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Medication Overuse Headache from Antimigraine Therapy

Clinical Features, Pathogenesis and Management

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Contents

Abstract

Medication overuse headache (MOH) is being recognised more often in headache, neurology and primary care clinics, but is still frequently overlooked. The most significant factor in the development of MOH is the lack of widespread awareness and understanding on the part of clinicians and patients. While the diagnosis of MOH may be suspected clinically, it can only be confirmed in retrospect. Diagnosis may take ≥3 months because of the need for prolonged observation after cessation of medication. Diagnosis must be based on observation of patterns of headaches and medication use, remembering that MOH is only seen in patients with migraine and not in those without.

MOH should be viewed as an entity that is caused or propagated by frequently used medication taken for headache symptomatic relief. Because of easy availability and low expense, the greatest problem appears to be associated with barbiturate-containing combination analgesics and over-the-counter caffeine-containing combination analgesics. Even though triptan overuse headache is not encountered with great frequency, all triptans should be considered potential inducers of MOH.

There are several different theories regarding the aetiology of MOH, including: (i) central sensitisation from repetitive activation of nociceptive pathways; (ii) a direct effect of the medication on the capacity of the brain to inhibit pain; (iii) a decrease in blood serotonin due to repetitive medication administration with attendant upregulation of serotonin receptors; (iv) cellular adaptation in the brain; and (v) changes in the periaqueductal grey matter.

The principal approach to management of MOH is built around cessation of overused medication. Without discontinuation of the offending medication, improvement is almost impossible to attain. A three-step approach to treating patients with analgesic rebound headaches includes: (i) a bridging or transition programme; (ii) nonpharmacological measures; and (iii) prophylactic medication started early in the course of treatment (after offending medication is successfully discontinued).

The best management advice is to raise awareness and strive for prevention. Prophylactic medications should be initiated for patients having ≥2 headache days per week. Anticipatory medication use should be discouraged and migraine-specific therapy should be considered as early as possible in the natural history of patients' headaches. Reduction in headache risk factors should include behavioural modification approaches to headache control earlier in the natural history of migraine.

Population studies show that approximately 4% of the American population suffers from headache >15 days per month.[1] According to the International Headache Society (IHS) classification system, patients with >15 headache days per month are categorised as having chronic daily headache, of which there are primary and secondary causes. The common primary aetiologies of chronic daily headache include chronic migraine, chronic tension-type headache, chronic trigeminal autonomic cephalgias (including cluster headache) and new daily persistent headache. The secondary causes of chronic daily headache are extensive and include such entities as pseudotumour cerebri, Arnold Chiari malformation, etc. Possibly the most common secondary cause of chronic daily headache is medication overuse headache (MOH). Unfortunately, the entity of MOH is all too often under-recognised and poorly understood by even the most conscientious clinicians. To complicate matters further, most patients with MOH have an underlying primary headache disorder which antedates their medication overuse and puts them at risk for escalation to daily headaches in the first place. Most of this population has a history of episodic migraine without aura that has transformed into a daily or near-daily headache syndrome. The majority present with overuse of analgesics or migraine abortive medication and are designated as having MOH, also referred to in the past as 'rebound headaches'. In fact, about 80% of patients with chronic daily headaches in the US use analgesics or migraine abortive medications on a daily or near-daily basis.[2] For these patients, the frequency of their headaches usually increases during the period of medication overuse and will eventually decrease after the offending medications have been stopped, although this improvement may take several weeks.

A Medline search using the web site of the National Library of Medicine (www.ncbi.nlm.nih.gov) and an Ovid search (www.gateway1.ovid.com) were performed to examine the literature for papers discussing MOH using the following terms: 'medication overuse headache', 'analgesic rebound headache', 'chronic daily headache', 'chronic migraine', 'medication induced headache' and 'transformed migraine'. Additional reviews of the journals *Headache* and *Cephalalgia* were also undertaken to identify additional literature pertaining to MOH. A total of 966 article titles were produced from this literature search. The abstracts were reviewed to identify papers describing controlled or uncontrolled medication trials, nonpharmacological treatment of MOH, and investigation into pathophysiology and epidemiology of MOH. Relevant papers or scientific presentations referenced in these articles were also obtained. All of the studies in the medical literature on MOH are small and most are not well controlled, but the data from these reports suggest some very good 'pearls' for clinical management of the disor-

der. This paper was written to give a narrative review of those concepts obtained from the literature search and discusses the pathogenesis, clinical presentation, differential diagnosis, management and prognosis of MOH.

