Chapter 118

Medication Overuse Headaches

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INTERNATIONAL HEADACHE SOCIETY CLASSIFICATION AND DEFINITION

Frequent intake of analgesics leads to chronic headache. This was probably first observed in Switzerland, where workers in the pharmaceutical industry were given free samples of the analgesic phenacetin (48). Peters and Horton (53) observed the same phenomenon in patients with excessive use of ergotamine preparations and later described 52 patients who took ergotamine on a daily basis, developed daily headache, and significantly improved after ergotamine was withdrawn (32). The literature up to 1988 is summarized by Diener and Wilkinson (16) and up to 2004 by Diener and Limmroth (15). Just 1 year after their introduction in 1993, it became evident that excessive triptan (5-$HT_{1B/D}$ agonists) use, like all other drugs for the treatment of headache, could lead to medication-overuse headache (MOH), but may cause a "pure" increase in migraine frequency (37,40) as well.

Many terms have served to describe this entity, which was first defined as *drug-induced headache* by The International Headache Society (IHS) in 1988 (27). This term has been criticized since the single intake of several drugs such as nitrates may also lead to headache. To emphasize the regular intake of drugs as the basis of this headache form the new name *medication-overuse headache* has now been introduced with the new IHS classification from 2004 (28). The new classification further extends the definition according to different clinical symptoms caused by different drugs (see Table 118-1).

DRUGS THAT MAY CAUSE MEDICATION-OVERUSE HEADACHE

There is now substantial evidence that all drugs used for the treatment of headache may cause MOH in patients with primary headache disorders. The use of drugs that lead to chronic MOH varies considerably from country to country and is influenced by cultural factors. In many patients it is difficult to identify a single "responsible" substance, since 90% of patients take more than one compound at a time and since each component contained in antimigraine drugs can potentially induce headache. This has been shown even for substances such as acetylsalicylic acid (ASA) and paracetamol (56).

Six studies have been performed to investigate the incidence of MOH with various drugs (3,4,10,46,47,58). Combination analgesics containing butalbital (short-acting barbiturate), caffeine, and ASA with or without codeine were the leading candidates for MOH in the American studies (4,46). Until the mid 1990s, combination analgesics with codeine or caffeine, or ergots combined with codeine were most frequently (mis)used in many European countries (3,10,47,58). The introduction of triptans and the fact that ergots have recently been withdrawn from some markets (e.g., in Germany) is now changing the picture. Sumatriptan-induced MOH was first observed in patients who abused ergotamine previously (7,37). De novo cases, however, were later reported (21,22,54). Reports of patients who developed MOH from naratriptan, zolmitriptan, or rizatriptan usually were published 1 year after a drug had been approved (34,40). Today, all available triptans undoubtedly cause MOH. Due to the delay between frequent triptan intake and the development of MOH, similar cases will probably be observed in the future, since other triptans (eletriptan, frovatriptan, and almotriptan) have been approved. Headache patients who have a previous history of analgesic and/or ergotamine misuse are at higher risk. It will be interesting to observe whether new treatment principles such as calcitonin gene-related peptide (CGRP) antagonism (51) will also lead to MOH once introduced into the treatment of migraine attacks.

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TABLE 118-1 Diagnostic Criteria of Medication-Overuse Headache According to the Second Classification of Headache Disorders (ICHD-II, Code 8.2, ICD 10: G44.4 or G44.83)

Type of MOH	*Diagnostic Criteria 8.2 Medication-Overuse Headache (MOH)*
MOH	**Diagnostic criteria:** A. Headache present on ≥15 days/month fulfilling criteria C and D B. Regular overuse for ≥10 days/month on a regular bases for ≥3 months[a] C. Headache has developed or markedly worsened during medication overuse D. Headache resolves or reverts to its previous pattern within 2 months after discontinuation of overused medication
Ergotamine-overuse headache (8.2.1, G44.411)	A. Meets criteria for 8.2 B. Ergotamine intake on ≥10 days/month on a regular basis for ≥3 months
Triptan-overuse headache (8.2.2, G44.41)	A. Meets criteria for 8.2 B. Triptan intake (any formulation) on ≥10 days/month on a regular basis for ≥3 months
Analgesic-overuse headache (8.2.3, G44.410)	A. Meets criteria for 8.2 B. Intake of simple analgesics on ≥15 days/month on a regular base for >3 months
Opioid-overuse headache (8.2.4, G44.83)	A. Meets criteria for 8.2 B. Opioid intake on ≥10 days/month for >3 months
Combination medication–overuse headache (8.2.5, G44.410)	A. Meets criteria for 8.2 B. Intake of simple analgesics on ≥10 days/month on a regular base for >3 months
8.2.6 Medication-overuse headache due to combination of acute medications	A. Meets criteria for 8.2 B. Intake of any acute medications on ≥15 days/month for >3 months
Probable medication-overuse headache (8.2.7, G44.41 or 44.83)	A. Headache fulfilling criteria A through C for any one of the subforms above B. One or other of the following: 1. Overused medication has not yet been withdrawn 2. Medication overuse has ceased within the last 2 months but headache has not so far resolved or reverted to its previous pattern

