BMJ Best Practice

Medication overuse headache

Straight to the point of care

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Table of Contents

Summary

Medication overuse headache (MOH) is a chronic secondary headache condition attributable to overuse of acute medication(s) by an individual with a preexisting primary headache disorder (almost always migraine or tension-type headache). Patients with MOH suffer from a headache on more days than not.

MOH is a clinical diagnosis based on careful history-taking and use of a headache diary, together with a normal neurologic examination. No investigations are required unless there are red flag symptoms or signs that suggest the need to exclude an alternative, more serious cause for the headache.

Education and advice is the first step in managing MOH and may be sufficient on its own to resolve the condition. Withdrawal from the acute medication may be abrupt or tapered, depending on the class of medication that is overused. Symptomatic treatment for withdrawal symptoms may be needed.

Initiation of a preventive regimen that targets the underlying headache disorder is typically used to facilitate withdrawal from the overused medication. For patients with underlying migraine, the recommended options are topiramate, onabotulinumtoxinA, or calcitonin gene-related peptide (CGRP) antagonists. For those with underlying tension-type headache, amitriptyline is most commonly used.

Inpatient treatment may be necessary for patients who are withdrawing from opioids, barbiturates, or benzodiazepines.

Definition

Medication overuse headache (MOH), also known as rebound headache, is defined as a secondary headache occurring on ≥15 days per month in a patient with a preexisting primary headache disorder who has been overusing acute/symptomatic headache medication. Overuse is defined by use of the acute medication(s) on ≥10 or ≥15 days/month (depending on the medication class) for more than 3 months.[1] Most individuals affected by MOH have a history of episodic migraine and/or tension-type headache (TTH) as the underlying primary headache disorder.[2] [3] [4] The typical history is for the primary headaches to increase in frequency, accompanied by escalated intake of acute headache medications, leading to a transition from an episodic to chronic headache.[5] [6] This topic covers MOH where the patient has a background of migraine or TTH as their primary headache disorder.

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Epidemiology

The Global Burden of Disease study conducted in 2015 estimated that around 59 million people worldwide suffered from MOH.[7] Epidemiologic data suggest that the prevalence of MOH in the general adult population ranges from 0.5% to 2.6%.[8] Peak prevalence of MOH occurs in the 50-60 years age group.[9] Data for children and adolescents are limited, although schools-based studies in African and Asian nations found that prevalence increases from childhood (mean 0.4%) to adolescence (mean 1.2%).[10] It is estimated that approximately one third of chronic migraine patients experience MOH, and this prevalence can be even higher in specialized healthcare centers.[11] [12] [13] [14]

The Nord-Trøndelag Health Survey (HUNT), an 11-year longitudinal population-based cohort study conducted in Norway, found an incidence rate for MOH of 0.72 cases per 1000 person-years.[4] It identified female sex, anxiety or depression, low educational level, migraine as the preexisting headache type, and use of sedatives as risk factors for developing MOH.[4] Cross-sectional studies provide further evidence that MOH is more common among females, and individuals with lower education and income levels.[15] [16]

Among migraine patients, acute headache medication overuse is associated with factors including increasing age, smoking, presence of psychological symptoms, scalp allodynia, migraine symptom severity, and higher headache intensity.[2] Triptans are the most commonly overused drugs, followed by opioids and barbiturates, while MOH is less frequent among nonsteroidal anti-inflammatory drug (NSAID) users.[2] Furthermore, conditions such as depression, anxiety, or chronic musculoskeletal disorders may contribute to medication overuse.[4]

MOH imposes a significant healthcare burden and incurs substantial costs, primarily due to lost productivity and frequent use of healthcare resources among those affected.[9] [10]

Etiology

The etiology of MOH is complex and involves multiple factors.[10] MOH typically arises when certain conditions are met:

- The presence of a primary headache disorder (which is migraine and/or tension-type headache in up to 90% of cases but rarely can be cluster headache or posttraumatic headache)
- Frequent use of acute headache medications (e.g., simple analgesics, triptans, opioids, or ergot derivatives), excluding oral calcitonin gene-related peptide (CGRP) antagonists (also known as gepants).

