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Headache from medication overuse

Headaches induced by medication overuse and by other trigger substances

This is a group of [secondary headache disorders](#) related to ingested or inhaled substances, both therapeutic and toxic. The types of headache attributable to medication and other ingested or inhaled substances (or their withdrawal) include:^[1]

- Headaches caused by acute substance use or exposure (including toxins, drugs and food substances).
- Medication-overuse headache (MOH) – previously called rebound headache, drug-induced headache or medication-misuse headache.
- Headaches as an adverse effect of chronic medication – eg, combined oral contraception, hormone replacement therapy.
- Headaches caused by substance withdrawal – including therapeutic (non-analgesic) substances, opioids and caffeine.

Headache induced by acute substance use or exposure

These are acute headaches triggered by ingested chemicals including therapeutic substances, environmental toxins and food. Vasodilatation is often but not always thought to be the final common path to head pain. Examples include:^[1]

- Carbon monoxide poisoning:
 - Typically, mild headache without gastrointestinal or neurological symptoms with carboxyhaemoglobin levels in the range 10–20%.
 - Moderate pulsating headache and irritability with levels of 20–30%.
 - Severe headache with nausea, vomiting and blurred vision with levels of 30–40%.
 - With higher carboxyhaemoglobin levels (>40%) headache is not usually a complaint because of changes in consciousness.
- Immediate alcohol-induced headache. Alcohol can be a potent vasodilator in some people.^[2]
- Headache induced by food components and additives. Examples include phenylethylamine, tyramine and aspartame and monosodium glutamate.
- Immediate nitric oxide donor-induced headache: all nitric oxide donors (eg, amyl nitrate, erythritol tetranitrate, glyceryl trinitrate (GTN), isosorbide mononitrate or dinitrate, sodium nitroprusside, mannitol hexanitrate, pentaerythrityl tetranitrate) can cause headache, especially in people who experience migraine.
- Illicit substance misuse: cocaine, amphetamine, cannabis.
- Histamine.
- Calcitonin gene-related peptide (CGRP)-induced headache (this substance is a vasodilator produced by the body and implicated in the pathophysiology of migraine).^[3]
- Therapeutic non-analgesic medications: headache has been reported after use of a number of drugs. Common examples include: atropine, digitalis, disulfiram, hydralazine, imipramine, nicotine, nifedipine, nimodipine.

- Headache has been reported after exposure to a number of organic and inorganic substances. Commonly responsible substances include:
 - Inorganic compounds: arsenic, borate, bromate, chlorate, copper, iodine, lead, lithium, mercury, tolazoline hydrochloride.
 - Organic compounds: alcohols (long-chain), aniline, balsam, benzene (found in aerosols), camphor, carbon disulfide, carbon tetrachloride, chlordecone, ethylenediaminetetraacetic acid (EDTA), heptachlor, hydrogen sulfide, kerosene, methyl alcohol, methyl bromide, methyl chloride, methyl iodine, naphthalene, organophosphate compounds (parathion, pyrethrum).
- Treatment of these headaches involves avoidance of exposure to the cause.

Medication-overuse headaches (MOHs)

MOHs are the most common type of headache after tension-type headache and migraine.^{[4] [5]}

MOH should be considered when headache is present for 15 days or more per month and has developed or worsened while taking regular symptomatic medication.^[6]

Medication-overuse headache is defined as:^[1]

- Headache present on at least 15 days per month.
- Occurs in a person with a pre-existing primary headache disorder, most commonly migraine.
- Develops as a consequence of regular overuse of one or more drugs that can be taken for acute and/or symptomatic treatment of headache, for more than three months.

- The following drugs can cause medication-overuse headache:
 - Triptans, opioids, ergots or combination preparations on at least 10 days per month; **or**
 - Paracetamol, aspirin (or other non-steroidal anti-inflammatory drugs (NSAIDs)) or combinations of these on at least 15 days per month.
- It usually, but not always, resolves after the over-used medication is stopped.

Cause of medication-overuse headache

The exact pathophysiology of medication-overuse headache is not yet known. It is believed to be a complex interaction between medication overuse and individual susceptibility.