[a] Overuse defined in terms of treatment days per month (28).

CLINICAL MANIFESTATION

Despite the IHS classification (28) and the fact that the diagnosis of MOH does not require any additional examinations (only to exclude symptomatic forms of chronic headache) and is based on the patient's history and the clinical presentation only, MOH is frequently overlooked. Almost no experimental work has been done in this field, and the following is based mainly on clinical series describing patients presenting at headache clinics with this problem, with subsequent treatment and follow-up. Several clinical characteristics may help identify MOH in patients with primary headache disorders (Table 118-2) (46).

A prospective study of 96 patients investigated the characteristics of MOH with regard to different substances (14,34). In this study, which was conducted between 1999 and 2001, triptan overuse outnumbered ergot overuse by far. This reflects that despite high costs, triptans have become widely used (and overused) and suggests that triptans are about to become the most important group to cause MOH. Unlike patients who suffer from MOH following ergot or analgesic overuse, migraine patients (but not tension-type headache [TTH] patients) with triptan-induced headache did not describe the typical tension-type daily headache, but rather a migraine-like daily headache (a unilateral, pulsating headache with autonomic disturbances) or a significant (and pure) increase in migraine attack frequency. Furthermore, the delay between the frequent medication intake and the development of daily headache was shortest for triptans (1.7 years), longer for ergots (2.7 years), and longest for analgesics (4.8 years). The intake frequency (single dosages per month) was lowest for triptans (18 single dosages per month), higher for ergots (37 single dosages per month), and highest for analgesics (114 single dosages per month). Hence, triptans do not only cause a different spectrum of clinical features, but are able to cause MOH faster and with lower dosages compared with other substance groups.

Diener and Dahlöf performed a meta-analysis summarizing 29 studies comprising a total of 2612 patients with chronic medication-overuse headache (11). Sixty-five percent of the patients reported migraine as their primary headache, 27% of patients reported TTH as their primary headache, and 8% of patients reported mixed or other headaches as their primary headache. Women were

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TABLE 118-2 Clinical Characteristics of Medication-Overuse Headache

General headache symptoms and observations	The headaches are refractory, daily, or nearly daily. The headache itself varies in its severity, type, and location from time to time. Physical or intellectual effort may bring on headache. In other words, the threshold for head pain appears to be low. Withdrawal symptoms are observed when patients are taken off pain medication abruptly. Spontaneous improvement of headache occurs when the medications are discontinued after a few days. Concomitant prophylactic medications are (and are reported) to be ineffective while the patients are consuming excess amounts of immediate-relief medication.
Associated symptoms	Asthenia, nausea, gastrointestinal symptoms. Irritability, anxiety, restlessness, depression. Memory problems and difficulty in intellectual concentration.
Special symptoms with ergot overuse	Cold extremities, tachycardia, paresthesias, "irritable bowel syndrome." Diminished pulse, hypertension, lightheadedness, muscle pain of the extremities, weakness of the legs.

more prone to MOH than men (3.5:1; 1533 women, 442 men). This ratio is slightly higher than would be expected from the gender differences in frequency of migraine. The mean duration of primary headache was 20.4 years. The mean admitted time of frequent drug intake was 10.3 years and the mean duration of daily headache was 5.9 years. Results from headache diaries show that the number of tablets or suppositories taken per day averages 4.9 (range 0.25 to 25). Patients take on average 2.5 to 5.8 different pharmacologic components simultaneously (range 1 to 14) (11). As seen in the recent study by Katsarava et al., the number of doses per day is much smaller in patients who abuse triptans (34).