1. Historical Literature

Chronic daily headache and medication overuse have probably been occurring for years, but were first linked in 1940 by Dreisbach,[3] who recognised the relationship between caffeine withdrawal and headache. This was followed by Wolfson and Graham in 1949,[4] who found that patients could develop tolerance to ergotamine if used regularly and a withdrawal headache when discontinued. In 1951 'rebound' headache was defined by Peters and Horton.[5] Over 30 years later, analgesics were implicated in rebound headache by both Kudrow[6] and Isler,[7] and Mathew[2] defined the phenomenon of intermittent headache escalating to daily headache as transformed migraine. Kudrow[6] went on to show a relationship between patients experiencing rebound headache and a lack of efficacy of their prophylactic medications. He showed that, once analgesic medication was discontinued, the efficacy of prophylactic medication improved in his patients.[6] Rapoport et al.[8] were the first to define an analgesic washout period of 12 weeks for patients with 'analgesic rebound headache' in 1986. Diener et al.[9] published the first detoxification protocol in 1988. Triptans were first implicated as rebound medications by Gobel et al.[10] in 1996. Clearly, the development of the concept of MOH has been one of an evolutive process and will likely continue to evolve as new discoveries are made, publicised and debated.

Over the years, MOH has had a variety of names, including analgesic rebound headache, medication rebound headache, transformed migraine and medication-induced headache. The IHS formalised the term MOH in 2004.[11] To be precise, it should be noted that some medications are known to cause headache through a direct pharmacodynamic mechanism and the headache would be correctly categorised as 'medication-induced headache' rather than MOH. Examples of such medications would include nitroglycerine and nifedipine. The scope of this paper is not intended to cover this topic, but rather to focus on MOH as it pertains to the clinical observations of 'rebound' patterns of headache from repeated use of symptomatic headache medications.

2. Pathogenesis

In order to understand the pathogenesis of MOH it is important to first examine the pathophysiology of migraine headache. To be technically accurate, it is most appropriate to say that we do not have all of the answers regarding the neurobiology of migraine. However, research into the aetiology of primary headache over the last decade has contributed greatly to our understanding. During a migraine, dysfunction occurs in the brainstem pathways that typically modulate sensory input. The pain impulse starts as trigeminovascular input from meningeal vessels, which pass through the trigeminal ganglion (see figure 1). These neurons continue the impulse through the quintothalamic tract and, after crossing in the brainstem, synapse with neurons in the thalamus. Functional brain imaging taken during migraine suggests that the modulation of trigeminovascular input is from the dorsal raphe nucleus, locus ceruleus, nucleus raphe magnus and the periaqueductal grey matter.[12]

The trigeminovascular system is clearly activated in MOH. However, there are still many unanswered questions regarding the pathogenesis of MOH. Clinical observation and scientific investigation have given us a new basis for understanding and are helping us begin to unravel the mystery of MOH, but we still have a lot to learn about its pathophysiology. There are several different theories as to why MOHs occur, and they may all contribute to the cause. These theories include central sensitisation from repetitive activation of nociceptive pathways, a direct effect of the medication on the capacity of the brain to inhibit pain, a decrease in blood serotonin due to repetitive medication administration with attendant upregulation of serotonin receptors, cellular adaptation in the brain and changes in the periaqueductal grey matter.