All simple analgesics and triptans are implicated. ^[7] ^[8]

- Opiate-containing medications cause problems most frequently. Codeine, both alone and in co-codamol, is probably the most common cause.
- Triptans are common culprits.
- Ergotamine.
- NSAIDs are less likely to cause MOH but can do so.
- For this reason ten days a month or more of triptan or opiate use is considered to be overuse, whereas fifteen days or more a month of paracetamol or NSAID use is considered as overuse.
- It is a combination of frequency AND regularity of medication use which seems to trigger the problem.
- The level of medication use which can lead to MOH is variable, but it is more likely to occur with use for more than three consecutive days per week for several weeks.

How common are medication-overuse headaches? (Epidemiology) ^[5]

- 1 year prevalence is estimated at 1-2%. ^[9]

- It affects up to 20–50% of people with chronic headache.^[9]
- Patients with migraine, frequent headaches, and those using opioid-containing medications or overusing triptans are at most risk.
- It is more prevalent in females than males (4:1).
- Prevalence is highest in the 40–49 year age group and appears to decrease with advancing age.
- Rebound headaches after analgesic use are common. Patients with frequent headaches (eg, [tension-type headaches](#) or [migraine](#)) self-medicate to pre-empt or cure headache and a vicious cycle occurs, of analgesia, rebound headache and more analgesia.
- Analgesic rebound headaches may be a common cause of post-traumatic headaches.^[10]

Medication-overuse headache symptoms and presentation

Diagnosis is made from the history and having a high level of suspicion:

- The patient has a pre-existing primary headache disorder and complains of headache on 15 or more days per month.
- Use of a headache diary may help clarify the diagnosis.
- Triptans, ergotamines, opioids or combination analgesics are taken on 10 days or more per month.
- Simple analgesics (paracetamol, NSAIDs) are taken on 15 days per month
- The headache is not better accounted for by another ICHD-3 diagnosis.
- Headache may vary in site, intensity and character.
- Headache may be worse early in the morning.
- There may be increasingly frequent and difficult-to-treat headache episodes, resulting in increased medication use.

Management of medication-overuse headaches

Patients usually have a long history by the time they consult a physician for care. Treatment is based on education, support, withdrawal treatment (detoxification), and prophylactic treatment. It also includes management of withdrawal headache.^[11]

Complete withdrawal of medication causes rebound worsening of headache. Withdrawal headaches typically last 2-10 days.^[12]

If there is another underlying headache process then after the withdrawal period headaches are reduced/returned to their previous pattern. After this a programme of preventative medication for the original, baseline headache management may be instituted.^[12]

Stages of management of medication-overuse headaches

Use of a diary to record symptoms and medication use during withdrawal is strongly recommended.^[6]

1. Explanation

- Management is dependent on gaining the patient's understanding and acceptance of the cause of their condition. It is no easy task to withdraw from medication for MOH and to withstand the rebound headaches that may follow this. The most important part of treatment is therefore for the patient to recognise and understand the cause of the headaches. A good diet, maintaining hydration, regular exercise and simple relaxation techniques should also be advised.
- Explain to the patient WHY they have developed MOH and WHAT to expect during and after withdrawal.
- A full headache history including details of the original headache pattern prior to the development of MOH (if there was one) will aid in this.

2. Advice on how to stop the overused medication(s)

- Advise the patient to stop taking all overused acute headache medication for at least one month.

- Withdrawal of ergots, triptans and non-opioid analgesics should be abrupt but it may be necessary to taper opioids and benzodiazepines in view of the risk of more serious withdrawal effects.
- Advise to keep a headache diary to record the frequency, duration and severity of headache and medication use during the withdrawal.
- Advise that rebound worsening of the headaches is likely to occur. Considerable willpower is needed to get through this period. Timing of the withdrawal should be planned according to the patient's lifestyle.
- For some patients, discontinuation and management of withdrawal will mean an inpatient stay.^[11]