ETIOLOGY AND PATHOPHYSIOLOGY

The cause of MOH is still widely unknown. Several mechanisms, however, appear to play an important role:

A. Genetic disposition: The association between analgesic overuse and headache has been studied in conditions other than primary headache disorders. Chronic overuse of analgesics does not cause increased headache in nonmigraineurs. For example, patients who were consuming fairly large amounts of analgesics regularly for arthritis did not show an increased incidence of headache (39). In patients with cluster headache, who consume often large amounts of analgesics, MOH is not reported. In contrast, it has recently been shown that patients with migraine who are forced to take analgesics for the treatment of other pain conditions than headache are significantly more likely to develop MOH than nonmigraineurs (2). The conclusion drawn from various clinical observations and studies is that MOH may be restricted to individuals who are already headache sufferers. The basis for this could either be genetic or the fact that migraine pain is more severe than, for example, joint pain.

B. Receptor and enzyme physiology and regulation: There is no doubt that the regular exposure to the same substance will induce substantial changes regarding expression and sensitization of receptors as well as changes for the threshold of receptor activation. The extent of these changes and the velocity in which these changes occur depend on the receptor type (e.g., ion channels or G-protein-coupled receptors) and the duration and concentration of drug exposure. Recently, it has been shown in rats that the regular (daily) exposure to triptans such as sumatriptan or zolmitriptan causes a significant downregulation of these receptors in various cortical regions, the extrapyramidal system, and the brainstem and influences the synthesis rate of serotonin (17,59). Moreover, from in vivo studies it is well known that downregulation of 5-HT receptors may occur as early as 24 to 96 hours following chronic exposure (62). Chronic or frequent exposure to 5-$HT_{1B/D}$ agonists in humans may lead to a downregulation of 5-HT receptors and change central inhibitory pathways significantly. The same mechanisms account for the regulation of enzymes such as cyclo-oxygenase I and II, which are the main pharmacologic targets of analgesics such as ASA or ibuprofen. Enzyme regulation, however, is slower and needs longer exposure time and higher drug concentration (72). These theoretical aspects, however, are well in line with clinical experience and a recently conducted trial on withdrawal symptoms (35) showing that MOH will develop faster with triptan than with analgesic misuse but that intensity and duration of withdrawal symptoms will be significantly milder and shorter when triptans had been misused. Thus, it is tempting to hypothesize that the downregulation of 5-HT receptors and/or prostaglandin-synthesizing enzymes within anatomic structures involved in the transmission or modulation of nociceptive signals such as the periaquiductal grey (PAG) (which exhibits serotonergic descending inhibitory pathways mainly to trigeminal nuclei) may lead to an impairment of antinociceptive activity and subsequently result in a permanent feeling of head pain.

C. Psychologic and behavioral mechanisms: Psychologic factors include the reinforcing properties of pain relief by drug consumption, a very powerful component of positive conditioning. Many patients report that they take migraine drugs prophylactically because they are worried about missing work or an important social event or they

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fear an imminent headache. They are often instructed by physicians or by the instructions supplied with the medication to take the migraine drug as early as possible at the start of either the aura or the headache phase of a migraine attack. Early treatment also bears the danger of patients consuming more medication than necessary and thereby steadily increasing their intake frequency even for headache attacks that would not have been treated otherwise. This model behavior can be relevant in families as children may learn the early and low-threshold consumption of analgesic from their parents.

Withdrawal headache is an additional factor. When the patient tries to stop or reduce the medication, the preexisting headache worsens. Barbiturates that are contained in drugs used to treat TTH have a high potency for addiction. The stimulating action of analgesics or migraine drugs and their psychotropic side effects, such as sedation or mild euphoria, may lead to drug dependency. Barbiturates, codeine, other opioids, and caffeine are most likely to have this effect. Caffeine increases vigilance, relieves fatigue, and improves performance and mood (24,25). The typical symptoms of caffeine withdrawal, such as irritability, nervousness, restlessness, and especially "caffeine withdrawal headache"(68,70), which may last for several days, encourage patients to continue their abuse.

