FROM DRUG AND THERAPEUTICS BULLETIN

Management of medication overuse headache

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Headache is one of the most frequent reasons for medical consultation in both general practice and specialist neurology clinics.[1] Prescribed and over-the-counter medications are taken to alleviate headaches, but may be used incorrectly.[2] In particular, use of some drugs both frequently and regularly can have a paradoxical effect, causing headaches rather than relieving them, and leading to medication overuse headache (MOH).[3] Such overuse is a common cause of frequent headache. Here we review MOH and its management.

About MOH

The *International Classification of Headache Disorders*, 2nd edition states that for a diagnosis of MOH, all of the following criteria must be present:

- headache occurring on 15 or more days per month;
- regular overuse for more than 3 months of one or more acute/symptomatic treatment drugs (ergotamine, triptans, opioids or combined analgesic medications [typically simple analgesics plus opioids or caffeine] on 10 or more days per month; or simple analgesics alone or any combination of ergotamine, triptans and analgesic opioids on 15 or more days per month); and
- development or marked worsening of headache during medication overuse.[4]

The preceding headache problem

Headaches may be primary (eg, migraine, tension-type headache, cluster headache) or secondary (eg, associated with trauma, subarachnoid haemorrhage, intracranial neoplasm, infection or the use or withdrawal of substances such as alcohol or drugs).[3 5] MOH occurs only in patients with a history of primary headache.[6 7] It is most likely to affect patients with migraine and/or tension-type headache,[7 8] but can also arise in association with cluster headache, particularly if there is a personal or family history of migraine or regular headache.[9]

Epidemiology

Studies from various countries suggest that the prevalence of MOH is around 1% of adults and 0.5% of adolescents (aged 13–18 years) in the general population[10]; around 25–64% in those attending tertiary care headache centres[7 11]; and 90% in patients experiencing chronic daily headache.[12] MOH is most prevalent in those aged around 40–50 years and affects about three times more women than men.[8 13]

Which drugs cause MOH and how?

Overuse of any acute or symptomatic headache treatment can cause MOH.[14 15] The mechanism by which overuse of NSAIDs (including aspirin), paracetamol, codeine or dihydrocodeine can cause the condition probably involves changes in neural pain pathways.[1] Combination analgesics containing caffeine and codeine may encourage development of MOH as a consequence of their addictive properties.[16] Ergot is very slowly eliminated from the body and readily accumulates if taken more than twice a week; it is thought that this may lead to chronic activation of central 5-hydroxytryptamine (5-HT) receptors, leading to their downregulation, reducing the activity of central serotonergic pain-reducing systems and thereby increasing headache.[1 17] Triptans do not accumulate but chronic use probably results in a similar downregulation of 5-HT receptors.[1 17]

Many patients with MOH use very large quantities of medication (eg, 35 doses per week; six different drugs); however, much lower quantities can induce MOH (eg, ergot or triptans taken on 10 or more days per month).[1] It is the frequency of doses rather than the absolute quantity of drug consumed that is important; lower daily doses carry a greater risk of causing MOH than larger weekly doses.[1]

A study of 96 patients with MOH found that the delay between frequent intake of the medication and onset of daily headache was shortest for triptans (around 1.7 years), longer for ergots (around 2.7 years), and longest for simple analgesics (around 4.8 years).[13]

Similarly, the number of doses associated with development of MOH was lowest for triptans (18 single doses per month), higher for ergots (37 single doses per month) and highest for analgesics (114 single doses per month).[13]

Clinical features of MOH

The type of headache that develops in MOH varies; for example, patients with underlying migraine who overuse triptans report a migraine-like daily headache (unilateral pulsating headache with autonomic disturbances) or marked increase in frequency of migraine attacks.[13] Those with tension-type headache who overuse combination analgesics generally develop a constant, pressing, diffuse (ie, tension-type) daily headache.[13] Those with cluster headache generally develop a migraine-like daily headache. MOH is often present and at its worst on waking in the morning.[1] Patients with MOH develop tolerance (reduced efficacy of medication and need for higher doses to achieve analgesic effect) and withdrawal symptoms (rebound headache), which are similar to signs of dependence on drugs traditionally classified as addictive.[18]