3. Review

- Headache usually improves 1-2 weeks after drug withdrawal, but recovery may continue to up to 3 months.
- Patients may experience other withdrawal symptoms for example:
 - Nausea, vomiting, reduced appetite.
 - Hypotension, tachycardia.
 - Poor sleep.
 - Restlessness.
 - Anxiety.
- These withdrawal symptoms are more likely when withdrawing from opiates. Nausea may be managed with antiemetics.^[11]

4. Management of further headache

- Once the MOH has ceased then regular, preventative treatment for headache may be commenced if needed and appropriate
- There is some evidence that early introduction of prophylaxis may be more effective than the established method of withdrawing the overused medication until headaches cease.^[13]

- The choice of prophylactic medication will depend on the underlying primary headache disorder.
- Prophylactic agents which may be effective for frequent headaches persisting after the overused medication has been withdrawn:
 - Prednisolone, naratriptan, amitriptyline, sodium valproate, gabapentin, topiramate and propranolol have been shown to be effective in patients abruptly withdrawing symptomatic medication.
 - A tapered dose of prednisolone has been successfully used to cover the first days of analgesia withdrawal, to counteract withdrawal headaches.
 - The European Federation of Neurological Societies (EFNS).^[11] recommends inpatient withdrawal therapy for patients overusing opioids, benzodiazepine, or barbiturates.
 - EFNS recommends commencing prophylactic drug treatment at the first day of withdrawal therapy or even before.
 - The only drug with moderate evidence for prophylactic treatment in chronic migraine and medication overuse is topiramate up to 200 mg.
 - Corticosteroids (at least 60 mg prednisone or prednisolone) and amitriptyline (up to 50 mg) are possibly effective in the treatment of withdrawal symptoms.
 - Naproxen has been shown to reduce withdrawal symptoms in ergotamine-induced headache
- If acute headache medication is needed two months following drug withdrawal, it should be taken no more than two days per week to reduce the risk of developing further medication-overuse headache.

5. Further assessment

- Assess for any associated conditions, for example: stress, depression, anxiety, sleep disorders or other chronic pain conditions. Manage these appropriately.

- After withdrawal therapy patients should be followed up regularly to support their continued headache management and prevent relapse of medication overuse.
- Review patients 4-8 weeks after medication has been withdrawn, to confirm diagnosis and assess progress.
- Reinforce use of headache diary.
- Seek specialist advice if there is uncertainty about the diagnosis, atypical symptoms, previous repeated withdrawal attempts have been unsuccessful, there are significant comorbidities requiring specialist management.

Complications

There are a number of complications of medication-overuse headache, including:^[5]

- Stress, anxiety and depression.^[9]
- Insomnia and sleep disturbance.
- Reduced quality of life, affecting home, work and social life.
- Increased risk of transition from episodic to chronic migraine.^[9]
- Prolonged use of analgesics may cause a variety of side-effects - eg, on the kidneys and liver and, with use of NSAIDs, on the upper gastrointestinal tract.

Prognosis

Most patients improve after the withdrawal of the the overused medication.^[5] The effectiveness of preventative drug treatment for the underlying headache also improves.^[9]

- Early intervention is important because the long-term prognosis depends on the duration of medication overuse.
- The headache usually starts to improve within two weeks and the improvement then continues for weeks or even months.
- The patient usually reverts to their original headache type.
- MOH is associated with considerable long-term morbidity and disability.

Headache attributed to substance withdrawal

- This type of headache usually follows daily intake of a substance for longer than three months, which is then interrupted.
- The headache develops in close temporal relation to withdrawal of the substance.
- The headache resolves within three months of withdrawal.
- Common examples of substances causing withdrawal headaches include:
 - Opioid-withdrawal headache (this overlaps with MOH, above, but is included here as it also occurs if the opiate is being taken for another use - eg, drug dependency management - rather than for headache).
 - Oestrogen-withdrawal headache (includes the combined oral contraceptive pill).
 - Caffeine.
- Management is as for MOH, avoiding acute headache relievers for the withdrawal headache (risking development of MOH) and instead considering prophylaxis where needed.

Dr Mary Lowth is an author or the original author of this leaflet.

Further reading

- [Headache - assessment](#); NICE CKS, March 2022 (UK access only)

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