D. Physical dependence: Headache patients have been reported to develop physical dependence on codeine and other opioids (19,73). Although some headache patients have been on codeine for as long as 10 years, no studies have investigated the effects of codeine intake over this time period (65). It should be remembered that up to 10% of codeine is metabolized to morphine. Ergotamine and dihydroergotamine (DHE) may lead to physical dependency (61). Many migraineurs take ergotamine as prophylactic treatment. The reason for the physical dependency on ergotamine remains obscure. One study found that the tyramine-induced mydriasis after ergotamine administration was increased during abuse but not after withdrawal of ergotamine, which would indicate a central inhibition of pupillary sympathetic activity during abuse (18). Thus, a possible central nervous system (CNS) effect of ergotamine can be observed after chronic use but not after a single dose of the drug. Other studies investigating the effect of chronic use of ergotamine on CNS regulation of the autonomic nervous system are needed.

EPIDEMIOLOGY

Cross-sectional population-based epidemiologic studies indicate that chronic headache is common, with prevalence rates between 2% and 5% (8,18,19,61,65,73), and a prevalence rate of chronic headache associated with medication overuse or probable MOH is seen in about 1% (6,42,71,74). Unfortunately, there is growing evidence that the overuse of analgesics and subsequent MOH are not only prevalent in the Western world but are also a growing problem in Asian countries such as China and Taiwan (71), with the same prevalence as observed in Europe. Furthermore, it seems that it completely escapes public attention that analgesic overuse and MOH are already a problem in early adolescence and even childhood (31). A recent study on caffeine-induced headache in children revealed that MOH may occur in children as early as age 6. In this study, children suffered from MOH on average for over 12 months, indicating that the overuse was initiated at age 4 or 5 (30). Although precise data on the prevalence of MOH in children are not available yet, the first reports on MOH withdrawal therapy in children clearly demonstrate the magnitude of this rising problem (69).

Most headache centers report that between 5% and 10% of the patients they see fulfill the criteria of MOH (23). Micieli et al. observed an incidence of 4.3% in 3000 consecutive headache patients (47). A survey of family doctors showed that MIH was the third most common cause of headache (55). In some specialized headache clinics in North America, medication overuse has been reported to be present in up to 70% of the cases (55).

A potential problem arises from the recent concept to recommend drug intake as early as possible (5,43,52,60). Although the degree of drug efficacy (triptans in particular) may improve in migraine attacks, it enhances the likelihood that the patient will take the medication more frequently than actually necessary and subsequently paves the way for the development of MOH. At least some of the early headaches may not develop into a migraine attack or may represent a phase of episodic TTH that requires a different type of treatment. Therefore, the general recommendation to treat as early as possible should only be given to patients who have been told about this aspect, who are suffering from migraine only, or who are able to distinguish migraine attacks from episodic TTH even in early phases of the headache.

Taken together, these studies indicate that MOH is a major health problem all over the world. Considering the potential secondary effects of chronic medication overuse on other organ systems, including chronic kidney failure (combination analgesics), gastrointestinal ulcers (nonsteroidal anti-inflammatory drugs [NSAIDs]), or ergotism (1,49,50), education on MOH should be mandatory for medical students and all physicians who treat headache patients.

MANAGEMENT

Patients with MOH can be difficult to treat, especially when the disorder is complicated by comorbid psychiatric disease, low frustration tolerance, and physical and emotional dependency. Patients can be started on preventive

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medication (to decrease reliance on acute medication), with the explicit understanding that the medication may not become fully effective until medication overuse has been eliminated. Some patients need to have their headache cycle terminated. Outpatient detoxification options, including outpatient infusion in an ambulatory infusion unit, are available. If outpatient treatment proves difficult or is dangerous, hospitalization may be required.

Drug withdrawal is required for MOH. However, no prospective or randomized trial on the natural course of MOH or the tapering of the offending drug is available. A survey of 22 studies dealing with therapy for MOH shows that most centers use drug withdrawal as the primary therapy. Clinical experience indicates that medical and behavioral headache treatment fails as long as the patient continues to take symptomatic drugs daily. No study until today, however, has prospectively treated MOH patients de novo with a migraine preventive drug to investigate whether headache frequency and intake of medication for treating acute headache can be influenced. Such a study is underway with topiramate (13).

The typical withdrawal symptoms last for 2 to 10 days (average 3.5 days) and include withdrawal headache, nausea, vomiting, arterial hypotension, tachycardia, sleep disturbances, restlessness, anxiety, and nervousness. The withdrawal phase is much shorter when patients are abusing only triptans. Seizures or hallucinations were only rarely observed, even in patients who were abusing barbiturate-containing migraine drugs.