In a study of 200 patients fulfilling the criteria for MOH, 79% had additional symptoms, including "asthenia" (weakness), nausea, restlessness, irritability, depression, concentration difficulties and memory problems.[19] Patients with MOH who have had pre-existing tension-type headache are more likely to have co-morbid psychiatric or mood disorders than those with chronic tension-type headache without medication overuse.[20]

Diagnosis of MOH

The diagnosis of MOH is made from the patient's history and clinical presentation. Among the pointers to check for are use of analgesics, including for reasons other than headache; use of over-the-counter as well as prescription drugs; acute medications becoming less effective; and escalation to using more drugs. Investigations are generally not required to diagnose MOH.[21] Assessment should also search for possible complications of regular drug intake (eg, recurrent gastric ulcers, anaemia).[13]

Prevention of MOH

Patients with primary headaches should be informed about the risk of medication overuse, and be encouraged to keep a diary to monitor headache frequency and drug use.[22] Prescriptions for acute migraine should be monitored closely to prevent overuse.[22] Medication for acute headache should be restricted in frequency: use of triptans to below 10 treatment days per month and analgesics to below 15 days per month; migraine drugs containing caffeine, opioids, or tranquillisers should be avoided.[23] Early migraine prophylaxis, with medical or behavioural treatment or acupuncture, aims to reduce the use of acute medication and may therefore help to prevent MOH.[23 24] A Cochrane systematic review, including data from two randomised controlled trials, involving a total of 241 patients, found that acupuncture and prophylactic drug treatment of migraine produced a similar reduction in analgesic use.[24]

Aims of management for MOH

The objectives in managing patients with MOH are to reduce the frequency and/or severity of headache; to reduce consumption of acute medication (and possibly dietary caffeine); to improve responsiveness to acute and preventive medication; and to alleviate disability and improve quality of life.[22] These are addressed by the following means:

- stopping the overused medication;
- managing withdrawal symptoms;
- reviewing and reassessing the underlying primary headache disorder; and
- preventing relapse.[1]

Stopping the overused medication

General principles of withdrawal

Guidelines from the British Association for the Study of Headache state that patients with MOH fare better if they are motivated and understand that their "treatment" is likely to be causing their frequent headache.[1] They should be forewarned that withdrawal initially aggravates symptoms (eg, withdrawal headache, which may be accompanied by nausea, vomiting, tachycardia, sleep disturbances, restlessness, anxiety, and nervousness).[1 13] Withdrawal should be planned in advance to avoid unnecessary lifestyle disruption, and done under the supervision of a doctor or headache specialist nurse.[1] It may be necessary to arrange absence from work for 1–2 weeks.[1] The guidelines also recommend a diary to record symptoms and medication use during withdrawal, and that good hydration should be maintained.[1]

Most drugs causing MOH can be stopped abruptly; the Scottish Intercollegiate Guideline Network suggests that opioids and benzodiazepines should be withdrawn gradually.[14] As with other drugs that produce a withdrawal syndrome, gradual reduction in caffeine intake may be preferable to abrupt withdrawal.[22 25]

How drug type affects outcome

The duration of withdrawal headache and associated autonomic symptoms varies depending on the types of medication that have been overused. For example, in a study involving 98 patients with MOH undergoing withdrawal as inpatients, the mean duration of withdrawal headache was 4.1 days for triptans; 6.7 days for ergots; and 9.5 days for analgesics.[17] Similarly, the number of days with associated symptoms (eg, nausea, vomiting, sleep disturbance) was lower for triptans than for either ergots or analgesics (1 day vs. 2.5 or 2.2 days, respectively). Overall improvement occurs within 7–10 days when the causative drug is a triptan; after 2–3 weeks when it is a simple analgesic; and after 2–4 weeks when it is an opioid.[1]

How headache type affects outcome

The initial type of headache appears to affect outcome. Evidence for this comes from a retrospective cohort study based on headache diaries from 337 patients with probable MOH, treated by withdrawal of the drug responsible without any other headache treatment for 2 months.[8] In the study, the response in patients with a previous diagnosis of migraine was better than in those with both migraine and tension-type headache (median reduction in headache frequency 67% vs. 37%) or tension-type headache alone or other type of headache (no reduction).

