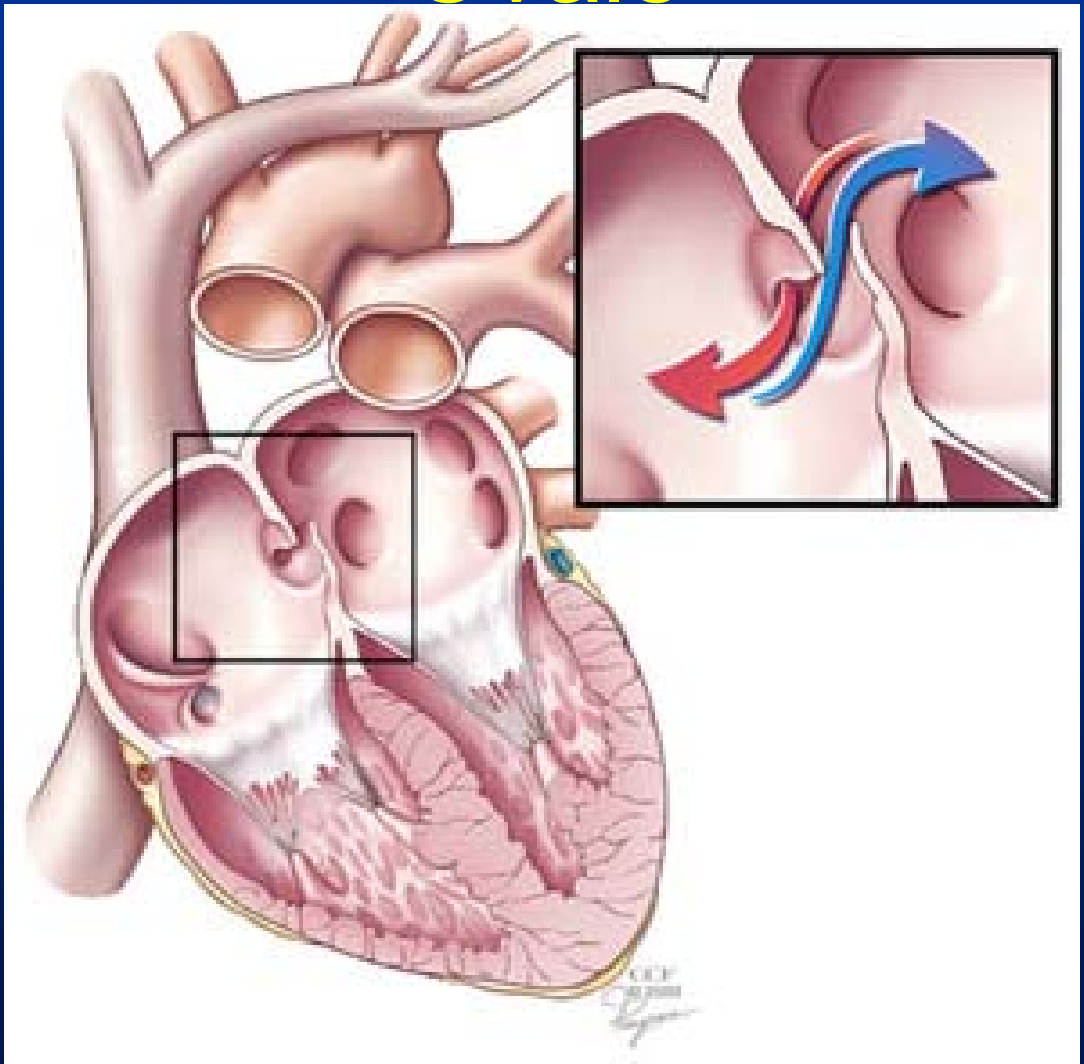
Migraine and Patent Foramen Ovale



Prophylaxis of Migraine by PFO Closure

Interventional Cardiology

Migraine Intervention With STARFlex Technology (MIST) Trial

A Prospective, Multicenter, Double-Blind, Sham-Controlled Trial to Evaluate the Effectiveness of Patent Foramen Ovale Closure With STARFlex Septal Repair Implant to Resolve Refractory Migraine Headache