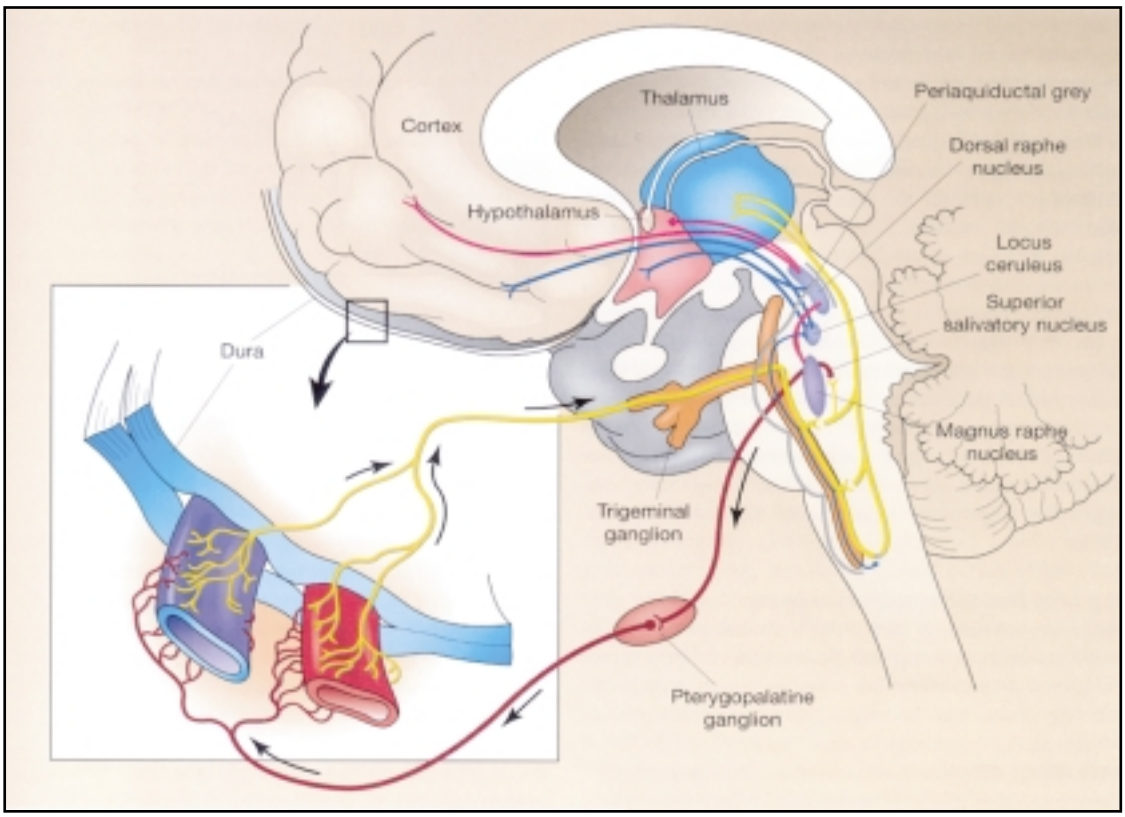

Fig. 1. The trigeminovascular pathway (reproduced from Silberstein et al.,[12] with permission).

The first theory for the pathogenesis of MOH is that increased nociception leads to central sensitisation. Central sensitisation occurs when repeated nociceptive stimuli activate the trigeminovascular system and increase the perceived pain intensity, even when there is no increased input. These neurons essentially become sensitised to the input as a result of repetitive intense neuronal stimulation (i.e. frequent headache). It is felt that incomplete headache treatment, with simple or combination analgesics that never adequately interrupt the migraine process, actually contributes to the development of chronic headache through this CNS wind-up that is allowed to happen. Clinically, the patient is able to dull the headache somewhat using analgesics, but not truly abort it, eventually repeating the failed treatment scenario until sensitisation occurs. According to this theory, if the offending medication is discontinued for a sufficient length of time, prophylactic medications will then become useful and acute migraine-specific abortive agents used intermittently with safeguards against overuse will be effective in interrupting the impetus for further and continued sensitisation.[13]

There also may be a direct effect of medication on the ability of the brain to modulate pain transmission, which is the second theory on the biology of MOH. In the ventromedial medulla of the brain there are neurons that are believed to modulate pain activity. These neurons include the 'off-cells', which inhibit nociception, and the 'on-cells', which facilitate nociception in the trigeminal nucleus caudalis. In animal models, activation of these on-cells in the ventromedial medulla has been shown to increase nociception.[14] Opioid withdrawal in mammals can increase the firing of on-cells, while de-

creasing the firing of off-cells, leading to increased nociception. A similar mechanism occurs during MOH, with daily headache resulting from increased nociception. Continual administration of the offending medication can actually reset the pain control mechanism in migraine patients by increasing the on-cell activity and increasing central sensitisation. Increased activity of on-cells in the pain modulation system of the brainstem may be involved in the production of rebound pain when medications are stopped.[15] This pain modulation system is the same system that is activated during opioid withdrawal. It is possible that long-term use of analgesics, especially opioids, in the treatment of migraine leads to further dysfunction of the CNS antinociceptive system, causing chronic daily headache.