Additionally, several comorbidities have been found to be associated with medication overuse, including anxiety, depression, obsessive-compulsive disorder, chronic musculoskeletal complaints, gastrointestinal problems, metabolic syndrome, and insomnia. These comorbidities can contribute to the development or exacerbation of MOH.[4] [9] [17] [18][19]

Pathophysiology

The pathophysiology of MOH is not completely understood. Genetic, behavioral/psychological, and sex-specific factors likely play a role.[10] MOH is not reported to occur in individuals who do not have an underlying headache disorder but overuse analgesia for other painful conditions, pointing to the hypothesis that MOH influences the neural pathways of the preexisting headache disorder.[10] Pathophysiologic mechanisms are thought to include altered descending pain modulation and central sensitization.[10]

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Potential genetic factors involved in MOH include insertion or deletion polymorphisms in ACE (encoding angiotensin-converting enzyme), mutations in BDNF (brain-derived neurotrophic factor), and polymorphisms in COMT (catechol-O-methyltransferase) and SLC6A4 (serotonin transporter).[20] These genetic factors are associated with abnormalities in metabolic pathways, serotonergic or dopaminergic transmission, and drug dependence.

Behavioral and psychological factors may also play a part in development of MOH. Individuals with MOH have an increased familial risk of substance use disorder or drug dependence, suggesting a possible genetic predisposition.[10]

Female sex hormones may also be a factor, as suggested by the role of menstruation as a trigger for migraine.[21] The reduced effectiveness of triptans for menstrual migraines and the longer duration of such episodes might lead to vulnerability to medication overuse.[22]

Neuroimaging reveals structural brain differences in MOH, including altered pain-modulating regions such as the hippocampus, periaqueductal gray area, cingulate cortex, thalamus, orbitofrontal cortex, and limbic system, with changes in gray matter volume and metabolism.[23] [24] Some of these differences have been found to normalize after medication withdrawal, although one study found persistent glucose hypometabolism in the orbitofrontal area. It is hypothesized that this may contribute to drug dependence and act as a risk factor for relapse in medication overuse and persistent MOH.[25]

Chronic exposure to analgesics may increase susceptibility to cortical spreading depression, promote central pain sensitization, alter descending pain modulation, and increase the susceptibility to developing cortical spreading depolarization.[26]

Case history

Case history #1

A 35-year-old woman with a history of infrequent migraine episodes since she was a teenager presents with a gradually progressive worsening of headache over the past year. Initially, she had more stress from work and started to take acetaminophen on a frequent basis for her increasingly frequent headaches, but the benefit wore off over time. Her family physician prescribed sumatriptan, which provided effective relief for a few months, but over the past 3 months she has been experiencing daily headaches despite using sumatriptan on most days. Her headache is holocephalic, moderate to severe in intensity, and occasionally associated with nausea and vomiting and sensitivity to light and sound. She reports no visual or headache pattern changes but has experienced worsening neck pain in conjunction with her headache, particularly a few hours after work. The headaches are not triggered by postural changes, exertion, or cough, except for head motion. On exam, no papilledema is observed; mild scalp allodynia and mild jaw and upper neck tenderness are noted. There are no signs of joint hypermobility, focal weakness, numbness, or other neurologic deficits. The persistent nature of her headaches has caused her to become depressed and she has had to take a leave of absence from work.

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Approach

Key points

- Medication overuse headache (MOH) is a chronic secondary headache disorder attributable to overuse of acute medications by a person with a preexisting primary headache (almost always migraine and/or tension-type headache).[1] [10]
- Overusing acute headache medications, such as simple analgesics, ergot derivatives, triptans, barbiturates, or opioids, often worsens the headache frequency in patients with underlying headache disorders, leading to a transition from an episodic to a chronic headache that occurs on more days than not.
- The diagnosis is clinical and requires careful history-taking and examination. Investigations are not required unless there are red flags to suggest an alternative cause for the headache.
- A headache diary is critical to determine the headache frequency and intensity, and quantify the use of acute medication.
- MOH is common but is preventable and is often treatable.