Andrew Dowson, MBBS, PhD; Michael J. Mullen, MBBS, MRCP, MD; Richard Peatfield, MD, FRCP; Keith Muir, MD, FRCP; Arif Anis Khan, MBBS, FCPS; Christopher Wells, MB, ChB, FRCA; Susan L. Lipscombe, MB, ChB, MRCP; Trevor Rees, MB, ChB; Joseph V. De Giovanni, MD, FRCP, FRCPCH, MOM; W. Lindsay Morrison, MD, FRCP; David Hildick-Smith, MD, FRCP; Giles Elrington, MD; W. Stewart Hillis, MB, ChB, FRCP, FRCS; Iqbal S. Malik, MA, MRCP, PhD; Anthony Rickards, MBBS, FRCP, FESC†

Population-based Study

Patent Foramen Ovale and Migraine

A Cross-Sectional Study From the Northern Manhattan Study (NOMAS)

Tatjana Rundek, MD, PhD; Mitchell S.V. Elkind, MD, MS; Marco R. Di Tullio, MD;
Emmanuel Carrera, MD; Zhezhen Jin, PhD; Ralph L. Sacco, MD, MS; Shunichi Homma, MD

Conclusions—In this multiethnic, elderly, population-based cohort, PFO detected with transthoracic echocardiography and agitated saline was not associated with self-reported migraine. The causal relationship between PFO and migraine remains uncertain, and the role of PFO closure among unselected patients with migraine remains questionable.
(*Circulation*. 2008;118:1419-1424.)

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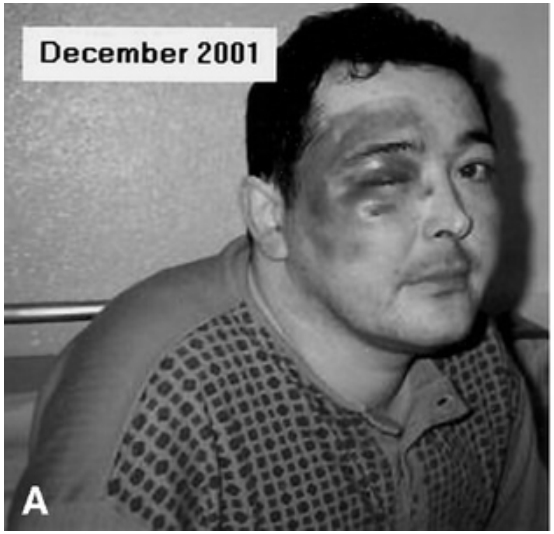
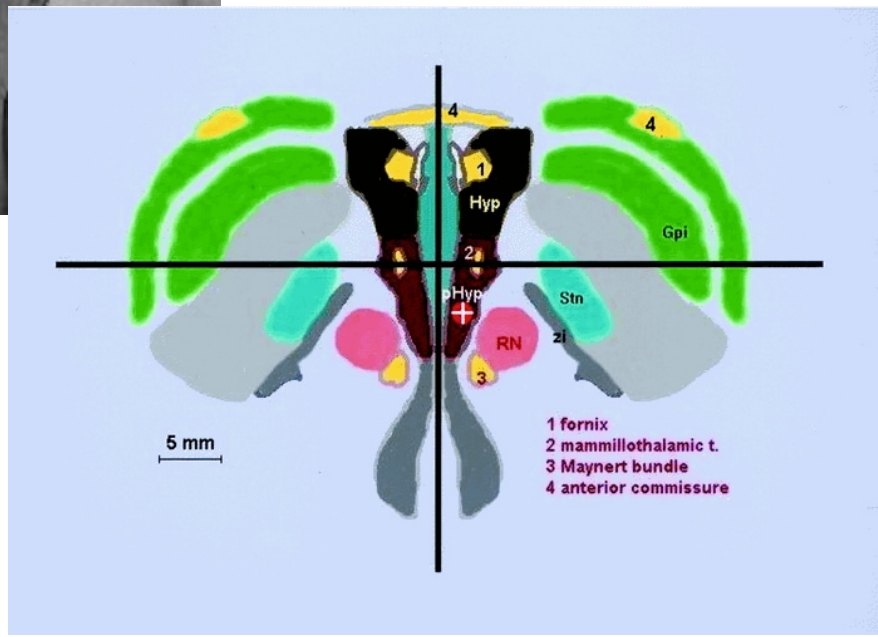
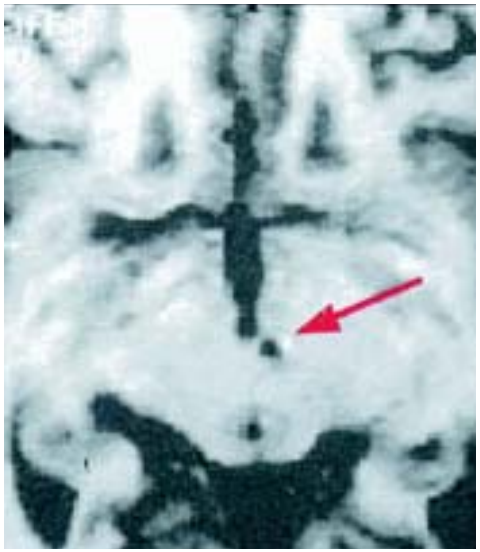
- Neurostimulation

