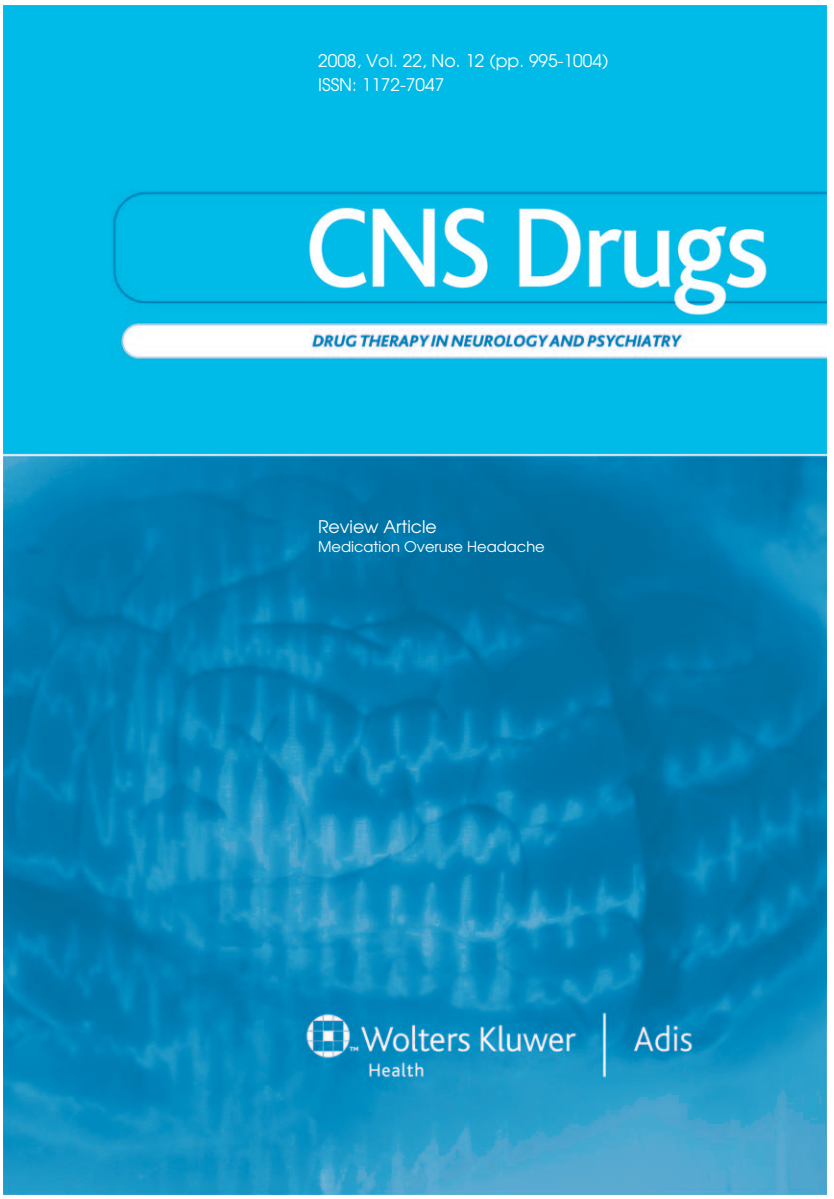

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Medication Overuse Headache
Awareness, Detection and Treatment

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Contents

Abstract

Episodic migraine is a disabling painful disease that can affect the normal function of daily routine activities such as performance at work and school, and home and social relationships. In addition to the physical disability during migraine, between attacks many patients experience a condition referred to as interictal burden, which can present as pre-event worry about future attacks and can result in the anticipatory use and/or overuse of acute care medications. The overuse of medication can often lead to medication overuse headaches (MOHs) and chronic migraine. Unfortunately, patients, and even some physicians, are often unaware of this phenomenon. Therefore, it is important for knowledgeable physicians to raise awareness and to address the risks of medication overuse with their patients through effective communication. Future management of medication overuse should include detoxification and a comprehensive programme that includes the use of preventive medications such as sodium valproate (divalproex sodium) and topiramate in order to reduce dependency on acute care medication. Also, MOHs may be most effectively managed with the initiation of preventive treatment prior to detoxification, in addition to the decreased use of acute care medication. A long-term treatment plan, including behavioural therapy, migraine preventive medication and appropriate acute care therapy, may be optimal in treating patients with MOHs.