General principles

MOH is a chronic secondary headache disorder attributable to overuse of acute medications by a person with a preexisting primary headache, usually migraine or tension-type headache (TTH).[1] [10] [30]

- The diagnosis of MOH is clinical and focuses on a careful history, together with an assessment for any red flags and exclusion of other potential causes of a secondary headache.[10] [27]
- Consider the possibility of MOH in any patient with a primary headache disorder who reports that an episodic headache has increased in frequency over time to become chronic (occurring on more days than not) and is associated with frequent use of single or combination acute medication.

Make a diagnosis of MOH if the patient meets all three of the criteria set out in the 2018 International Classification of Headache Disorders (ICHD-3):[1]

- **Headache on ≥15 days per month** on a background of a preexisting primary headache disorder.
- **Regular overuse for >3 months of acute treatments** (at any dose) for the preexisting headache disorder. Overuse is defined by:
    - Use of simple analgesics on ≥15 days per month (acetaminophen, aspirin, or other nonsteroidal anti-inflammatory drug [NSAID], alone or in any combination), *or*
    - Use of a triptan, opioid, or ergot derivative on ≥10 days per month, *or*
    - Use of a combination of analgesics from different classes on ≥10 days per month.
- **No other ICHD-3 headache diagnosis** better accounts for the symptoms.

History

Ask about the **history of the primary headache** disorder, when the headaches started to increase in frequency, and how often they now occur. Be aware that migraine is by far the most common underlying headache.

- Migraine is the underlying primary headache condition affecting around 80% of adults with MOH.[27] [28] Up to 90% of patients with MOH have a history of migraine and/or TTH.[2] [3] [4]

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- Adults newly diagnosed with MOH have typically had a diagnosis of the underlying headache disorder for an average of 20 years.[10] The peak prevalence of MOH occurs in the 50-60 years age group.[9]
- The typical history is a background of migraine that has increased in frequency and/or severity over months or years, accompanied by escalating use of acute or symptomatic medication, which leads to a transition from an episodic to a chronic pattern of headache.[5] [6]

Ask **which acute medications are being used and how often** each is being taken. Ensure this covers both prescription medications and over-the-counter drugs.[30] It is important to get specific information on this as the details can have an impact on the most appropriate treatment approach.[27]

- Common medications associated with MOH are triptans, ergot derivatives, simple analgesics (including aspirin and other NSAIDs, or acetaminophen), opioids, barbiturates, or benzodiazepines.
- A cross-sectional survey of 13,649 US adults with migraine found that medication overuse was more common in those using triptans, opioids, and barbiturates and less likely in those using NSAIDs.[2]
- Some evidence suggests that MOH develops over a shorter period when triptans, opioids, or combination analgesics are overused compared with simple analgesics.[6] [30] One study found that the average time period between first use of the acute medication and development of daily MOH was 1.7 years for triptans, 2.7 years for ergot derivatives, and 4.8 years for analgesics.[32]
- Bear in mind that the individual may be overusing >1 medication.[27] If the patient is using multiple drug classes for symptomatic treatment of the underlying headache, they can be diagnosed with MOH if acute medication is being used on ≥10 days/month, even if no individual drug class is being overused.[1]
- Data from clinical trials suggest that frequent use of oral calcitonin gene-related peptide (CGRP) antagonists does not seem to lead to MOH.[10] [33]
- Among children and adolescents with a primary headache disorder, the literature reports overuse of medication in 10% to 60%.[34] NSAIDs are the most commonly overused medications, followed by acetaminophen and triptans.[35]

Ask the patient whether any pain medication is being used for a different medical condition (e.g., a musculoskeletal disorder).

- MOH can develop in an individual with an episodic primary headache who is using pain medication for another condition (rather than for the primary headache disorder).[27]

Ask about the **characteristics and duration** of the headache. These vary widely in MOH and can be affected by the primary underlying headache and the type of medication that is being overused.[27]

- The patient may develop a new type of headache or experience a worsening frequency of their preexisting headache.
- One prospective study found that patients with migraine and/or TTH who overused analgesic medication were more likely to develop a dull, diffuse, holocranial headache without migrainous symptoms. In contrast, those who overused triptans for underlying migraine were more likely to develop a daily migrainous headache (unilateral pulsating headache with autonomic disturbances).[32]

Use of a headache diary

If you suspect MOH based on the history, ask the patient to keep a headache diary or calendar.[10] [30] This is a **key tool to quantify headache frequency and use of acute medication** and thereby confirm that the diagnostic thresholds for MOH have been reached.

