Chapter

Medication Overuse Headache

Dhruv Bansal, Pritesh Pranay and Fayyaz Ahmed

Abstract

Medication overuse headache (MOH) is defined in the latest ICHD-3 criteria as a secondary headache caused by worsening of a pre-existing headache (usually a primary headache) owing to overuse of one or more attack-aborting or pain-relieving medications. MOH can be debilitating and results from biochemical and functional brain changes induced by certain medications taken too frequently. Various risk factors some modifiable, other non-modifiable (Multiple Gene Polymorphisms) have been hypothesised in MOH. Psychiatric co-morbidities in MOH are noticeably (anxiety and depression) found to be co morbid disorders by more than chance. This has to be managed effectively along with treatment strategies for MOH for efficacious response to withdrawal treatment. Ample literature and clinical evidence shown in prospective trials, that withdrawal therapy is the best treatment for MOH. The mainstay of MOH treatment is not only to detoxify the patients and to stop the chronic headache but also, most likely, to improve responsiveness to acute or prophylactic drugs. Studies advocating prophylactic treatment with good response to mainly topiramate and OnabotulinumtoxinA do exist, less prominent for prednisolone, however, not recommended for every patient. Management may be complex and must be done via MDT approach with involvement of specialists when needed along with incorporating adequate treatment of acute withdrawal symptoms, educational and behavioural programs to ensure patient understanding of the condition and compliance. There are arguments on either sides of inpatient and outpatient withdrawal for MOH patients dependent heavily on the individual circumstances i.e. patient's motivation, the duration of the overuse, the type of overused drugs, possible previous history of detoxification failures and co morbidities. Treatment trials are still required to determine for clinicians the best evidence-based approach for helping these patients break their headache cycle.

Keywords: medication overuse, chronic migraine, chronic daily headaches, rebound headaches, painkillers

1. Introduction

Medication-overuse headache (MOH) is defined by the International Classification of Headache Disorders (ICHD) as a headache in patients with primary headache disorders occurring on ≥15 days per month for >3 months, that is induced by overuse of medications taken as symptomatic treatment for acute headaches.

In ICHD-3, chronic headache syndromes are described by professional consensus as headache disorders that share traits with pre-existing headache syndromes, happen for a specific duration of time (at least three months in Chronic tension-type headache (CTTH), Chronic migraine (CM); or at least 12 months in Chronic trigeminal autonomic cephalalgia (TAC)) and have an extra time-rule

(e.g.headache days per month in CTTH and CM, or the absence of remissions for greater than three months in TAC's).

MOH occurs if the number of days of acute medicine taken for headache per month exceeds a threshold level [1] i.e., 15 or more days for simple painkillers and 10 or more days for triptans, opioids and combination analgesics. The diagnosis of MOH as per ICHD-3 is given as follows:

2. Diagnosis of medication-overuse headache

2.1 According to the ICHD-3 beta diagnostic criteria1, each of the criteria A–C have to be fulfilled for the diagnosis of medication overuse headache

A

- Headache on ≥15 days/month
- Pre-existing headache disorder

B

- Overuse of acute and/or symptomatic headache medications for >3 months*C
- Not better represented by any other ICHD-3 diagnosis

*Regular consumption of tablets on ≥10 days/month for ergotamines, triptans, opioids and mixture analgesics and on ≥15 days/month for paracetamol (also recognised as acetaminophen), acetylsalicylic acid and NSAIDs.

As ICHD defines MOH as a secondary headache, one must identify the primary headache disorder associated with it for example episodic or chronic migraine. The classification identifies further sub-groups based on the substance misused (e.g., 2.2.1.2 triptan-overuse headache). Many sufferers take more than one drug [2] or are overusing combination analgesics and/or multiple drugs at different times which are identified in the classification as headache attributed to numerous drug classes (2.2.5). The comprehensive classification of MOH from ICHD-3 is given here:

2.2 International classification of headache disorders third edition (ICHD-3) criteria for medication-overuse headache (MOH)