Episodic migraine is a disabling painful disease that can escalate to chronic migraine, a condition in which headaches occur ≥15 days/month for >3 months.[1-3] At one specialized headache centre in Germany, 14% of the 450 episodic migraine patients developed chronic headache within

1 year.[4] In a population-based study in the US, 3% of patients with episodic migraine developed chronic migraine.[5] Many patients with migraine have an interictal burden and often worry about their next attack and how it will affect their functioning. This pre-event worry creates an incentive for them to overuse their pain medications, sometimes taking them even before an attack has started. When episodic migraine is accompanied by acute medication overuse (MO), rebound headaches can occur and can lead to chronic medication overuse headache (MOH).[6,7]

Overuse of pain medications for headache has long been recognized. In 1982, Kudrow[8] conducted a randomized, placebo-controlled study with 200 patients who experienced daily headaches and described what he termed a paradoxical effect of frequent analgesic use. He found that the mean headache improvement rate of amitriptyline-treated patients who were randomized to discontinue analgesic use was more than twice the improvement rate of those who were allowed to continue using analgesics without restriction (baseline average 6.2 pills/day).[8] Other studies further investigated improvements in headache frequency after withdrawal of analgesics in patients with analgesic rebound headache (summarized by Rapoport[9]). Together, these studies demonstrated that overused analgesics did not consistently relieve headache and could actually perpetuate and worsen it.[8,9]

In a survey of generalist and specialist physicians, MO was the third most common cause of their patients' headaches.[10] Moreover, MO is one of the most common causes of chronic headache[6,11] (chronic headache has a prevalence rate of 2–5%[2,4,12] and is 7-fold more likely to occur in patients who overuse medications compared with those who do not).[13] Whereas the proportion of patients with chronic migraine who overuse acute medications is 30–50% in the general population,[4,14] this number can reach 80% in specialty headache clinics.[14,15] A high initial frequency of headaches and MO are both predominant risk factors for escalation from episodic to chronic migraine.[4,14,16] MO can also increase the frequency and severity of headaches in established chronic migraine.[17] However, there is much debate as to whether MO is a cause of increased migraine frequency or whether it is an adaptive mechanism to naturally increasing frequency.

The prevalence of MOH, which can affect both migraineurs and patients with other types of chronic headache, is 1–2% in North America, Europe and Asia.[2,3,7,12,15,17-19] In some North American headache centres, up to 59% of patients have been diagnosed with MOH.[12] MOH is characterized by daily (or almost daily) headache, substantial disability and decreased health-related quality of life,[2,20] particularly when associated with chronic migraine.[21] When MOH is suspected, current standard treatment includes withdrawal of the overused agent, often with detoxification therapy.[6,15,22-25] Nevertheless, patients are susceptible to relapsing to overuse of their medications again after withdrawal,[6,13,15,22,23] particularly in the first year.[7,13] Migraine preventive medications decrease the frequency of attacks and have the potential to reduce the amount of acute medications used[14,17,26] and increase the efficacy of reduced medications.[26] However, a US study of >160 000 respondents, the AMPP (American Migraine Prevalence and Prevention) study, demonstrated that preventive medications are underutilized as a treatment option for migraine. Almost 40% of the respondents with migraine were candidates for migraine preventive medications by expert criteria, but fewer than 13% of respondents were receiving these medications.[16] Currently, MO is believed to counteract the efficacy of migraine preventive pharmacotherapy.[2,6,13,14,18,22,27]

In this review, we examine the challenges of MO and MOH, and highlight the role of the clinician in recognizing and treating MOH. This will include a discussion of effective physician-patient communication and patient education as an essential component of MOH detection, prevention and management.[17,25] We also present evidence for the use of preventive migraine medications as a viable MOH treatment option.