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- In addition to determining the frequency of headache and tracking use of acute or symptomatic medication, the headache diary can also help to indicate headache features, identify patterns or triggers, and act as a baseline to monitor the effectiveness of treatment.
- Electronic diaries are available that prompt the patient to complete daily reports. Such diaries often include options for recording the presence of a headache, a scale to rate its severity, and boxes to note specific symptomatic features (e.g., aura, photophobia, vomiting). They also allow the patient to record use of different medication classes used to relieve symptoms.[10] [American Headache Society: weekly headache diary] (https://americanheadachesociety.org/wp-content/uploads/2018/05/Weekly_Headache_Diary.pdf) [National Headache Foundation: headache diary] (https://headaches.org/wp-content/uploads/2021/05/HEADACHE-DIARY.pdf)

Common comorbidities and other risk factors

Be aware of comorbidities that are commonly associated with MOH as they may contribute to the development or exacerbation of the condition and, in some cases, reduce the likelihood of successful treatment. In practice, however, it can be difficult to distinguish whether such conditions are true risk factors for MOH or simple comorbidities.[10]

- **Depression and anxiety** are strong independent risk factors for chronification of the primary headache, which can lead in turn to medication overuse. They are the most frequent comorbidities among patients with MOH and are predictors of a worse outcome from treatment.[9] [17] [18][19] [30]
- Chronic **musculoskeletal disorders** have been found to be associated with a twofold increased risk of MOH.[4] Note that MOH can develop in a patient with an episodic primary headache who uses pain medication for a condition such as arthritis (rather than for the primary headache disorder).[27]
- There have also been suggestions that patients with MOH are more likely than the general population to have gastrointestinal problems, insomnia, hypothyroidism, and metabolic syndrome, although the evidence for this is limited.[10]
- Check for any history of **substance misuse disorder**. Evidence suggests a possible link in some patients between overuse of medication or the development of MOH and substance misuse disorder. Moreover, emerging findings indicate that individuals with MOH have an increased familial risk of drug dependence and a possible genetic association with dopaminergic and drug-dependence molecular pathways.[10] [36] [37] The Severity of Dependence Scale (SDS) score is a significant predictor of medication overuse among patients with headache disorders.[1]

Female sex is another significant risk factor for MOH.

- MOH is more common in women than in men. A prospective longitudinal study of 25,596 individuals in Norway with an 11-year follow-up found female sex was associated with a 1.9-fold increased risk of MOH compared with male sex (95% CI 1.4 to 2.6), and an epidemiologic survey of 44,300 randomly selected women in Sweden reported a female-to-male ratio of 2.8:1.[4] [16]
- This reflects the predominance of migraine among females. Evidence suggests that the sex ratio associated with migraine changes from 1:1 in pre-pubertal children to a 2:1 predominance of girls during adolescence.[38] Functional MRI (fMRI) studies of pre- and post-pubertal individuals with migraine have found that distinct changes in brain connectivity during puberty are associated with an increased post-pubertal headache burden in females.[39]

One longitudinal study found that a lower level of education and lower household income were also associated with MOH.[4]

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Red flags in the history

Check for any red flags in the history that should raise suspicion of an alternative cause of secondary headache. These include some elements of the SNOOP4 or SNNOOP10 mnemonics for red flag symptoms and signs in a patient who presents with headache.[40] [41] The red flags that are most relevant in the context of a patient suspected of having MOH are:[40] [41]

- **Abnormal neurologic symptoms**: could be suggestive of a variety of conditions that need to be ruled out, such as brain tumor, brain abscess, spontaneous intracranial hypotension, cerebral venous sinus thrombosis.
- Headache **aggravated by postural changes or Valsalva maneuver**: may be a feature of intracranial hypertension or hypotension.
- **Systemic symptoms** or features, such as fever or weight loss: fever could indicate a secondary headache attributable to infection, particularly if the patient has a history of HIV or other immunosuppression. Weight loss might be a symptom of malignancy.
- A history of **cancer**: potential for brain metastasis.
- Older age **(>50 years)**: consider the possibility of giant cell arteritis.[30]
- History of **trauma**: may indicate the possibility of a persistent headache attributable to traumatic brain injury.
- **Pregnancy** or puerperium: exclude preeclampsia, cerebral sinus thrombosis, hypothyroidism, anemia, gestational diabetes.