The third possible theory regarding MOH is a decrease in blood serotonin levels, leading to an increase in pain receptors in the brain. The action of analgesic medications on the arachidonic acid pathway is well understood. Less well known is the effect of analgesics on the serotonergic system. Investigations have suggested that a decrease in blood serotonin may be caused by symptomatic medications.[16] This decrease in blood serotonin may indirectly lead to increased headache due to a corresponding upregulation of serotonin 5-HT_2 receptors in the brain.[15] The 5-HT_2 receptors are pronociceptive in nature and when stimulated or upregulated will increase the occurrence of migraine attacks. This leads to the creation of a hyperalgesic state that is propagated by additional medication use.[17] In a controlled study monitoring the 5-HT_{2A} receptor binding in platelets, which is reflective of the activity of 5-HT_{2A} receptors in the CNS, an increased number of the 5-HT_{2A} receptors were shown in patients with medication overuse, offering evidence of upregulation of this receptor subtype. The number of receptors decreased after withdrawal of the offending medication.[18] In another study, depressed serotonin levels were noted with long-term analgesic overuse, and these levels increased after cessation of the medication. The reverse is also true, as increased serotonin levels in blood have been shown to accompany a decrease in the number of headache days.[16] Interestingly, the changes in these receptor populations take about 3 months to resolve after cessation of the offending medication, which is about the same length of time it takes for detoxification from medication overuse.

Cellular adaptation to exposure of analgesics is the fourth possible explanation for MOH. During medication use, it is believed that cells actually adapt to the constant exposure to analgesics. Cell membrane transduction is involved in the packaging and transporting of proteins and other components of receptors, messengers and cell membranes. In a landmark study, abnormal platelet membrane transduction was found as a marker in MOH.[18] This marker was also found to normalise after the offending medication was stopped. It is believed that patients with migraine have an inherently abnormal membrane transduction process, which, under the influence of long-term analgesics or other abortive headache medications, becomes significant, impairing modulatory neurons in the CNS, thereby allowing the development of chronic daily headache. During medication overuse, there is a described state of refractoriness to prophylactic agents that may be due to this exacerbation of inherent abnormal membrane transduction in certain areas of the CNS.[18]

Lastly, changes in the periaqueductal grey matter may also help to explain what occurs in the brain during MOH. A recent study demonstrated increased iron deposition in the periaqueductal grey matter of chronic daily headache patients, indicating tissue damage or dysfunction caused by free oxygen radicals. This iron deposition is indicative of possible free radical injury due to repeated migraine attacks. Not surprisingly, the highest iron levels were found in patients with the longest duration of headache burden, and in patients taking the largest quantities of medication.[19] Unfortunately, there are anywhere from 10% to 50% of patients who do not revert to intermittent headache patterns after detoxification. A possible explanation for this is that protracted long-term use of the offending medication and/or poorly controlled headache over time may lead to irreversible oxidative changes in the peri-

aqueductal grey matter. These changes may explain chronic daily headache that does not respond to medication cessation, as well as the clinical entity of chronic migraine without medication overuse.

Some debate is likely to continue regarding the pathophysiology of MOHs, as there are multiple facets to this complicated medical problem. For now, MOH should be viewed as a complex syndrome of head pain, which, at least initially, has a component that is caused or propagated by frequently used medication.

3. Clinical Presentation

Researchers and headache specialists have noted certain characteristics of MOH that may serve as clues to the diagnosis. For patients with MOH, the associated symptoms of migraine tend to become less prominent over time, with many patients experiencing much less nausea, vomiting, photophobia and phonophobia during their daily headache attacks. Also, the intensity of each individual headache may be highly variable, which contributes to uncertainty of the patient and physician regarding treatment. In many instances MOH patients will resort to using symptomatic medications in an anticipatory fashion, thereby further increasing the amount of medication they take, unwittingly contributing to the vicious cycle of MOH. The withdrawal of symptomatic medications may result in an immediate worsening of headache, but the general rule is that of subsequent improvement over time after cessation of the offending medication. Importantly, medication overuse can make headaches refractory to prophylactic medication, a frustration that may baffle patients and physicians alike.[20] Finally, frequent use of opioids and sedative medications will, in many cases, produce dependence or outright addiction, which can complicate the clinical care of that patient. All of these different characteristics of MOHs make the diagnosis and clinical management extremely difficult for many clinicians.

MOH is a difficult diagnosis to make for several reasons. One reason is that, while the diagnosis may be suspected clinically, it can only be confirmed in retrospect and this may take ≥3 months to demonstrate. Once the offending medication has been withdrawn for a protracted period (usually at least 12 weeks) and the patient experiences relief, then and only then may the diagnosis be confirmed. Furthermore, MOH has not been demonstrated in clinical trials and probably never will be because of ethical issues. Therefore, the characterisation of MOH for clinical purposes must be done based on observation of patterns of headaches and medication use. However, it is important to note that MOHs are only seen in migraineurs, and not in non-migraineurs.[21]

The 2004 revision of the IHS diagnostic criteria for MOH[11] are demonstrated as follows.