2.2.1 Medication-overuse headache (MOH)

A. Headache happening on ≥15 days/month in a affected person with a pre-existing headache disorder

B. Regular overuse for > three months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache

C. Not better represented by means of any other ICHD-3 diagnosis.

2.2.1.1 Ergotamine-overuse headache

A. Headache satisfying standards for 2.2.1 Medication- overuse headache

B. Regular consumption of ergotamine on ≥10 days/month for >three months.

2.2.1.2 Triptan-overuse headache

A. Headache satisfying criteria for 2.2.1 Medication- overuse headache

B. Regular consumption of one or greater triptans, 1 in any formulation, on ≥10 days/month for >3 months.

2.2.1.3 Non-opioid analgesic-overuse headache

2.2.1.3.1 Paracetamol (acetaminophen)-overuse headache

A. Headache satisfying criteria for 2.2.1 Medication- overuse headache

B. Regular consumption of paracetamol on ≥15 days/month for > three months.

2.2.1.4 Non-steroidal anti-inflammatory drug (NSAID)- overuse headache

A. Headache satisfying criteria for 2.2.1 Medication- overuse headache

B. Regular consumption of one or extra non-steroidal anti- inflammatory drugs (NSAIDs) (other than acetylsalicylic acid) on ≥15 days/month for >3 months.

2.2.1.4.1 Acetylsalicylic acid-overuse headache

A. Headache satisfying criteria for 2.2.1 Medication- overuse headache

B. Regular intake of acetylsalicylic acid on ≥15 days/month for >three months.

2.2.1.5 Other non-opioid analgesic-overuse headache

A. Headache satisfying criteria for 2.2.1 Medication- overuse headache

B. Regular intake of a non-opioid analgesic other than paracetamol or non-steroidal anti-inflammatory tablets (including acetylsalicylic acid) on ≥15 days/month for> three months.

2.2.2 Opioid-overuse headache

A. Headache satisfying criteria for 2.2.1 Medication- overuse headache

B. Regular consumption of one or more opioids on ≥10 days/month for >3 months.

2.2.3 Combination-analgesic-overuse headache

A. Headache fulfilling standards for 2.2.1 Medication- overuse headache

B. Regular consumption of one or more combination-analgesic medicines on ≥10 days/month for >three months.

2.2.4 Medication-overuse headache attributed to combination drug classes not individually overused

A. Headache satisfying standards for 2.2.1 Medication- overuse headache

B. Regular intake of any aggregate of ergotamine, triptans, non-opioid analgesics and/or opioids on a total of ≥10 days/month for >3 months besides overuse of any single drug or drug type alone.

2.2.5 Medication-overuse headache attributed to unspecified or unverified overuse of numerous drug classes

A. Headache satisfying standards for 2.2.1 Medication- overuse headache

B. Both of the following: 1. regular consumption of any mixture of ergotamine, triptans, non-opioid analgesics and/or opioids on ≥10 days/month for >3 months

2.2.6 Medication-overuse headache attributed to different medication

A. Headache fulfilling standards for 2.2.1 Medication- overuse headache

B. Regular overuse, on ≥10 days/month for >3 months, of one or greater medicines other than these described above, 1 taken for acute or symptomatic cure of headache

3. Background and pathophysiology

MOH was first identified in 1951 in relation to overuse of ergotamine [3]. It was in 1984 that relationship between analgesic consumption and exacerbation of headaches were recognised with improvement in headaches on stopping them [4]. It was given the name as 'drug-induced headache' in the first classification of the headache disorders (ICHD-1) [5]. The ICHD-2 described this as 'medication-overuse headache' in 2004. The condition was said to be probable as the definitive diagnosis was only given following reduction of headache days 2 months after withdrawal of the overused medication [6]. The 2006 modification broadened the definition [7] by abolishing the required improvement after discontinuation and this has persisted in both ICHD-3 beta and ICHD-3 criteria [8].

4. Clinical characteristics

The headache of medication overuse is that of the primary headache disorder [9]. Patients with migraines who overuse triptan will observe increase in the frequency of pre-existing headaches to almost daily in frequency that exacerbates intermittently and more so if a dose of triptan is missed. The patient gets in a vicious circle with increasing headaches proportional to the triptans consumed. In the same way patients with tension-type headache will report exacerbation of their featureless headaches [9]. A few people are able to differentiate between their primary headaches and a constant dull and diffuse headache that they attribute as MOH. It has been observed that MOH develops more quickly with triptan and resolves more

quickly on withdrawal compared to combination and simple analgesics. This perception was confirmed by a French study [10].

The diagnostic criteria for MOH do not fully demonstrate the complexity of making the diagnosis of MOH. It is important to realise that medication overuse and MOH are two different entities that can have different implications and outcomes. Medication-overuse only signifies the number of days a person consumes painkiller and not necessarily a cause for on-going headache. In certain chronic painful conditions e.g., back pain; arthritis etc. there is medication overuse but no accompanying headache. Another observation has been that not every individual will develop headache with acute medication overuse [11]. It is not entirely clear why overuse worsens headache in some and not the others. Considered a secondary headache disorder, MOH should be identified by the type of medication being overused. The primary headache disorder must also be identified.