1. Characteristics of Medication Overuse (MO) and Medication Overuse Headache (MOH)

In 2004, the second edition of the International Classification of Headache Disorders (ICHD-2) defined MO as the use of ergots, triptans, opioids, combinations of the above or combination analgesics on ≥10 days/month, or the use of simple analgesics or any combination of simple analgesics, opioids and caffeine on ≥10 days/month.[3] A recent update in 2006 further qualified MO as the use of ergotamine, triptans, opioids or combination analgesics for ≥10 days/month, or the use of simple analgesics or any combination of ergotamines, triptans, analgesics or opioids on ≥15 days/month.[28] Factors that may contribute to MO include stress from the need to function (at work and at home) and worry about the next migraine headache.[7,13] Although acute care medications may work best when taken early during a migraine attack, some patients take them even before the premonitory symptoms in response to worry about how their functioning and daily activities may be affected. This behaviour puts patients at risk of overusing their medications.[7,13] In all cases, acute migraine prescriptions should be tailored to the individual patient and monitored closely to prevent overuse.

According to the ICHD-2 criteria published in 2004, the diagnosis of MOH could be applied retrospectively if the patient's condition improved following discontinuation of the overused medication.[3] This rather unsatisfactory definition may have discouraged physicians from attempting to treat the condition because it could not be diagnosed without medication withdrawal followed by improvement, therefore the patient no longer had the condition. As such, a 2006 revision to the ICHD-2 diagnostic criteria defined MOH as (i) headache that is present on ≥15 days/month; (ii) regular overuse of acute treatment drugs for >3 months (ergotamine, triptans, opioids or combination analgesic medications on ≥10 days/month; or simple analgesics or any combination of ergotamine, triptans, analgesic opioids on ≥15 days/month without overuse of any single class alone); and (iii) headache that has developed or worsened during MO.[28] Because some patients will not improve after withdrawal alone but will respond to preventive medication, in revising the criteria for MOH the classification committee deemed that MOH should be the default diagnosis if MO is present.[28] Improvement after withdrawal is no longer part of the official definition. If patients do not improve 2 months after their acute care medications are withdrawn, they are diagnosed with chronic migraine.

All acute care headache medications have the potential to cause MOH, including over-the-counter drugs such as aspirin (acetylsalicylic acid) and paracetamol (acetaminophen), combination medications containing paracetamol and aspirin, NSAIDs (controversial), antimigraine abortive medications (ergots and triptans), barbiturate-containing medications (primarily butalbital), opioids (codeine, hydrocodone, oxycodone, meperidine and morphine) and opioid agonist/antagonist agents (butorphanol and nalbuphine).[7,9,12,18]

When overused, the different acute care medications can cause a variety of headache types; however, there is no consensus on which medications cause which phenotype headache.[7,19] There is some controversy in the field because some acute medications that may cause MOH in some patients are protective at a population level (e.g. aspirin).[5] There is some evidence that triptans may induce MOH faster and at a lower daily intake than ergots or analgesics.[7,19,22,24] In one study, as few as ten doses of triptans per month, taken for periods as short as 6 months, induced MOH.[19] However, it has also been shown that patients who took a triptan initially for an acute migraine attack were less likely to need additional medication for the same attack than those who took a nontriptan acute medication.[29] Thus, the aggregate amounts of medications taken, the increasing need for more medication for the same effect, and perhaps even the risk for eventual MOH, may be less in patients who primarily use triptans for acute attacks.