When withdrawal fails

The mean success rate for withdrawal therapy (defined as at least a 50% reduction in headache days) over 1–6 months is around 72% (based on data from 17 studies, involving a total of 1 101 patients).[21] Factors that affect the likelihood of successful withdrawal include:

- the duration of regular drug intake (a longer duration is associated with a worse prognosis);
- the specific drug overused (eg, withdrawal from triptans has a better prognosis than other drugs);
- the underlying headache type (eg, tension-type headache plus combined tension-type and migraine have a higher relapse risk than other headache types);
- low self-reported sleep quality (associated with a worse prognosis); and
- high self-reported bodily pain (associated with a worse prognosis).[23 26]

Any lack of commitment from the patient to the withdrawal process should be addressed by greater efforts to inform and support him/her; evidence of psychological dependence may require referral for cognitive behavioural therapy (CBT).[1] In either of these scenarios, there is a potential role for counselling, but this has not been formally assessed in MOH.[1]

Sometimes, withdrawal of overused medication does not lead to recovery, with chronic daily headache persisting more or less unabated. This requires a review of the diagnosis and is an indication for specialist referral.[1]

Managing withdrawal symptoms

Treatment of vomiting

Patients with vomiting during withdrawal can be treated with an antiemetic (for example, metoclopramide, domperidone).[13]

Use of NSAIDs

Withdrawal headache can be managed by offering the patient naproxen (250 mg three times daily or 500 mg twice daily), to be taken regularly or as symptoms require.[1 27] Some specialists recommend that naproxen is prescribed for a course of 3–4 weeks, and not repeated, or taken for a 6 week course (three times daily for 2 weeks, twice daily for 2 weeks, once daily for 2 weeks) and then stopped.[1] There are no published studies to support or refute these strategies, and manufacturers of NSAIDs have pointed out that this is an unlicensed indication.

Use of corticosteroids

Studies on the management of withdrawal headache using prednisolone have produced mixed results.[28 29]

A randomised placebo-controlled trial, involving 100 patients with probable MOH undergoing drug withdrawal (with the first 3 days in hospital), assessed prednisolone with an initial dose 60 mg daily, tapered down over 6 days.[28] There was no difference between the prednisolone and placebo groups on a combined measure of the intensity and number of days with headache in the first 6 days after withdrawal.

A much smaller randomised placebo-controlled trial, involving 20 patients undergoing inpatient withdrawal for MOH, showed that withdrawal headache was reduced in the group taking prednisolone 100 mg daily for 5 days (number of hours with severe or moderate headache in the first 72 hours of withdrawal, the primary outcome measure: 18.1 vs. 36.7 on placebo, p=0.031).[29]

Use of triptans

In a non-blinded trial, 150 patients with MOH, who were abruptly withdrawing symptomatic medication as outpatients, were randomised to one of three strategies (in addition to receiving "orientation" and education before withdrawal): naratriptan 2.5 mg twice daily for 6 days; prednisolone 60 mg daily tapered over 6 days; or no regular medication.[30] There was no significant difference between the groups in the proportion of patients having severe, moderate, mild or no headache over the first 6 days. Fewer patients on naratriptan or prednisolone reported withdrawal symptoms over the first 6 days (68.6% and 81.8%, respectively, vs. 97.5% on no treatment, p=0.003 for difference between the three groups). Compared with the no-treatment group, fewer patients on naratriptan or prednisolone required symptomatic medication (17.2% with naratriptan vs. 46.4%, p=0.007, or 20.5% with prednisolone, p=0.011).