5. Prevalence and general risk factors

Majority of research have reported the general prevalence of MOH in the normal population to be 0.5–2.6% [12]. Higher rates have been seen in Russia (7.6%) [13] and Iran (4.6%), where medication overuse is a lot more frequent than in other nations [14]. However, no speculative reason or hypothesis has been provided for this.

The prevalence for MOH is 0.5–2.6% although it varies based on the availability of painkillers over the counter (OTC) and hence reported much higher in Russia (7.6%) and Iran (4.6%). The availability of OTC varies with codeine-based analgesics available in the UK, while barbiturates containing painkillers in the USA. Figures from the third world countries such as India and Pakistan are difficult to obtain considering all forms of painkillers are available over the counter with no definitive prescription system existing in the country. The prevalence is less common in adolescents (0.3%–0.5%) than adults observed in two epidemiological studies in Norway and Taiwan [15, 16]. Overall females are affected more than males (5:4) and those with chronic migraine have a very high incidence of medication overuse (11–70%) much more than observed in the general population [17].

6. Risk factors

On the basis of current scientific knowledge, all pain medications have the capacity to cause MOH. Dependency-like behaviour is most commonly seen in patients who overuse opioids, although it is also seen in patients overusing triptans [18–20]. Medication overuse was found to be an important risk factor for chronification of primary headaches [21]. A study in the USA found majority of patients with medication overuse were taking combined painkillers containing caffeine or opioids than simple painkillers [22]. They concluded that the risk of MOH is less with simple painkillers although this does not prove a link between overuse and a specific medication.

In a large prospective population-based study, Hagen et al. studied 25.596 patients who did not suffer from chronic daily headache at baseline but had MOH 11 years later (n = 201,0.8%) and the risk factors that were found to be associated with development of MOH: regular use of tranquillisers, combination of chronic musculoskeletal complaints, gastrointestinal complaints and hospital anxiety depression scale (HADS) score > =11, physical inactivity and smoking [23]. Migraine headaches was more strongly linked with MOH than non-migraine headaches and the risk was higher with those having a high frequency i.e., 7–14 days per

month, although it remains unclear as to whether this is because of a higher analgesic intake or frequent migraine attacks. Some of the non-modifiable risk factors for MOH include young age, female gender, family history of analgesic or substance overuse and low education level. Smoking and physical inactivity were other risk factors for MOH that were not associated with chronic daily headache without medication overuse suggesting that the two conditions are phenotypically different [23]. In 80% of patients with MOH, migraine is the underlying primary headache disorder [24] and majority of remaining patients have tension-type headache or more rarely post traumatic headache [25–27].

7. Main risk factors for MOH

RISK FACTOR OR (95% CI)
Demographics
AGE(<50 years) 1.8(1.3–2.4)
Female sex 1.9(1.4–2.6)
Low degree of education 1.9(1.2–3.0)
Complaints that were self-disclosed
Chronic Musculoskeletal problems 1.9(1.4–2.7)
Gastrointestinal problems 1.6(1.1–2.2)
Depression or Anxiety (HADS score ≥ 11) 4.7(2.4–9.0)
Medications
Tranquillisers 5.2(3.0–9.0)
Aspirin 0.5(0.3–0.9)
Ibuprofen 0.7(0.5–1.0)
Opioids 2.3(1.3–3.9)
Lifestyle
Smoking 1.8(1.2–2.5)
Physical Inactivity 2.7(1.2–6.3)
Metabolic Syndrome 5.3(1.6–24.6)
High daily Caffeine intake 1.4(0.8–2.5) (>540 mg versus ≤240 mg)

Figure shown are derived from population-based studies [23] in Norway [15, 16], the USA [22] and China.CI, confidence interval; HADS, Hospital Anxiety and Depression; MOH, medication-overuse headache; OR, odds ratio.