Deep Brain Stimulation (Cluster Headache)

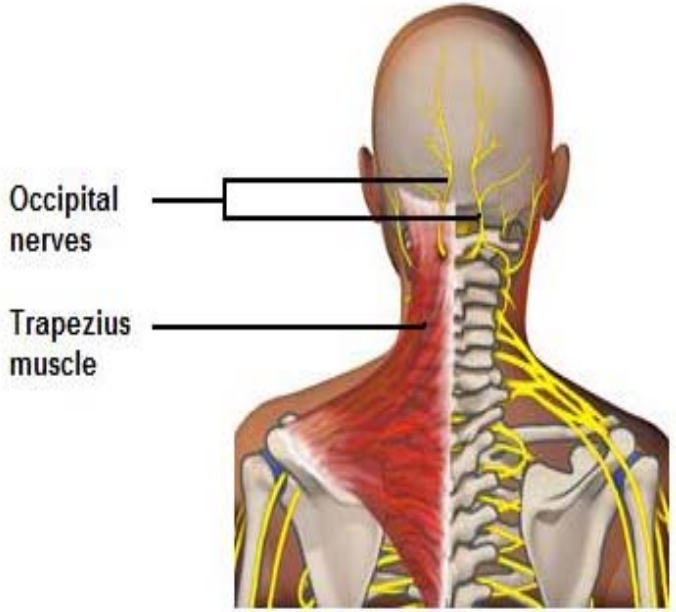






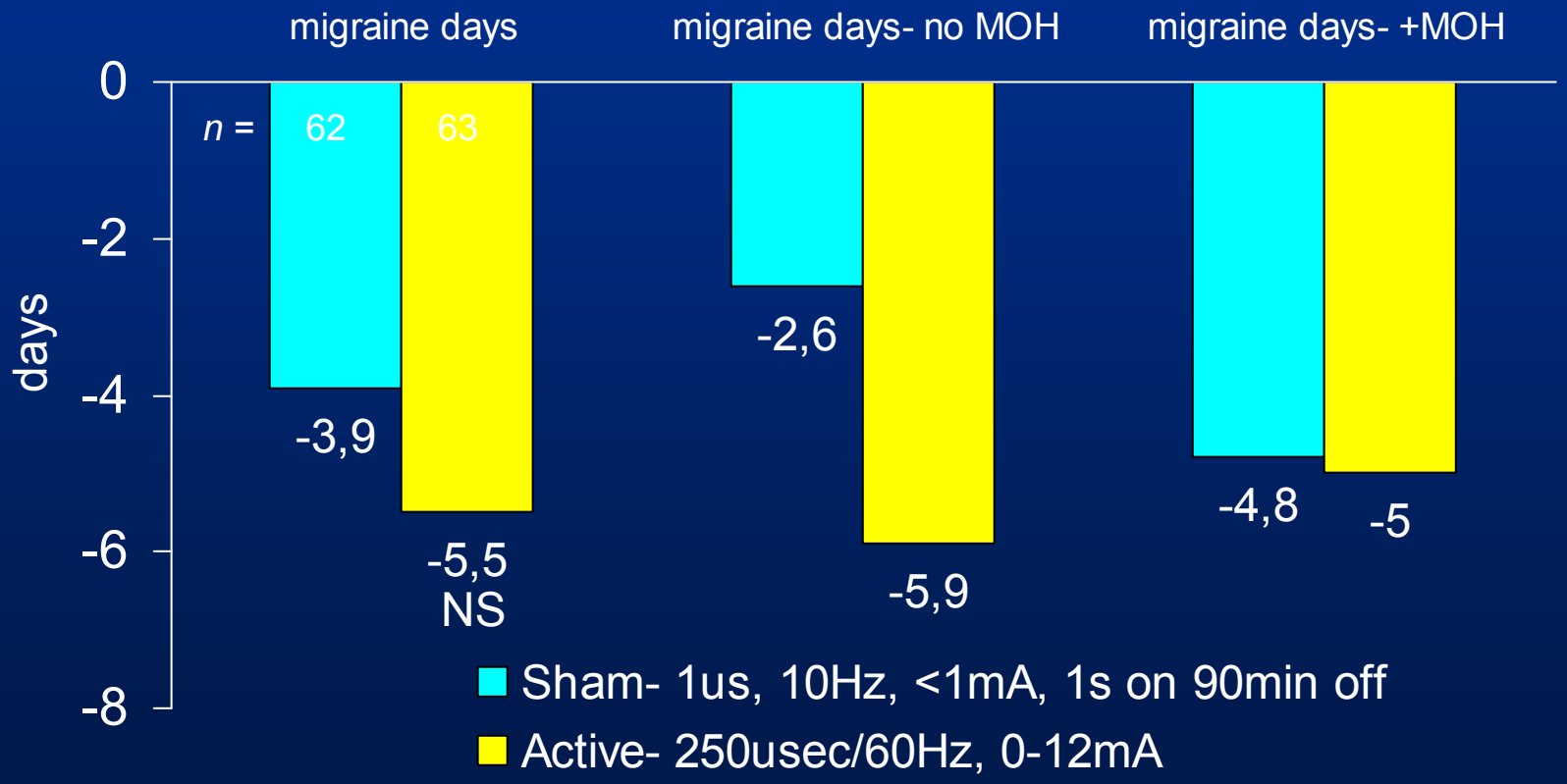
Franzni, Leone. Stimulation of the posterior hypothalamus for the treatment of chronic intractable Cluster Neurosurgery 2003;52:1095-9