- MOH diagnostic criteria: (a) very frequent headaches (≥15 days/month); (b) minimum dose of medication required ≥10 days/month (2–3 treatment days every week) taken both frequently and regularly; (c) headache has developed or worsened during medication overuse; and (d) headache resolves or reverts to its previous pattern within 2 months after discontinuation of medication.
- Ergotamine-overuse headache: intake of ergotamine ≥10 days/month on a regular basis for ≥3 months. Minimum dose cannot be defined because of variability in bioavailability of various products.
- Triptan-overuse headache: intake of triptans (any formulation) on a regular basis ≥10 days/month on a regular basis for ≥3 months. Triptan-overuse headache tends to have features of migraine more consistently (unilateral, pulsatile, moderate-to-severe pain associated with nausea, vomiting, photophobia and phonophobia). Limited evidence suggests progression to chronic headache may occur sooner with triptans than with other acute migraine medications.
- Analgesic-overuse headache: intake of simple analgesics on a regular basis ≥15 days/month for >3 months.
- Opioid-overuse headache: opioid intake ≥10 days/month for >3 months regularly. Patients

Table I. Risk of medication overuse headache from symptomatic headache medication

High	Moderate	Low
Aspirin (acetylsalicylic acid)/paracetamol (acetaminophen)/caffeine	Triptans	Long-acting NSAIDs
Butalbital-containing combination analgesics	Simple analgesic	Tramadol
Opioids	Short-acting NSAIDs	Dihydroergotamine mesilate

who overuse opioids have the highest relapse rate after withdrawal.

- Combination medication-overuse headache: intake of combination medications for ≥10 days/month for >3 months. The combination medications usually implicated are simple analgesics combined with opioids, butalbital and/or caffeine.
- Headache attributed to other medication overuse: regular overuse for >3 months of a medication other than those described earlier.
- Probable medication-overuse headache: overused medication has not yet been withdrawn or medication use has been ceased in the last 2 months, but headache has not so far resolved or reverted to its previous pattern.

It is noted that MOH can be facilitated by virtually any medication that may be used for headache symptomatic relief, including triptans (see table I). In a recent study, Limmroth et al.[22] retrospectively reviewed the medication history of patients who had been successfully detoxified from MOH. Their results showed that the mean duration of medication overuse was the shortest for triptans (1.7 years), longer for ergot alkaloids (2.7 years) and longer still for analgesics (4.8 years). The monthly dosage of medication was also lowest for triptans (18 doses), higher for ergot alkaloids (37 doses) and highest for analgesics (114 doses).[22] Despite these data, MOH due to triptans is not encountered with great frequency in clinical practice. Perhaps the clinical occurrence of triptan-associated MOH is not seen very frequently because of the high cost of the medication or managed care prescription quantity restrictions for the drug class. At any rate, it appears that all triptans should be considered potential inducers of rebound headaches. It remains to be seen whether the triptans with longer half-life distinguish themselves from the drugs with shorter half-life with regard to MOH, although some suggest this may be the case.[7]

For now, in the US, the greatest problem appears to be associated with barbiturate containing combination analgesics and over-the-counter caffeine-containing combination analgesics. This may be partially due to their easy availability and low expense. There does not seem to be any difference in propensity among the simple analgesics to cause MOH, but caffeine-containing combination products seem to be more highly associated with MOH. Conversely, NSAIDs, especially the long-acting ones, are less likely to be associated with MOH.[23] Perhaps the most significant factor in the development of MOH is the lack of widespread awareness and understanding of the entity on the part of clinicians and patients.

4. Differential Diagnosis

Before starting the treatment it is pertinent to differentiate MOH from chronic migraine (figure 2).

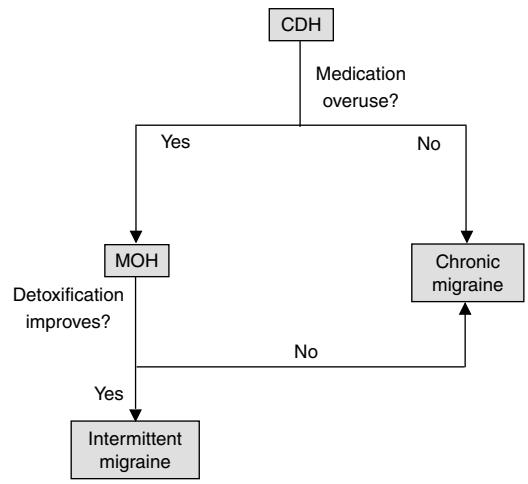

Fig. 2. How to approach chronic migraine vs medication overuse headache (MOH)? **CDH** = chronic daily headache.