8. Pathophysiology

The pathophysiology of MOH remains unclear. The fact that patients with migraine or tension type headache are more likely to develop MOH may mean that the underlying mechanism for MOH could be related to a brain with these primary headache disorders [28]. Patients with cluster headache (another primary headache disorder) do not develop MOH in spite of regular painkillers unless they also suffer from or have a family history for migraine [29]. It is possible that a genetic risk

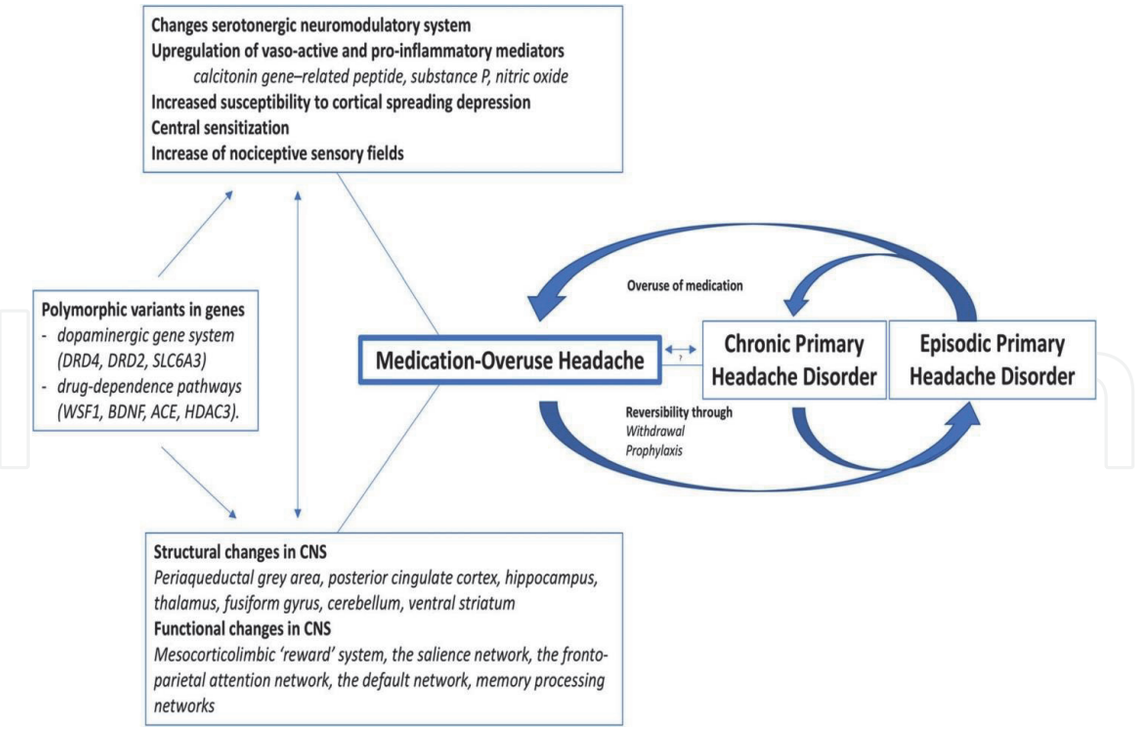

Figure 1.
Current perception of the pathophysiology of medication-overuse headache (MOH) [30]. The understanding on the pathophysiology of MOH entails transformation from and reversion to primary headache disorders, displaying changes in physiological processes, functional connectivity, and structural changes of the central nervous system, in patients with underlying genetic predisposition. Abbreviations: MOH: Medication-overuse headache; CNS: Central nervous system (figure obtained from article 'medication overuse headache: A widely recognised entity amidst on-going debate' (open access)) [30] (http://creativecommons.org/licenses/by/4.0/).

factor in a migrainous brain could make the person more susceptible to MOH (**Figure 1**).

9. Genetic risk factors

9.1 Angiotensin-converting enzyme polymorphism

The renin-angiotensin system is well known for blood pressure control. Angiotensin II can cause increase in blood pressure and require Angiotensin-converting enzyme (ACE) for its formation from Angiotensin I. It also has a role in regulating neural plasticity [31] and its interaction with monoaminergic synaptic transmission contributes towards dependence behaviour [32]. Polymorphism (insertion/deletion) in the gene that encodes ACE may well play a role in the condition particularly the D/D genotype [33].

9.2 Brain derived neurotrophic factor polymorphism

Brain-derived neurotrophic factor (BDNF) has been linked to substance overuse [34, 35]. Certain BDNF genotypes (non G/G) [36, 37] are associated with increased consumption behaviour for the painkillers than others.

9.3 Serotonin transporter polymorphism

Many affective disorders such as depression, anxiety and substance abuse are associated with variants of SLC6A4 that encodes for SERT (Serotonin transporter) [38, 39].