Addressing the primary headache

The patient should be reviewed after 2–3 weeks to ensure withdrawal has been achieved.[1] Recovery continues slowly for weeks to months and follow-up is necessary.[1] Most patients revert to their original headache type within 2 months.[1]

Symptomatic relief

Overused medications (if needed) may be reintroduced for symptomatic relief after 2 months, with explicit restrictions to ensure that the frequency of use does not usually exceed 2 days per week on a regular basis.[1]

Prophylaxis for primary headache

In patients whose headache stops responding to prophylactic treatment while overusing symptomatic medications, the prophylactic efficacy may return after successful withdrawal of the overused medication.[14]

Recent studies suggest that topiramate offers a modest benefit in reducing headache frequency, even in the absence of drug withdrawal.[15 31 32] The rationale for the use of this drug is based on the fact that patients with chronic headache and medication overuse have upregulation of cerebral cortex activity; the effect of topiramate is to inhibit neuronal activity.[32] However, topiramate also has potential unwanted effects (eg, cognitive impairment, depression) which may limit its use.

Preventing relapse

Definition of relapse into medication overuse

Relapse is defined as frequent use of any acute headache medication on more than 15 days per month for at least 3 months after recovery from previous MOH.[33]

What are the risks for relapse?

Most relapses occur within the first year after withdrawal.[34] For example, a prospective 4-year follow-up

study of 96 patients with MOH treated with drug withdrawal found that 31% of participants relapsed within the first 6 months after withdrawal; 41% had relapsed by 1 year and 45% by 4 years after withdrawal.[34] Reported risk factors for relapse include tension-type headache or a combination of migraine plus tension-type headache, rather than migraine alone; longer duration of migraine with more than 8 headache days per month; lower improvement after drug withdrawal; greater number of previous preventive treatments tried; male gender; and intake of combined analgesic drugs (eg, combination of one or more NSAIDs with caffeine or codeine).[34-36]

How can relapse be prevented?

Patients with risk factors for relapse should be informed about these and monitored regularly, and combination drugs should be avoided; many patients require extended support to prevent relapse.

The primary headache must be treated using a different approach rather than medication.[22] Massage, acupuncture and behavioural therapies (eg, CBT, stress reduction, biofeedback training) may help.[22] Amitriptyline can also help to alleviate associated symptoms of MOH, particularly mood and sleep disorders; however, evidence on this is limited[37] and the drug may have troublesome unwanted effects.

Prophylactic treatment can be introduced and is more likely to be effective in the absence of MOH; it should follow the standard recommendations of titration to an effective tolerated dose and continuation for 3-6 months.[1 38]

Comparison of management strategies

A non-blinded randomised controlled trial comparing strategies to manage medication withdrawal involved 120 patients with migraine, probable MOH and low medical needs (ie, not requiring specific additional medical interventions, with exclusion criteria such as no overuse of opioids, barbiturates or benzodiazepines; no significant physical or psychiatric co-morbidity; no previous experience of detoxification).[39] Participants were allocated to one of three strategies: advice to withdraw the overused medication; outpatient detoxification with advice, prednisolone (tapered down from 60 mg daily over 8 days) and personalised prophylaxis; or inpatient detoxification with advice, prednisolone (as above), prophylaxis, parenteral fluid replacement and antiemetics (intravenous metoclopramide 10 mg twice daily). Treatment was considered successful if, 2 months after starting withdrawal, the patient had no headache or reverted to episodic headache and to an intake of symptomatic medication on fewer than 10 days per month. There was no difference in outcome between the three treatment groups, with around 75% of patients in each being treated successfully.

In a non-blinded study, 56 patients with MOH were randomised to one of three treatment strategies for 5 months: outpatient detoxification without prophylaxis; prophylactic treatment without detoxification; or neither new preventive medication nor direct advice to stop medication (the control group; after 5 months, these patients were offered a choice of withdrawal or prophylactic treatment).[40] The reduction in headache days per month at month 3 (the major primary outcome measure) did not differ significantly between groups (a reduction of 4.1 days in the detoxification group, 7.2 days in the prophylactic treatment group and 1.6 days in the control group).