5. Management

It is clear that the principal approach to management of MOH is built around the cessation of the overused medication. Typically, without discontinuation of the offending medication, improvement is almost impossible to attain. Furthermore, any programme that facilitates discontinuation of the offending medication, without introducing another agent known to cause MOH when used long-term, will lead to improvement. A three-faceted approach to treating patients with MOHs includes a transition or bridging programme, use of nonpharmacological measures and initiation of a prophylactic medication.

Patients frequently have a great deal of trepidation when it comes to stopping pain medication, even though they may know that their headache syndrome is propagated by that medication. Patients' insecurity, fear and pill-taking behaviours, as well as the fact that the pain may seem unbearable in the early process of withdrawal, makes it difficult for them to stop taking the medication. Therefore, a transition or bridging regimen is usually necessary, entailing pharmacological and nonpharmacological support, with the goal of increasing the patient's tolerability of the withdrawal process without putting them at risk of rebounding from another pharmacotherapeutic agent or agents.

5.1 Transitional Pharmacological Support

A number of these transitional regimens have been described in the headache literature. The best described, but perhaps the most difficult to implement would be the use of parenteral dihydroergotamine mesilate. In an inpatient trial, 109 patients with chronic daily headache were studied.[24] Fifty-five of these patients were given intravenous dihydroergotamine mesilate every 8 hours until headache-free, while the other 54 patients were given intravenous diazepam for the same amount of time. Of the 55 patients in the dihydroergotamine mesilate category, 36 were rebounding from their headache medications, the vast majority of these from analgesics, with the remaining few rebounding from ergotamine and diazepam. The patients were given dihydroergotamine mesilate 0.5–1mg with metoclopramide 10mg intravenously every 8 hours. A smaller dose of dihydroergotamine mesilate 0.3mg was used if the larger dose was not tolerated. Once headache-free, the patients were sent home with dihydroergotamine mesilate 2mg suppositories or dihydroergotamine mesilate 1mg subcutaneous injections to be used for abortive treatment. For prophylaxis, propranolol 60mg was given two times daily, and the patients were scheduled for follow-up in 10 days. Forty-nine of the dihydroergotamine mesilate-treated patients were headache-free within 48 hours, while only seven of the diazepam-treated patients reached this state in 3–6 days. At 16 months, 39 of the dihydroergotamine mesilate-treated patients still reported good results.[24]

Using a low dose of tizanidine along with a long-acting NSAID or cyclo-oxygenase (COX)-2 inhibitor given daily is another successful bridging programme that is a little easier to implement. In an outpatient study, 87 MOH patients were started on tizanidine 2mg (which was titrated up to 16mg if needed) at bedtime, along with a morning dose of a COX-2 inhibitor or NSAID (such as piroxicam 20mg, rofecoxib 25mg, naproxen 500mg, ketoprofen sustained release 200mg or celecoxib 200mg) for 12 weeks. These patients were given either oral dihydroergotamine mesilate or triptans to relieve acute headaches. If the patients were frequent triptan users at baseline, they were presumed to be rebounding from their triptans. Those patients were given dihydroergotamine mesilate only as abortive therapy. Sixty-nine percent of patients following this regimen had complete cessation of daily headaches at 12 weeks, with reversion to intermittent headache in observed in almost all patients.[25]

Another transitional regimen reported to be successful includes the use of daily doses of triptans (sumatriptan, naratriptan) for up to 10 days to bridge the immediate withdrawal period.[26,27] In one study, sumatriptan 25mg was given orally three times daily for 10 days or until the patient had been headache-free for 24 hours.[26] Twenty-six MOH patients with average daily headache duration of 8.2 years were studied. These patients were rebounding from short-

acting NSAIDS, paracetamol (acetaminophen)/aspirin (acetylsalicylic acid)/caffeine tablets, ergot alkaloids, paracetamol, butalbital/paracetamol/caffeine tablets, butalbital/aspirin/caffeine tablets, opioids, and isometheptene/dichloralphenazone/paracetamol tablets. Prophylactic medications were started in conjunction with sumatriptan, and patients were followed up for 6 months. By 1 month 58% of the patients showed improvement, and a 69% success rate was reported at 6 months.[26] In this programme, regular use of sumatriptan was discontinued after the initial 10 days so as to avoid a triptan rebound effect.