Patients with SLC6A4 variants that have MOH are extremely difficult to respond to withdrawal therapy and have a high relapse rate following withdrawal [40].

9.4 Catechol-O-methyltransferase (COMT) polymorphism

COMT is an enzyme that metabolises catecholamines such as dopamine, adrenaline and nor-adrenaline and influences pain modulation [41]. Certain genotypes of COMTSNP (rs4680 and rs6269) have a low rate of relapse following withdrawal of analgesics than others indicating its role [40].

10. Pain medications role

All forms of painkillers are associated with MOH although certain classes of analgesics can cause the condition much quicker than others. For example patients with triptan overuse develop MOH much quicker than opioids, ergotamine and combination analgesics [42]. In the same way triptans withdrawal responds much quicker and has a much lower relapse rate. This indicates that the underlying pathophysiological mechanism may be medication specific. Platelets of those with migraine and medication overuse have higher 5-HT2 receptors than those without medication overuse [43]. The research has also shown a reduction of serotonin levels and a reduction of the primary endogenous cannabinoids, anandamide and 2-acylglycerol in those with Migraine and medication overuse compared to those without it [44]. Research has also shown that those with MOH have a high consumption of other medicines such as nasal decongestants, eye drops, laxatives, tranquillisers and sleeping drugs.

11. Activation of trigeminovascular system

One of the pathways for head pain in migraine is activation of the trigeminal primary afferent neurons innervating the intracranial and dural blood vessels. Stimulation of these vessels have shown to induce pain similar to migrainous headache [45, 46], although the exact underlying mechanism that activates the trigeminovascular system remains unclear. Among possible explanations include the spreading depression with subsequent neuronal depolarisation and activation of the trigeminovascular system and release of chemicals that produce neurogenic inflammation around the intracranial and dural blood vessels. Chronic use of paracetamol has shown to be associated with an increased activation of the nociceptive pathway involved in headache. Hence it is proposed that prolonged exposure to analgesics may lead to MOH via up-regulation of neural regulators of vasodilation and neurogenic inflammation. It has been known for some time that sustained systemic delivery of morphine exposure increases CGRP content in dorsal root ganglion neurons [47, 48]. Plentiful studies documenting continuous, persistent exposure of rats to triptans for a period of days was shown to result in a marked increase in the numbers of trigeminal ganglion cell bodies expressing CGRP and a modest increase in expression of substance P.

Imaging studies have demonstrated functional [49–51], structural [52, 53] and metabolic [54] adjustments of the central pain network in patients with MOH. In a voxel-based morphometric study [55] of individuals with MOH, grey matter volume was increased in the thalamus, midbrain, and striatum, and reduced in the frontal regions [52] that resolved in sufferers who show clinical improvement of

MOH [53]. Another study indicated that grey matter volume of the orbitofrontal cortex estimated response to medication-overuse treatment [56].

Functional MRI studies have shown MOH associated hypoactivitiy in certain cortical region including the right supramarginal gyrus, right inferior and superior parietal area that constitute the lateral pain system [49, 50]. This was further demonstrated in PET study where hypometabolism was also demonstrated in thalami and cerebellar vermis [54]. These changes resolved at the end of the overuse except in the orbito-frontal cortex [54]. It is to be emphasised that such changes are not unique to MOH and can be seen to some extent in other headache disorders (migraine) and pain conditions [55].

12. CO-morbidities

Co- morbidity is defined as the presence of one and more additional conditions co-occurring with a primary condition. Psychiatric co-morbidities in MOH are noticeably frequent and have been studied extensively since the earliest literature of patients with MOH [57]. MOH and mood disorders such as anxiety and depression are thought to be co morbid disorders by more than chance [57–60].

In the Norwegian BIMOH study, (double-blind pragmatic cluster randomised controlled trial carried out among 50 general practitioners in Norway) sixty MOH patients and 40 population controls were included. The MOH patients had significantly higher headache disability and anxiety scores than the population controls. Hospital Anxiety and Depression Scale (HADS) scores were collected in patients with MOH (before and after a brief intervention) and controls. MOH patients were found to show significantly higher HADS scores for anxiety [61].

In the European and Latina "COMOESTAS" trial, (694 patients with MOH from six centres had been included, of whom 492 completed the study) in a seven-month cohort study. The study used Hospital Anxiety and Depression (HAD) scoring and found more than half (56%) of MOH patients had anxiety while 40% suffered from depression [62]. Similar findings were seen in the 'Eurolight' trial conducted in ten European countries. The association was considerably stronger in contrast to a group of patients with migraine without overuse [63]. A study on Sodium Valproate in Medication Overuse Headache (SAMOHA) found substantially higher number of patients with moderate to severe anxiety compared to those with episodic migraine or healthy controls [64]. Moreover, MOH are more likely to have one or more psychiatric co-morbidities and some authors found a third of patient with clinically relevant obsessive–compulsive disorders (OCD) [65].