Drug withdrawal is performed differently. Most colleagues prefer inpatient programs (Table 118-3). Hering and Steiner (29) abruptly withdrew the offending drugs on an outpatient basis utilizing adequate explanation of the disorder, regular follow-up, and amitriptyline (10 mg at night) and naproxen (500 mg) for relief of headache symptoms. A consensus paper by the German Migraine Society (26) recommends outpatient withdrawal for patients who do not take barbiturates or tranquilizers with their analgesics and are highly motivated. Inpatient treatment should be performed in patients who (1) take tranquilizers, codeine, or barbiturates; (2) failed to withdraw from the drugs as outpatients; or (3) have a high depression score.

Treatment recommendations for the acute phase of drug withdrawal vary considerably between studies. They include fluid replacement, analgesics, tranquilizers, neuroleptics, amitriptyline, valproate, intravenous DHE, oxygen, and electrical stimulation. Valproate has been shown to have beneficial effects in the prophylactic treatment of chronic daily headache complicated by excessive analgesic intake (45). A recent large open trial showed that cortisone effectively reduces withdrawal symptoms, including rebound headache (38). A double-blind study showed a single subcutaneous dose of sumatriptan to be better than placebo in the treatment of ergotamine withdrawal headache, but the headache reappeared within 12 hours (13). An open randomized study indicated that naproxen was better than symptomatic treatment with antiemetics and analgesics (44). Further double-blind controlled trials are needed.

TABLE 118-3 Clinical Criteria Suggesting Outpatient or Inpatient Withdrawal Therapy

Outpatient withdrawal	Patient is highly motivated and self-disciplined. Patient overuses triptans or other monosubstance drugs only; patient does not use drugs containing barbiturates or tranquilizers, or several different drugs. Other typical signs or side effects of medication overuse are absent (ergotism, peptic ulcers, sleep disturbances). Patient does not suffer from other disorders such as depression or anxiety.
Inpatient withdrawal	Patient already underwent outpatient withdrawal. Patient overuses drugs containing barbiturates or tranquilizers, or several different drugs. Patient suffers from other signs or side effects of medication overuse such as ergotism, peptic ulcers, diarrhea, or anemia. Patient suffers from depression or anxiety.

A short hospital stay is recommended if MOH has lasted more than 5 years when additional tranquilizer, barbiturate, or opioid intake exists. It is further indicated in patients who have failed outpatient withdrawal or have concomitant depression or anxiety disorder. In the hospital, all pain or headache medications are stopped abruptly. Fluids are replaced by infusion if frequent vomiting occurs. Vomiting can be treated with antiemetics (e.g., metoclopramide or domperidone). The withdrawal headache can be treated with NSAIDs (e.g., naproxen 500 mg twice daily). In some countries, ASA is available in injectable forms and 1000 mg are given every 8 to 12 hours. If the headache has migrainous features and the patient previously has not abused ergots or triptans, intravenous DHE 1 to 2 mg every 8 hours is given (57,66,69). Prednisone, 100 mg on the first day, tapering by 20 mg for the next 7 to 14 days, is very effective. Symptoms of opioid withdrawal can be treated with clonidine. The initial dose is 0.1 to 0.2 mg three times daily, and this is titrated up or down based on withdrawal symptoms (tachycardia, tremor, sleeping disturbances). Some patients may require anxiolytic medication; this should be given for no longer than a week. Patients need support by the treating physicians and nurses as well as encouragement from family and friends. Behavioral techniques, such as relaxation therapy and stress management, should be initiated as soon as the withdrawal symptoms fade.

Outpatient treatment is advised for patients who take monosubstances or analgesic mixtures not containing

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barbiturates or codeine. Patients whose original headache is migraine (and who are scheduled for withdrawal therapy on outpatient bases) can start prophylactic medication 4 weeks before withdrawal. β-Blockers will improve withdrawal symptoms such as restlessness, tachycardia, or tremor. Patients who have chronic TTH may be started on a tricyclic antidepressant 4 weeks prior to detoxification (e.g., amitriptyline 10 mg increasing to 25 to 75 mg at nighttime). Ergots, triptans, and nonopioid drugs should be stopped abruptly. Opioids and barbiturates should be withdrawn more slowly depending on the dose and duration of intake. Withdrawal headache after ergots and triptans can be treated with oral or parenteral NSAIDs (e.g., 500 mg naproxen three times per day for 5 to 7 days).