In 1999, Sheftell et al.[27] described three patients who successfully withdrew from analgesics supported by oral naratriptan. The first patient was rebounding from butalbital and isometheptene compounds, NSAIDs, ergotamine and sumatriptan. She had been hospitalised and treated with parenteral dihydroergotamine mesilate with good results, but relapsed shortly after discharge. Naratriptan 2.5mg each morning was started, with an additional dose used later in the day during menses. She showed a vast improvement at her 4-month follow-up visit, and was continuing on this regimen at the time of reporting this study. The second patient was using 20 butalbital compound tablets per day, and had been doing so for approximately 1 year. He had also been admitted to the hospital for parenteral dihydroergotamine mesilate administration and had done well for a while, but then relapsed. He was started on naratriptan 2.5mg twice daily, and was pain-free at his 2-month follow-up. The third patient was using butalbital compound tablets 4–6 days per week and had been experiencing daily headaches for years. She was given naratriptan 2.5mg to take in the morning, with an additional dose in the afternoon if needed. This patient has had sustained relief for 4 months at the time of reporting this study.[27]

Another study used combinations of different agents including amitriptyline, dexamethasone and sumatriptan to treat MOH.[28] Twenty patients with daily headache for an average of 8.5 years, taking an average of 19.7 analgesic-containing tablets per week, were treated with amitriptyline 25 mg/day for 1 week, which was then increased to 50 mg/day. They also received dexamethasone 4 mg/day intramuscularly for 2 weeks and were given sumatriptan 6mg subcutaneously, and aluminium and magnesium hydroxide tablets on an as-needed basis. The patients were seen in the clinic once a week for 2 weeks, then every month for 6 months. At 6 months, 85% of the patients had abstained from analgesic use and had a decrease in the intensity and frequency of headaches. Bonuccelli et al.[28] believed this study showed that the long-term administration of amitriptyline may reset the antinociceptive system.

It should be emphasised that if triptans are used in the transitional period, it is necessary for the patient to be instructed to diminish or stop the triptan after the initial period of withdrawal so that they do not develop MOH secondary to the triptan. If the patient is rebounding from a triptan, then they should be treated with short-term dihydroergotamine mesilate therapy. It has been hypothesised by some researchers that the long-acting triptans (i.e. frovatriptan and naratriptan) are less likely to cause MOH.[29]

5.2 Nonpharmacological Support

Nonpharmacological measures are also an important step in withdrawing a patient from medication. It is very common for headache patients to have disturbances in mood and function, and behavioural methods of pain management are often required. While patients are being detoxified from their offending medication, they will need lots of support (not just from the physician and staff, but from family members as well), reassurance, counselling, education, relaxation therapy, physical therapy and biofeedback.

Biofeedback-assisted relaxation is one measure that is fairly easy to implement, and could help any headache patient. A recent study showed that medication overuse patients treated with both biofeedback and pharmacological methods showed greater sustained improvement than those treated with pharmacological methods only.[30] Sixty-one MOH patients were hospitalised for treatment and had the offending medication discontinued. They were then

given a treatment regimen of parenteral medications. On day 6, prophylactic medication was started with one of the following: flunarizine 5–10mg, pizotifen 2–3mg, propranolol 40–80mg or amitriptyline 10–30mg. Of the 61 patients, 19 also received biofeedback-assisted relaxation treatment that began in the hospital, and was continued on an outpatient basis. In the hospital, patients attended a total of eight sessions per week, with the first four sessions devoted to progressive muscle relaxation training. Electromyographic biofeedback was started at session five and was used to further direct relaxation treatment. Upon discharge, these patients were sent home with a biofeedback audiocassette tape, with instructions to use this tape on a daily basis. After 3 years, the patients who had also used biofeedback had fewer headache days per month (11.2 vs 18.1 days), lower relapse rate (10% vs 20%) and lower analgesic use per month (4.9 vs 20.1 tablets) compared with those who received pharmacological treatment only. This study showed that the patients who received biofeedback training in addition to a medication treatment regimen clearly fared better than those who only received medication, and further illustrates that MOH patients need a comprehensive treatment strategy. The treatment components used in this study were discontinuation of the offending medication, introduction of appropriate prophylactic medication, close medical supervision, acquisition of alternative self-regulatory coping skills, provision of therapist contact and support over time.[30]

Finally, the best treatment of all is prevention. Physicians should screen every patient presenting with chronic daily headaches for medication overuse. In order to do this, they need to be educated about MOH. Patients should also be educated on analgesic overuse and MOH. Even if they are not currently having daily headaches, they should be made aware of MOH so that they do not begin to overuse medications.