Subclinical OCD may be an additional risk factor for chronic headaches [64, 65]. MOH can also be associated to substance-related disorder spectrum, moreover since MOH and dependence share common neurobiological pathways; noticeably MOH patients do not share common personality characteristics seen with drug addicts [66, 67].

In a Chinese cohort, an association was found between MOH and metabolic disturbances namely obesity and hypertension was shown in female patients [68]. A Danish cross-sectional analysis confirmed an association between MOH and those metabolic derangements (smoking, physical inactivity and obesity, although causality could not be proven [69]. Lastly, patients with chronic headache and MOH present with a high prevalence of sleep symptomatology [70].

13. Treatment

There is adequate evidence that withdrawal therapy is the best treatment for MOH. The aim is not only to break the cycle of regular analgesic consumption but to

improve responsiveness to both acute and prophylactic medications [71]. The following questions remain under discussion among headache experts:

1. Should preventive treatments be commenced at the time or following withdrawal of the analgesics?

2. Should the withdrawal be abrupt or gradual?

3. Should this be done as out-patient or done through in-patient admission.

13.1 Preventive treatment before or following withdrawal

There is argument on both sides and researchers are divided with respect to whether prophylactic medications are given at the time of withdrawal or after withdrawal. Study conducted in Germany found all patients should be offered a non-drug treatment and in the majority, additional preventive drug therapy. Taking evidence from randomised controlled trials into consideration, topiramate or OnabotulinumtoxinA should be offered as a treatment for this condition. About 50% of patients with chronic migraine and medication overuse will respond and show a significant reduction in headache days [72]. Similar results were seen with OnabotulinumtoxinA treatment in a large prospective study from Hull, UK. OnabotulinumtoxinA significantly reduced the headache and migraine days whilst increasing headache-free days and the benefit is equally seen in those with or without co-existing medication overuse. We acknowledge the value of analgesic withdrawal although we recommend that this can be achieved alongside preventive treatment [73].

No study has ever compared abrupt withdrawal with tapered withdrawal in prospective randomised trials; therefore, no formal evidence-based recommendation or guideline can be deduced. However, the majority of headache specialists consider drug withdrawal to be more effective if done abruptly than gradual [74–76].

13.2 Abrupt or gradual withdrawal

Abrupt withdrawal is recommended for overuse of triptans, ergots, paracetamol, aspirin and NSAIDs and could be done in outpatients. Most patients have a less protracted suffering and resolution of withdrawal symptoms is much quicker. Those on opioids, barbiturates, benzodiazepines and combination analgesics a tapered withdrawal is more appropriate as withdrawal symptoms are more severe. Patients are warned that their headaches may get worse before getting better and symptoms of nausea, vomiting, sleep disturbances, palpitations, restlessness and anxiety are troublesome for a week to 10 days and in some cases may persist for up to 4 weeks before showing improvement. The duration of worsening is shorter with triptans (4.1 days) than ergotamine (6.7 days) and NSAID (9.5 days) [77].

A study in Italy of 137 patients aiming to study the effectiveness of an educational strategy (advice to withdraw the overused medication/s) with that of two structured pharmacological detoxification programmes in patients with complicated medication overuse headache (MOH) plus migraine concluded that inpatient withdrawal is significantly more effective than advice alone or an outpatient strategy in complicated MOH patients [78]. Another multicentre study (N = 376) on MOH subjects in four European and two Latin American centres comparing in-patient or out-patient detoxification programme with optional prophylaxis and a follow up for 6 months concluded equal effectiveness of both strategies with or

without prophylaxis [79]. Carlsen et al. (N = 72) in a prospective, outpatient study randomised patients to two groups with one taking no analgesic or acute migraine-medication and the other restricted to no more than two days of painkillers per week. Patients were followed up for 12 months. The primary outcome was percentage reduction in headache days per month after 6 months. The outcome was better in complete withdrawal and more patients reverted to episodic migraine in this group [80].