Some experts delay preventive treatment until withdrawal is completed. If a patient then experiences more than three migraine attacks a month, they introduce medical and behavioral prophylaxis. Clinical experience shows that many patients respond to prophylactic treatment with β-adrenergic blockers, flunarizine, or valproic acid after drug withdrawal, despite the fact that these drugs had been unsuccessful before. Ergotamine, triptans, and possibly analgesics counteract the action of prophylactic therapy and will not improve MOH. The same phenomenon can be observed for the action of amitriptyline and behavioral therapy in patients with TTH.

PREVENTION

The most important preventive measure is proper instruction and appropriate surveillance of patients. The migraine patients at risk often have a mixture of migraine and TTH and should be carefully instructed to use specific antimigraine drugs for migraine attacks only. This point was already stressed in 1951 by Peters and Horton concerning ergotamine abuse, that is, complications can be avoided if enough time is taken for proper instruction of the patient, so that he or she can distinguish between "vasodilating" and "nondilating headache" (53).

Restricting the dose of ergotamine per attack (4 mg ergotamine), per week (no more than twice per week), and per month (no more than 20 mg ergotamine) is also helpful in avoiding dependency. In a similar way, the number of doses of triptans should be limited per attack and to 10 single doses per month (41). Migraine drugs that contain barbiturates, caffeine, codeine, or tranquilizers, as well as mixed analgesics, should be avoided. Patients who take over-the-counter (OTC) medications should be advised to avoid caffeine combinations. A headache diary is important for patients with frequent headache to detect a further increase of attack frequency or medication usage as early as possible. Early migraine prophylaxis, either by medical or behavioral treatment, can be a preventive measure to avoid MOH.

PROGNOSIS

The mean success rate of withdrawal therapy within a time window of 1 to 6 months is 72.4% (17 studies, $n = 1101$ patients). Success is defined as no headache at all or an improvement of more than 50% in terms of headache days. Three older studies (pretriptan era) had longer observation periods (between 9 and 35 months) (3,12,64). The success rates in these studies were 60%, 70%, and 73%, respectively. A 5-year follow-up study found a relapse rate of 40% (64). Recent studies included patients with MOH following the misuse of triptans as well (20,33,35). Two prospectively conducted studies indicated relapse rates for the first year after successful withdrawal therapy to be 38% and to be around 42% after 4 years (33,35). This suggests that patients are at greatest risk to suffer from a relapse within the first 12 months, but on the other hand have low risk to experience a relapse when they avoided medication overuse for at least 12 months after withdrawal therapy. Interestingly, a subgroup analysis (33) revealed that the risk of relapse mainly depends on two aspects: (1) the type of primary headache and (2) the type of drug that was overused. Patients with TTH as their primary headache entity had a significant higher relapse rate than patients with migraine (73% vs. 22%, respectively). Moreover, patients who initially overuses analgesics (mostly combination analgesics) showed significant higher relapse rates than patients overusing ergots or triptans (58% vs. 22% vs. 19%, respectively, for the first 12 months). Unexpectedly, other predictors such as duration of drug overuse, duration of disorder, and presence of prophylactic treatment did not influence the relapse rate, neither within the first 12 months nor within 48 months.

Although some data are available regarding the prevalence of MOH and the prognosis after withdrawal therapy, the question to what extent patients with migraine are at risk to develop MOH has not been clarified completely. This question, however, was recently addressed by a prospective study on over 600 consecutive migraine patients without MOH or chronic daily headache. Patients were followed prospectively for 12 months (36). Fourteen percent of this cohort developed chronic daily headache within 1 year and two thirds or almost 10% of these patients fulfilled the criteria of MOH. Two main predictors could be identified: (1) a high initial frequency of headache events and (2) medication overuse. This confirms findings that have been reported from population-based studies suggesting that analgesic overuse predicted the persistence of chronic daily headache (42,71). In one of the few prospective population-based studies, Zwart et al. (74) showed that overuse of analgesics strongly predicted chronic pain associated with analgesic overuse 11 years later, particularly among those with chronic migraine. More recently, the same group in a follow-up study could convincingly show that analgesic overuse is significantly stronger

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associated with chronic headache than with other chronic pain conditions such as chronic neck pain or chronic low back pain (75). These findings again highlight the need for a clear restriction of acute medication and early initiation preventive medication in patients with headache.