Diagnostic details

The diagnosis of MOH is made in addition to the diagnosis of the underlying headache disorder.[1]

A diagnosis of MOH implies that the overused medication is the cause of the frequent headache.[10]

- However, while the 2004 edition of the ICHD diagnostic criteria required an improvement in the headache after withdrawal of the causative medication, this requirement was removed in 2018 as part of ICHD-3.[1] [42]
- The ICHD-3 criteria state that MOH usually, but not invariably, resolves after withdrawal of the overused acute medication.[1]
- In clinical practice, this can sometimes make it difficult to distinguish MOH from a scenario in which a rising frequency of headache from the preexisting headache disorder has led to increasing use of acute medication.[10]
- Some patients who meet the diagnostic criteria for MOH do not see an improvement after withdrawal of the overused medication, with the proportion varying between studies that used different withdrawal protocols.[27] It is also worth noting that not every individual with an episodic primary headache disorder who overuses acute medication (either for the headache or for another chronic condition) will transition to an increased headache frequency. As such, it can be difficult in practice to distinguish between medication overuse as a cause of MOH and a scenario in which the medication overuse is a consequence rather than a cause of increasingly frequent headaches.[10]

Categorize the patient's MOH as **uncomplicated or complicated**. This may have implications for the most appropriate management plan.[27]

- Uncomplicated MOH refers to individuals who overuse simple analgesics, triptans, or ergot derivatives; have no significant psychiatric comorbidity; and have no past history of an MOH relapse.

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- Complicated MOH refers to individuals who overuse opioids, benzodiazepines, barbiturates, or other sedatives, *and/or* have a significant psychiatric comorbidity and/or have a history of relapse after previous treatment for MOH.

Be aware that MOH has a substantial negative impact on quality of life and daily functioning, with patients experiencing lower scores than the general population on validated measures such as SF-36 and SF-12, including reduced Physical Health Composite Scores (PCS-12) and Mental Health Composite Scores (MCS-12), as observed in both clinical and population-based studies.[15]

- MOH is a significantly disabling condition, often requiring frequent routine or urgent care consultations. Effective treatment can lead to lower healthcare and wider economic costs in addition to improving quality of life.[18] [43] [44]

Note that medication overuse in general is distinct from MOH because patients without an underlying headache disorder who overuse analgesia for other pain conditions do not develop chronic headache.[27]

Physical exam

The diagnostic criteria for MOH do not include any physical signs, and there are usually **no findings of note on examination**.[1]

- An unremarkable neurologic exam is an important prerequisite for diagnosing MOH.[10]
- Any motor weakness or sensory deficit should prompt suspicion for a brain tumor.[40]

Focus the physical exam on excluding **red flags** and identifying any other potential signs of an alternative cause for secondary headache.[30] Serious causes of secondary headache are very uncommon.[30] Among the most concerning signs to look for (and the potential underlying conditions that need to be ruled out if present) are:[40]

- Papilledema on ophthalmologic examination (idiopathic intracranial hypertension [also known as pseudotumor cerebri] or brain tumor)[30]
- Visual field defect (pituitary tumor)
- Neck tenderness with limited range of motion (cervical myofascial pain syndrome)
- Localized pain, induration, tenderness, or erythematous nodules over or along both temporal arteries (giant cell arteritis, especially if >50 years of age)
- Jaw tenderness (temporomandibular joint disorder)
- Joint hypermobility (cerebral spinal fluid leak)
- Cranial nerve palsy (chronic meningitis)
- Orthostatic tachycardia (postural orthostatic tachycardia syndrome).