Bilateral Occipital Nerve Stimulation



Occipital nerve stimulation in migraine & chronic migraine- PRISM

- Double-blind randomized parallel group sham stimulation controlled study
- Migraine ≥6 days/month or chronic migraine (ICHD-II)
- Failed two preventives/two attack treatments



(Lipton *et al*., Cephalalgia 2009;29:30- IHC2009)

- **Adverse event**: non-target sensory symptoms

Neurostimulation approaches to primary headache disorders

Thorsten Bartsch[a], Koen Paemeleire[b] and Peter J. Goadsby[c]

Table 1 Effects of occipital nerve stimulation in primary headache syndromes: synopsis of published cases

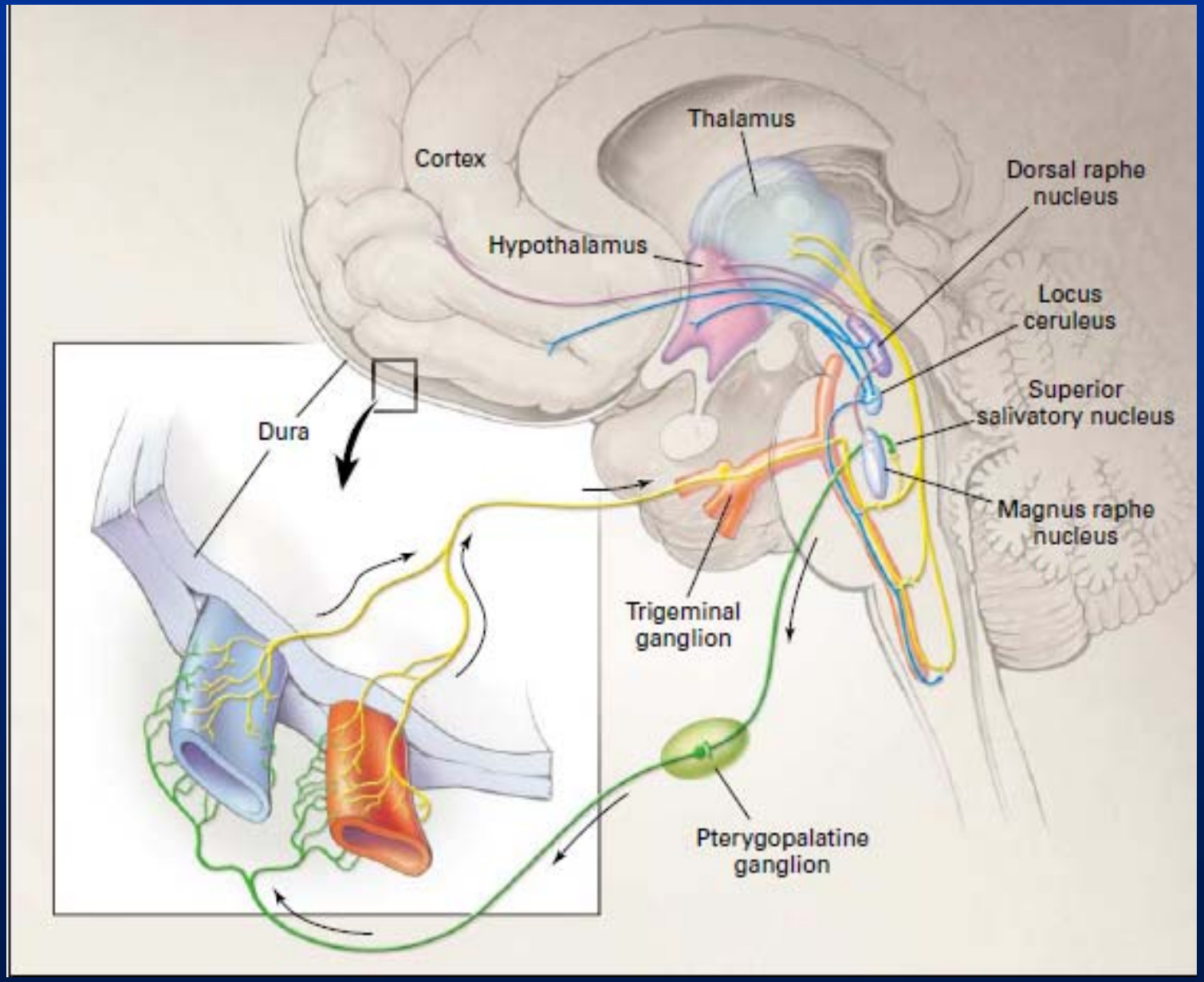
Study	Headache syndrome	Diagnostic criteria	Type of study	Number of patients	Mean disease duration (years) before implantation	No. of improved patients (>50% relief)/(%)	Follow-up (years)
Popeney and Alo [4]	Transformed migraine	IHS	P	25	10	22 (88)	1.5
Oh *et al.* [5]	Transformed migraine	IHS	P	10	12 +	10 (100)	0.5
Matharu *et al.* [6]	Chronic migraine	IHS	O	8	5.8	8 (100)	1.5
Schwedt *et al.* [7]	Chronic CH	IHS	R	1	5	1 (100)	n.s.