When to refer

UK guidelines suggest that patients with MOH should be referred to a neurologist if attempted withdrawal in primary care fails.[14 41] Patients who also have psychiatric co-morbidity or dependence behaviour should have these conditions treated additionally; referral to a psychiatrist or clinical psychologist may be necessary.[14]

Conclusion

Medication overuse headache (MOH) is common, and should be suspected in a patient with increasing headache frequency, taking triptans, ergots, combined analgesics or opioids on 10 or more days a month, or analgesics or NSAIDs on 15 or more days a month, over a number of months. The type of headache may be tension-type daily headache and/or migraine-like attacks. Associated symptoms can include nausea and gastrointestinal symptoms, irritability, anxiety, depression, concentration difficulties and memory problems.

Measures to prevent the development of MOH include restricting consumption of the medications commonly responsible, and avoiding dietary caffeine and drugs containing caffeine or codeine. Early prophylaxis, either medical or behavioural, may be appropriate in patients with frequent headaches.

Once MOH has developed, management involves education of the patient on the cause, as well as drug withdrawal. Amitriptyline or topiramate may help reduce withdrawal symptoms, but there are few data to support these interventions and their unwanted effects should be borne in mind. Patients should be reviewed following drug withdrawal and, if frequent headaches persist, specialist referral should be considered. Patients with frequent headache not taking prophylaxis may find previously ineffective prophylactic drugs become effective once MOH has been diagnosed and the patient treated; acupuncture is an alternative. Patients should be followed up regularly to prevent relapse, which is most likely in the first year after withdrawal.

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ANSWERS TO ENDGAMES, p 983. For long answers go to the Education channel on bmj.com

STATISTICAL QUESTION

P values

Answers *a* and *b* can be concluded; answers *c* and *d* cannot.

Fig 1 Haematoxylin and eosin staining showing the presence of sulphur granules (arrow) surrounded by inflammatory cells characteristic of *Actinomyces* colonies

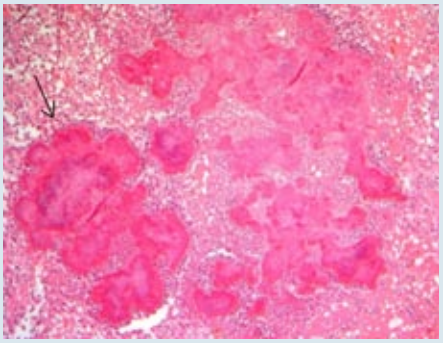
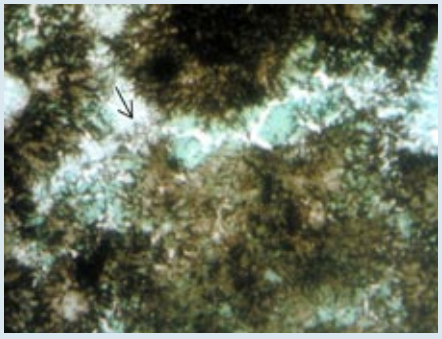


Fig 2 Grocott's silver methenamine staining showing clusters of short filamentous branching organisms (arrow)



PICTURE QUIZ

Haemoptysis, weight loss, and pulmonary shadowing in a smoker

1 The diagnosis is thoracic actinomycosis, caused by the anaerobic bacterium *Actinomyces israelii*. Haematoxylin and eosin staining showed characteristic sulphur granules (fig 1) and Grocott's silver methenamine staining showed short filamentous branching organisms typical of *Actinomyces* (fig 2).
2 The diagnosis can be confirmed by isolation of *Actinomyces* on culture of clinical specimens and by identification of the bacterium on histopathological examination.
3 High dose intravenous penicillin followed by oral penicillin for six to 12 months is the treatment of choice.