2. Pathogenesis of MOH

Although the pathogenesis of MOH is not understood, a number of theories have been proposed. Frequent use of acute medications that are ineffective in aborting the headache process may trigger MOH through a wind-up phenomenon, in which repetitive stimulation of nociceptive pathways leads to central sensitization.[6,30-34] It has also been postulated that MOH occurs as a result of cellular adaptation to excessive analgesic exposure, whereby membrane transduction impairment causes the CNS to become refractory to treatment.[6,34] Another potential mechanism underlying the development of MOH involves the direct inhibitory effect of headache medications on the pain-modulating capacity of the brain.[6,34] Evidence has shown that MOH may be associated with a decrease in blood serotonin levels, with the subsequent upregulation of serotonin receptors in the brain leading to the establishment of a hyperalgesic state.[6,31-34] According to another hypothesis, MOH may be related to headache- and/or medication-induced changes to the periaqueductal grey matter, which plays a central role in pain modulation.[6,30,31,34] It has also been suggested that metabolic dysfunction of the orbitofrontal cortex may contribute to the development of MOH.[32]

Research has demonstrated that an overlap may exist between the pathophysiological mechanisms underlying MOH and those associated with other forms of substance dependence and psychiatric disorders such as obsessive compulsive disorder.[6,31,32,35] Furthermore, evidence indicates that patients with MOH have an increased prevalence of psychiatric co-morbidities such as depression, anxiety and panic disorders.[6,31,35,36] Such observations, combined with continued study of the neurobiological features common to these disorders, may provide further insights into the pathogenesis of MOH, and may ultimately lead to new approaches for MOH management.

3. Detecting and Preventing MO and MOH: Communicating Effectively

In a study conducted in Italy, it was shown that most patients are not aware that overusing acute migraine medications can worsen their headache problem.[25] They consider their medication use a reasonable and necessary response to migraine and may deny overuse if it is not fully explained.[18] Patients with MOH who have, over time, developed tolerance and increased their drug intake to achieve relief, must be convinced that their rebound headaches are not due to an insufficient quantity of acute medications. Unless the patient 'buys in' to the concept of MOH, treatment will not succeed.[13] If MOH is explained carefully to the patient and the questions are presented as a way to collaborate in understanding and solving the headache problem, the patient can accept the possibility of MOH and participate in effective treatment. To prevent MO and MOH, it is crucial for the patient to understand that overuse of headache medications can lead to a worsening of headache frequency or severity.[13,22,25] Clinicians must ensure that their patients with migraine are properly informed about the correct use of their acute medications and the potential risk of MOH.[6,7,17]

MO can be detected by routinely asking questions about medication use,[13] such as:

- Do you ever take a pill before social events or work meetings, or because you are anxious before migraine symptoms start?
- Do you ever take a pill, just in case?
- Do you use acute care medication 3 or more days/week?
- In addition to your prescription medications, approximately how often do you take over-the-counter pain medications?

Other effective communication strategies to identify MO involve the detection of the overall impact of migraine on the patient, both during and between attacks. The American Migraine Communication Studies[37,38] demonstrated that physicians do not ask patients the most effective questions to uncover the true impact of migraine. Open-ended questions such as "How does migraine affect your daily life?" elicit more information about impact than close-ended, yes or no questions, without increasing office visit time (table I).[38-40] Headache diaries or calendars, which should be used by all

Table I. Techniques for communicating with patients

'Ask-tell-ask': Assess frequency of headache and medication use[37]
"How many headaches do you get each month?"
"How many rescue medications do you take?"
Rephrase patient's answers for confirmation: "So you have 20 headache days/month and you take four acute medications per day – that is about 100 tablets per month?"
Ask open-ended questions to assess medication use[40]
"How has your use of rescue medications changed?"
"Tell me about how your migraines and medications make you feel."
Ask closed-ended questions to assess the use of headache medications
"Do you use any preventive medications for your headaches?"
"Which medications do you take?"

headache patients, can also reveal increasing headache frequency and increasing medication use, which are possible signs of developing MOH.[7]

Therefore, it is important for clinicians and patients to work together with the understanding that ceasing to overuse acute care migraine medications can help to alleviate MOH and will lay the foundation for successful preventive treatment of the original migraine condition.[13] Clinicians should also inform patients undergoing withdrawal from overused acute medications about possible transient worsening before improvement, the time needed for headache improvement and the risk of relapse.[13]