13.3 Inpatient or outpatient

The decision has to be taken on individual circumstances that include the type of overused medication, length of the overuse, patients' motivation and history of previous detoxification failures and presence of co-morbidities. Out-patient withdrawal is more suited to simple analgesic, brief overuse period and highly motivated patients [81]. Evidence in favour of inpatient withdrawal comes from an observational study from Austria showing statistically significant improvement of quality of life, depression and anxiety at 6-month follow-up [82]. Alternatively a study conducted in Milan has shown that direct comparison between inpatient withdrawal and outpatient withdrawal treatment showed that both methods were effective and revealed a significant reduction in headache days per month after 12 months and a decrease in the scores of migraine disability without superiority of one method [83].

There is no standardised accepted protocol for both in-patient withdrawal. Every clinic use their own method that does include intravenous dehydration, complete stoppage of oral painkillers and treatment with anti-emetics and intramuscular painkillers as and when required with or without steroids [84–88].

With respect to corticosteroids, there is low evidence for change in various headache outcome measures (i.e. use of rescue medication, days with severe or moderate headache, days without headache, headache days, and frequency of headache) [89, 90]. There is plentiful literature evidence to suggest that majority of patients will get worse before they get better [91].

14. Prophylaxis

Early and effective prophylaxis remains the key to avoid chronification of episodic migraine. As nearly two-thirds of patients with chronic migraine have co-existing medication overuse, the question remains largely unanswered whether prophylaxis should commence before or after analgesic withdrawal. There are arguments on both sides and the jury remains out as to which approach is better. Some argue that patients with previous failure would show a good prophylactic response following withdrawal [92]; others recommend prophylaxis at the same time as withdrawal [93].

There are open-label studies showing improved outcome for using valproic acid and topiramate in patients with chronic daily headache with medication overuse. A double-blind study on topiramate in patients with chronic migraine and medication overuse showed reduction of migraine days per month significantly higher in the topiramate group (−3.5 vs. 0.2 in placebo $p < 0.05$), although side effects were considerably higher in the topiramate group (75% versus 37% in placebo) [94]. This supported using topiramate use before analgesic withdrawal although the reduction on headache days were not large enough to change it to episodic form. A similar observation was observed in another topiramate study where the reduction in

migraine days per month was significantly higher for topiramate than placebo (6.4 versus 4.7) [95].

In a Danish study consisting of 335 patients with MOH where abrupt detoxification was initiated, the headache frequency was reduced by 67% in migraine patients and by 37% in those with combined migraine and tension-type headache after a 2-month observation period without prophylactic medication [92]. There are randomised controlled trials to show that with patients affected by chronic migraine and MOH suggest the use of onabotulinumtoxinA and topiramate without early discontinuation. However, the quality of the data is limited due to the fact that it is based on post hoc analysis [96]. Two further studies in the states have shown improvement in headache days in patients with chronic migraine and medication overuse treated with onabotulinumtoxinA and concluded that withdrawal prior to prophylaxis may not be required in all patients with MOH [97].

15. Bridging therapy

Steroids and NSAID have so far been studied but their effectiveness remains inconclusive. Few studies have used a short course of steroids as bridging treatment with different outcomes. The first study from Brazil used a short course of oral prednisolone in an out-patient setting. They studied 400 patients with daily headaches for longer than 6 months. Symptomatic medications were stopped suddenly and prednisone was initiated in tapering doses during 6 days, followed by the introduction of preventive treatment. The study found eighty-five per cent of the patients experienced a reduction in headache frequency and no patients presented severe attacks during the first 6 days. 10 day follow up, 46% of the patients experienced at least 2 days without headache and 58% less intense attacks [98]. Another German randomised, placebo-controlled, double-blind study showed efficacy of prednisone for the treatment of withdrawal symptoms in patients with MOH (N = 20). The total number of hours with severe or moderate headache within the first 72 and 120 h was significantly lower in the prednisone group. The results show that prednisone might be effective in the treatment of medication withdrawal headache [99]. Another randomised, double-blind, and placebo controlled Norwegian study negated the use of steroids as prophylaxis in MOH. Patients (N = 100) were randomly assigned to prednisolone or placebo pills for six days. Study concluded prednisolone has no effect on withdrawal headache in unselected patients with chronic daily headache and medication overuse [100]. A brief period of prophylaxis with naproxen 500 mg bd for 10–20 days has been recommended based on experience [101], there are other doses used for different durations [102, 103].