Finally, it should be mentioned that many patients with chronic daily headache do not overuse their medication. In these cases, other biologic and psychologic pathomechanisms as well as other risks may play a pivotal role (63). The uncovering of those mechanisms leading to pain chronification in humans will be one of the most interesting and rewarding pieces of medical science in the hopefully near future.

HEADACHE ATTRIBUTED TO SUBSTANCE WITHDRAWAL (8.4)

The new IHS classification has specific criteria for caffeine-withdrawal headache (8.4.1), opioid-withdrawal headache (8.4.2), estrogen-withdrawal headache (8.4.3), and headache attributed to withdrawal from chronic use of other substances (8.4.4).

Caffeine-Withdrawal Headache (8.4.1)

Criteria for the diagnosis of caffeine-withdrawal headache (ICHD-II) are as follows:

A. Bilateral and/or pulsating headache fulfilling criteria C and D.
B. Caffeine consumption of ≥200 mg/day for >2 weeks, which is interrupted or delayed.
C. Headache develops within 24 hours after the last caffeine intake and is relieved within 1 hour by 100 mg of caffeine.
D. Headache resolves within 7 days after total caffeine withdrawal.

Stopping daily low-dose caffeine intake frequently results in withdrawal headache (68). In a controlled study of caffeine withdrawal, 64 normal adults (71% women) with low to moderate caffeine intake (the equivalent of about 2.5 cups of coffee a day) were given a two-day caffeine-free diet and either placebo or replacement caffeine. Under double-blind conditions, 50% of the patients who were given placebo had a headache by day 2, compared with 6% of those given caffeine. Nausea, depression, and flulike symptoms were very common in the placebo group. This study is relevant since caffeine is frequently used by headache sufferers for pain relief, often in combination with analgesics or ergotamine. The study is a model for short-term caffeine withdrawal, but does not demonstrate the long-term consequences of detoxification. In a community-based telephone survey of 11,112 subjects in Lincoln and Omaha, Nebraska, 61% reported daily caffeine consumption, and 11% of the caffeine consumers reported symptoms upon stopping coffee (9). A group of those who reported withdrawal symptoms were assigned to one of three regimes: abrupt caffeine withdrawal, gradual withdrawal, and no change. One third of the abrupt-withdrawal group and an occasional member of the gradual-withdrawal group had symptoms that included headache and tiredness.

Opioid-Withdrawal Headache (8.4.2)

Criteria for the diagnosis of opioid-withdrawal headache (ICHD-II) are as follows:

A. Bilateral and/or pulsating headache fulfilling criteria C and D.
B. Opioid intake daily for >3 months, which is interrupted.
C. Headache develops within 24 hours after last opioid intake.
D. Headache resolves within 7 days after total opioid withdrawal.

Diagnostic criteria for estrogen withdrawal headache (ICHD-II) are as follows:

Estrogen-Withdrawal Headache (8.4.3)

A. Headache or migraine fulfilling criteria C and D.
B. Daily use of exogenous estrogen for ≥3 weeks, which is interrupted.
C. Headache or migraine develops within 5 days after the last use of estrogen.
D. Headache or migraine resolves within 3 days.

Estrogen withdrawal follows cessation of a course of exogenous estrogens (such as during the pill-free interval of combined oral contraceptives or following a course of replacement or supplementary estrogen) and can induce headache and/or migraine.

Headache Attributed to Withdrawal From Chronic Use of Other Substances (8.4.4)

The criteria for headache attributed to withdrawal from chronic use of other substances (ICHD-II) are as follows:

A. Bilateral and/or pulsating headache fulfilling criteria C and D.
B. Daily intake of a substance other than those described above for >3 months, which is interrupted.
C. Headache develops in close temporal relation to withdrawal of the substance.
D. Headache resolves within 3 months after withdrawal.

Finally, it has been suggested, but without sufficient evidence, that withdrawal of the following substances may

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cause headache: corticosteroids, tricyclic antidepressants, selective serotonin reuptake inhibitors, and NSAIDs.

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