4. Managing MOH

The goals for treating and managing MOH should be to reduce the frequency and/or severity of headache, reduce acute medication consumption, improve responsiveness to acute and preventive treatments, alleviate disability and improve quality of life.[41] Standard strategies for MOH management include withdrawal of the overused medication, institution of behavioural treatment, which includes limiting the future frequency of acute care medication use, and initiation of migraine preventive therapy to treat the primary headache disorder.[10,18,42]

Multiple studies have documented abrupt and gradual withdrawal of overused agents on an inpatient or outpatient basis.[6,7,14,15,18,22-25,42,43] Some medications (e.g. paracetamol) can be withdrawn abruptly if clinically indicated. However, others (e.g. barbiturates, benzodiazepines and usually opioids) should be withdrawn gradually.[27,44,45] Caffeine also requires tapering rather than abrupt withdrawal.[7,14] Even when medications are tapered gradually, it is usually necessary to treat withdrawal symptoms such as rebound headaches. In addition to necessary headache treatment, outpatient, and sometimes inpatient, pharmacological therapies may be needed to treat nausea, vomiting, anxiety and sleep disturbances induced by medication withdrawal.[6,7,44] Depending on the agent withdrawn, therapy might include intranasal or parenteral dihydroergotamine mesilate, NSAIDs, corticosteroids, antipsychotics, antidepressants and tizanidine.[7,14,17,18,42] If the MOH agent was an opioid, clonidine is a good choice for the treatment of withdrawal symptoms.[42]

Withdrawing acute headache medications may be difficult, and headache improvement usually takes time.[9,13] Patients who withdraw overused medications run a high risk of relapse. Studies have shown relapse rates of up to 41% within 1 year (reviewed by Lake[13]). Relapse rates are somewhat dependent on the intensity and frequency of the follow-up visits. Unfortunately, there is a lack of blinded, placebo-controlled studies to support current withdrawal strategies. Moreover, although withdrawal alone may result in fewer headaches in some patients,[22,24,25,27,46] others see no improvement.[14,27,46] Discontinuing the overused medication will not necessarily alleviate the underlying headache problem if the patient has chronic migraine or chronic tension-type headache.[22] To prevent relapse into overuse, the primary headache must be effectively treated using an alternative approach.[22] Massage and behavioural therapies such as cognitive-behavioural therapy, stress reduction and biofeedback training may help (table II).[13,14,17,22,24,47-52] Clinicians and patients should be prepared to commit to a long-term treatment strategy with regular clinic visits to treat the primary headache and prevent relapse into overuse.[22,42]

Migraine preventive medications are an important component of withdrawal therapy.[13,14] How-

Table II. Nonpharmacological strategies for the treatment of headache

Biofeedback[49,50]
Patients taught to increase awareness and bring involuntary processes under voluntary control
Includes sympathetic arousal, circulation (finger temperature) and muscle tension
Relaxation techniques[50,51]
Used to minimize physiological responses to stress
Includes breathing techniques such as diaphragmatic breathing, visual imagery, meditation, prayer, yoga, listening to music, self hypnosis and listening to guided relaxation CDs or tapes
Cognitive-behavioural therapy[52]
Helps patients build or improve coping skills
Includes identifying triggers, promoting healthy lifestyle habits and keeping headache diaries

ever, some clinicians and researchers believe that preventive treatment is compromised for patients with MOH if started before complete withdrawal. Evidence has demonstrated the benefits of withdrawal followed by long-term preventive treatment,[13,14,25,46] and recent clinical trials suggest preventive medications are effective even when MO is still present.[17,53,54]

In addition, even if that is not always the case, the author prefers to start preventive therapy prior to withdrawal so the medication can be gradually titrated to effective doses with appropriate blood concentrations. Patients will then have a drug available when they go through the withdrawal period.

5. Managing MOH with Migraine Preventive Medications

Migraine preventive medications aim to decrease the frequency of headache attacks and headache days per month and, therefore, have the potential to decrease the use of acute medications and possible MO and MOH.[14,17,26] The US Headache Consortium has recommended preventive therapy in migraine associated with the overuse of acute care medications.[55] In migraine patients, decreasing headache frequency may help alleviate the fear of an impending attack and worry about impaired functioning, and thus the incentive to overuse medications.