16. Prognosis of withdrawal treatment

As a rule of thumb, overuse of acute treatment can lead to a poor prognosis of chronic headache and lower quality of life by itself [104]. The outcome for MOH patients withdrawing from their acute treatments has been reported in multiple literature citations. An accepted endpoint as mentioned in many studies for good response to therapy is a ≥ 50% reduction from baseline headache frequency and/or headache index. Successful withdrawal was found in around 50–70% of MOH patients after 1 year [105–113]. Managing to retain full withdrawal after 1 year was found to be a good predictor for long-term success [114, 115].A successful withdrawal leads to a better response for prophylactic treatment, even in patients with little improvement in headache frequency [116].Tension-type headache have

documented to have a higher relapse risk [105–107, 117, 118]. Patients who kept overusing medication in the long-term had a poor response to withdrawal therapy and had a higher frequency of chronic headache [114]. Risk factors for short term relapse (1 year) were: high number of acute treatments, smoking, alcohol consumption and return to overused drugs [119]. Patients withdrawn from triptans have a lower relapse risk, while combined drug therapy had a higher relapse rate [106, 118, 120]. Drugs with codeine, low self-reported sleep quality and high self-reported bodily pain are probable predictors for poor outcome after 1 yr. [113]. A prospective study from Germany followed 96 patients with MOH of which 75 completed 4 years. 26 patients (31%) relapsed within first six months and a total of 32 (41%) in the first year. The following three years only two more relapsed totalling 34 (45%). The authors concluded that most of the patients who relapse do that in the first year (94%) and the long-term success is dependent on the type of primary headache and the type of overused painkiller [121].

Most recent evidence on the most effective treatment strategy comes from an Open-label, randomised clinical trial to compare 3 treatment strategies for MOH [122] which was conducted at the Danish headache Centre, Glostrup form October 2016 to June 2019. Random assignments (1:1:1 allocation) to 1 of the 3 outpatient treatments consisted of [1] Withdrawal Plus Preventive treatment [2] Preventive treatment without Withdrawal, or [3] Withdrawal with optional Preventive treatment 2 months after Withdrawal. The Primary outcome was change in the headache days per month after 6 months. Of 120 patients, 102 completed the 6 month follow-up and the headache days per month were reduced by 12.3 (95% CI, 9.3–15.3) in the withdrawal plus preventive group, by 9.9 (95% CI,7.2–12.6) in the preventive group, and by 8.5 (95% CI 5.6–11.5) in the withdrawal group (P = 0.20). In the withdrawal plus preventive group, 23 of 31 patients (74.2%) reverted to episodic migraine, compared with 21 of 35 (60%) in the preventive group and 15 of 36 (41.7%) in the withdrawal group (P = 0.03). Moreover, 30 of 31 patients (96.8%) were cured of MOH in the withdrawal plus preventive group, compared with 26 of 35 (74.3%) in the preventive group and 32 of 36 (88.9%) in the withdrawal group (P = 0.03). These findings correspond to a 30% (RR, 1.3; 95% CI 1.1–.16) increased chance of MOH cure in the withdrawal plus preventive group compared with the preventive group (P = 0.03), therefore based on these findings, withdrawal therapy combined with preventive medication from the start of the withdrawal is recommended as the preferred management for MOH.

17. Conclusion

MOH is a common and worldwide problem with a prevalence of 1% in the general population but accounts for nearly 11 to 70% in those with chronic daily headaches, often under-recognised and un treated correlates with a significant negative impact on the patient's quality of life. Opiates and combination analgesics carry an increased risk for MOH needs to be recognised and accepted as per literature. Among the multiple risk factors for the development of MOH, some are noted to be modifiable and require MDT approach for attention and action. Anxiety and depression are the most common co morbidities, and up to approximately 50% of patients show dependence-type behaviours like tolerance or inability to control pain medication usage.

Treatment trials are still required to determine for clinicians the best evidence-based approach for helping these patients break their obnoxious headache cycle (?), but intervention will require patient counselling, detoxification, and prevention therapy. The future needs to be tailored to include a focus on increased awareness of

MOH for the general population and primary prevention strategies for patients and providers. To achieve success in treatment, it is essential that the primary care provider, nurse practitioner, pharmacist, and hospital doctors openly communicate with the neurologist when MOH is suspected.

Author details

Dhruv Bansal[1], Pritesh Pranay[1] and Fayyaz Ahmed[1,2*]

1 Hull University Teaching Hospitals NHS Trust, Hull Royal Infirmary, Anlaby Road Hull HU3 2JZ

2 Hull York Medical School

*Address all correspondence to: fayyaz.ahmed@hey.nhs.uk

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