5.3 Prophylactic Medication for Migraine

Once a bridging programme has been initiated, it is time to consider prophylactic medication. If possible, the preventive medication should be tailored to the patient. Medications should be considered based on their adverse effect profiles, the patient's comorbid conditions and specific indications for the medication. For instance, if a patient has depression or fibromyalgia, it may be a good idea to try a tricyclic antidepressant. It is important to start the medication at a low dose, thus keeping the possibility for adverse effects low, and then gradually increase the dose until efficacy has been reached, if needed. Realistic expectations need to be discussed with the patient, and they should also be informed that it may take 3–6 weeks for the medication to take effect and may take even longer in a medication overuse patient, as the medication is not likely to work until the rebound process has ceased.[15]

There are many classes of prophylactic medications to choose from. Table II lists some common choices, as well as the starting daily dosages. These medications may need to be titrated up as needed, and as tolerated.

Sometimes patients do not respond to prophylactic medications and, when this happens, other factors should be considered. If the optimal dose of a medication has been tried without response, a different category of medication may be needed. It is also possible that some exacerbating features could have been missed. For example, caffeine overuse, dietary or lifestyle triggers, psychosocial factors or other medications that the patient is taking could trigger headaches. If the patient has a comorbid psychiatric illness, this may need to be treated first, before the chronic daily headache can resolve.[15]

There are a few other options to consider when treating a patient with MOH. A corticosteroid burst may be appropriate (methylprednisolone dosepak or triamcinolone 40–60mg intramuscularly) in the hope of minimising the withdrawal headache in the very critical first few days of medication cessation.[28] Patients rebounding from barbiturate-containing preparations should not be stopped 'cold turkey'; they should be slowly withdrawn from the offending medication. Alternatively, the offending medication may be stopped abruptly with the addition of phenobarbital 60–120 mg/day and institution

Table II. Prophylactic medications for migraine and their initial daily dosages

Tricyclic antidepressants
Nortriptyline 10mg
Amitriptyline 10mg
Doxepin 10mg
Protriptyline 5mg
Selective serotonin reuptake inhibitors
Fluoxetine 20mg
Nefazodone 150mg
Paroxetine 10mg
β-Adrenoceptor antagonists
Propranolol 20mg
Nadolol 20mg
Calcium channel antagonists
Verapamil 120mg
Flunarizine 5mg
Antiepileptic drugs
Valproate semisodium 125mg
Topiramate 25mg
Zonisamide 100mg
Gabapentin 300mg
Oxcarbazepine 150mg
NSAIDs
Ketoprofen 200mg
Meloxicam 15mg
Piroxicam 20mg
Cyclo-oxygenase-2 inhibitors
Celecoxib 200mg
Valdecoxib 20mg
Rofecoxib 25mg

of one of the bridging programs mentioned earlier. The phenobarbital may be gradually weaned off at a later date. Sometimes drug dependency issues are best handled in a short-term inpatient facility with the assistance of an experienced addictionologist. It may also be appropriate to refer a MOH patient to a headache clinic or neurologist if difficulty with treatment is encountered.

6. Conclusion

In summary, the 'best treatment' of MOH includes several aspects, but awareness and prevention are the most important. Prevention and early intervention are critical, and prophylactic medications should be initiated for patients having ≥2 headache days per week. Anticipatory medication use should be discouraged (but not early migraine abortive treatment), and migraine-specific therapy should be considered as early as possible in the natural history of the patient's headaches. Patients should also work on reducing their headache risk factors.

MOH accounts for the majority of chronic daily headache, with success rates in treating these patients ranging from 58% to 89%. These headaches are believed to be caused by a serotonin modulation abnormality, with under-treatment of headache possibly causing irreversible damage to descending antinociceptive brainstem pathways. Withdrawal of analgesics or migraine abortive medications will result in improvement in most patients, with help from a bridging or transitional scheme. Long-term outcomes suggest a one-third recurrence rate over 5 years.[31]

Perhaps the best management advice would be to raise awareness and strive for prevention of the syndrome in the first place. This may be accomplished by setting limits to abortive medication use, improving utilisation of prophylactic medication, behavioural modification and nonpharmacological approaches to headache control earlier in the natural history of migraine, without resorting to medication overuse.

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