Some patients with MOH who do not respond to the withdrawal of overused medications do respond to preventive therapy.[46] In one study (n = 175), some patients (n = 88) did not improve for 2 months after complete drug withdrawal, but when they went on to receive preventive therapy they experienced a 26% decrease in headache frequency.[46] Recent well controlled clinical trials suggest that preventive medications may be effective even when the overused acute medication(s) continue to be used.[17,54,56] Unfortunately, there is a lack of well controlled trials evaluating the effectiveness of specific migraine preventive medications in alleviating MO and MOH. The author usually starts a preventive medication 4–6 weeks prior to the withdrawal of overused medications. Whether or not it is effective in that month, when withdrawal begins, there will be a therapeutic plasma concentration of the preventive drug, which could shorten the time to effective treatment.

The neurostabilizer sodium valproate (divalproex sodium) is an antiepileptic drug (AED) that has been demonstrated to be an effective migraine preventive medication in randomized, double-blind, placebo-controlled, multicentre trials.[57,58] In the study by Mathew et al.,[58] patients treated with valproate used significantly less acute care medication per migraine episode than those receiving placebo. A prospective case series of extended-release valproate also supports the efficacy of this migraine preventive medication in patients with probable chronic migraine and probable MO.[59] The most common adverse events occurring with valproate therapy include gastrointestinal symptoms (nausea, dyspepsia, diarrhoea, vomiting, abdominal pain, increased appetite), asthenia, somnolence, dizziness, tremor, weight gain, back pain and alopecia.[60]

The neurostabilizer topiramate is another AED that significantly reduces migraine attack frequency and use of rescue medication for acute attacks, and has demonstrated a consistent therapeutic effect across a broad range of migraine frequencies, including episodic and chronic migraine.[26,41,54-56,61] A recent randomized, double-blind, placebo-controlled, multicentre study (n = 306) including patients

with acute medication use on ≤4 days/week demonstrated that topiramate was effective in treating patients with chronic migraine.[54] In a *post hoc* analysis of the subgroup with MO (n = 115), topiramate resulted in reductions in migraine headache days, although this reduction was not statistically significant.[62] Similar results were obtained for the non-MO patient cohort. In another randomized, double-blind, placebo-controlled trial, the entire sample group (n = 35) had MO and patients received either topiramate 100 mg/day or placebo while continuing to take triptans for acute attacks.[26] The group receiving topiramate had significant reductions in the number of headache days and mean amount of acute medications taken (figure 1).[26] The most common adverse events associated with topiramate 100 mg/day include paraesthesia, fatigue, nausea, anorexia, dizziness, difficulty with concentration or memory, and taste perversion.[41,54-56,61]

In addition to valproate and topiramate, evidence indicates that a number of other AEDs may be effective off-label as migraine preventive therapy. These include gabapentin, zonisamide, levetiracetam and clonazepam (reviewed in Mathew,[63] Bigal et al.[64] and Kaniecki[65]). It is postulated that the efficacy of AEDs in migraine prevention is related to pathogenetic mechanisms that, according to hypothesis, are common to both migraine and epilepsy. [66] However, it is important to note that not all AEDs are effective for migraine prevention. The reasons for this are not clear.[66] Thus far, the AEDs that have proven to be successful in migraine preventive therapy have multiple mechanisms of action, which include inhibition of voltage-gated Na^+ and Ca^{2+} channels, and modulation of glutamate- and GABA-mediated transmission.[66,67] Valproate, for example, may participate in the inhibition of central pain transmission through potentiation of the GABA-ergic inhibitory system. [68] Topiramate acts on many receptor-gated and voltage-sensitive ion channels, including voltage-activated Na^+ and Ca^{2+} channels and non-NMDA receptors. These receptors have been implicated in the pathophysiology of both epilepsy and migraine.[69] Gabapentin has also been shown to increase cerebral GABA levels.[70]