	Hemicrania continua			1	12	1 (100)	
Magis *et al.* [8]	Chronic CH	IHS	P	8	13.6	5 (62)	1.2
Schwedt *et al.* [9]	Chronic migraine	IHS	R	8	n.s.	3 (38)	1.5
Dodick *et al.* [10]	Chronic CH			3		1 (33)	1.7
	Hemicrania continua			2		2 (100)	1.4
Burns *et al.* [11••]	Hemicrania continua	IHS	P	6	18	4 (66)	1.1
Burns *et al.* [12]	Chronic CH	IHS	R	14	6	5 (36)	1.4

n.s., not stated. CH, cluster headache; IHS, International Headache Society; O, observational; P, prospective; R, retrospective.

Current Opinion in Neurology, 2009

New Targets for Migraine Prevention: Summary

- Carisbamate
- Tonabersat
- Telmisartan
- Botulinum toxin
- PFO closure
- Neurostimulation


Thalamus
Cortex
Dorsal raphe nucleus
Hypothalamus
Locus ceruleus
Superior salivatory nucleus
Dura
Magnus raphe nucleus
Trigeminal ganglion
Pterygopalatine ganglion

Thank You!


GRAND VIN MISÉRABLE
CHÂTEAU MIGRAINE
DOMAINE SCHARLATAN
APPELLATION SOUTERRAINE PAS CONTRÔLÉE
DERNIER CRU
MIS EN BOUTEILLES AU CHÂTEAU
PRODUCE OF FRANCE

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