Another agent that has been used effectively in a clinical environment and tested as a migraine preventive therapy, but not yet approved, is botulinum toxin A. One open-label study found reduced headache frequency and intensity with botulinum toxin A, but patients with chronic migraine were less likely to respond than those with episodic migraine, and patients with chronic migraine and MO were less likely to respond than those without MO (result not statistically significant).[71] A review of randomized, double-blind, placebo-controlled trials concluded that positive evidence for botulinum toxin A in chronic daily headache and MOH is lacking.[72] Two large phase III trials using botulinum toxin A in patients with frequent migraine who were not taking

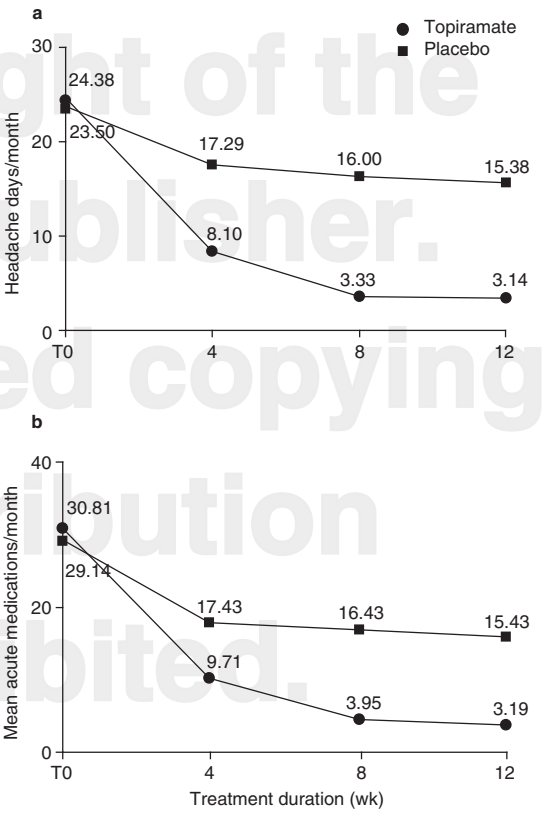

Fig. 1. The effects of topiramate vs placebo on (**a**) the number of days per month with headache; and (**b**) the number of acute medications taken monthly in 35 patients with chronic migraine and medication overuse (reproduced from Mei et al.,[26] with permission. © 2006 Lippincott Williams & Wilkins).

preventive medication have recently been completed and results are expected by the end of 2008.

Much of the data presented challenge the widespread assumption that preventive treatment is ineffective in the presence of MO and suggest that withdrawal before initiating preventive therapy is not necessary.[26,56,59] There is a clear need for additional large, well powered, randomized, controlled trials to identify the risks of developing chronic migraine and to evaluate the efficacy of migraine preventive medications in managing chronic migraine and MOH. However, current evidence supports a combination of preventive therapy, withdrawal of the overused acute medication, and behavioural treatments, including frequent follow-up. For long-term treatment of MOH, behavioural therapy combined with preventive medication can decrease the risk of relapse, compared with preventive and acute rescue pharmacotherapy alone.[13,47]

6. Conclusions

MO is the most common factor leading to the escalation from episodic to chronic migraine, and MOH should be the default diagnosis for chronic headache co-occurring with MO. Identifying MO and MOH is accomplished by addressing the issue directly with the patient, using open communication techniques and educating the patient with migraine about the risks and proper use of acute care medications. Managing MOH can include withdrawal of the overused medication(s), but this carries the risk of immediate, transient worsening. Migraine preventive medications can effectively reduce migraine frequency and reduce the dependency on acute medications. The best time to initiate preventive medication may be before detoxification begins, to ensure that the preventive agent reaches therapeutic concentrations, which often takes a minimum of 4–6 weeks. A long-term treatment plan, including behavioural therapy, use of headache diaries or calendars, frequent revisits, migraine preventive medication and appropriate acute care therapy with frequency limitations, will lead to optimal therapy and often to improvement for the patient with MOH.

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