Initial tests

The diagnosis of MOH is clinical, based on the ICHD-3 criteria.[1] No specific biomarkers, blood tests, or neuroimaging studies are available to confirm the diagnosis. Such tests are only indicated if there are red flags or other symptoms or signs that indicate the need to rule out an alternative diagnosis.[45]

Other tests

If there are any red flags or other symptoms or signs in the history or physical exam that suggest an alternative diagnosis, consider ordering further tests. These may include neuroimaging, blood tests, lumbar puncture, and cerebrospinal fluid (CSF) studies.[10] [40]

Magnetic resonance imaging (MRI) (either without contrast, or both without and with contrast) is the recommended test for most adult patients who have one or more red flags and is recommended

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for any child with a secondary headache.[45] Computed tomography (CT) without contrast may be appropriate if intracranial hypertension is suspected, or there are neurologic deficits or a history of cancer or immunosuppression.[45]

Blood tests may reveal signs of infection or giant cell arteritis (elevated erythrocyte sedimentation rate). Lumbar puncture may be indicated if there is suspicion of meningitis or encephalitis and can also be used to measure cerebrospinal fluid pressure in patients with papilledema.

History and exam

Key diagnostic factors

underlying primary headache disorder (common)

- MOH is a chronic secondary headache disorder attributable to overuse of acute medications by a person with a preexisting primary headache.[1] [10]
- - Migraine is the underlying primary headache condition in around 80% of patients with MOH.[27] [28] Up to 90% of patients with MOH have a history of either migraine or tension-type headache or both.[2] [3] [4]
  - Adults newly diagnosed with MOH have had a diagnosis of the underlying headache disorder for an average of 20 years.[10] The peak prevalence of MOH occurs in the 50-60 years age group.[9]
- Make a diagnosis of MOH if the patient meets all three of the criteria set out in the 2018 International Classification of Headache Disorders (ICHD-3):[1]
- - Headache on ≥15 days per month on a background of a preexisting primary headache disorder.
  - Regular overuse for >3 months of acute treatments (at any dose) for the preexisting headache disorder. Overuse is defined by: use of simple analgesics on ≥15 days per month (acetaminophen, aspirin, or other nonsteroidal anti-inflammatory drug [NSAID], alone or in any combination); *or* use of a triptan, opioid, or ergot derivative on ≥10 days per month; *or* use of a combination of analgesics from different classes on ≥10 days per month.
  - No other ICHD-3 headache diagnosis better accounts for the symptoms.
- Make the diagnosis of MOH in addition to the diagnosis of the underlying headache disorder.[1]

headache on ≥15 days per month (common)

- MOH is defined by a headache occurring on ≥15 days per month in a patient who has been overusing acute medication for a preexisting primary headache disorder (almost always migraine and/or tension-type headache [TTH]) and who has no red flags or other symptoms or signs to suggest an alternative diagnosis.[1]
- Consider the possibility of MOH in any patient with a primary headache disorder who reports that an episodic headache has increased in frequency over time to become chronic (occurring on more days than not) and is associated with frequent use of single or combination acute medication.
- - The typical history is a background of migraine that has increased in frequency and/or severity over months or years, accompanied by escalating use of acute or symptomatic medication, which leads to a transition from an episodic to a chronic pattern of headache.[5] [6]

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- The features of the headache vary widely and can be affected by the primary underlying headache and the type of medication that is being overused.[27] One prospective study found that patients with migraine and/or TTH who overused analgesic medication were more likely to develop a dull, diffuse, holocranial headache without migrainous symptoms. In contrast, those who overused triptans for underlying migraine were more likely to develop a daily migrainous headache (unilateral pulsating headache with autonomic disturbances).[32]

- Only make a diagnosis of MOH if the patient meets the other two criteria set out in the 2018 International Classification of Headache Disorders (ICHD-3) (in addition to having a headache on ≥15 days per month on a background of a preexisting primary headache disorder):[1]
  - Regular overuse for >3 months of acute treatments (at any dose) for the preexisting headache disorder. Overuse is defined by: use of simple analgesics on ≥15 days per month (acetaminophen, aspirin, or other nonsteroidal anti-inflammatory drug [NSAID], alone or in any combination); *or* use of a triptan, opioid, or ergot derivative on ≥10 days per month; *or* use of a combination of analgesics from different classes on ≥10 days per month.
  - No other ICHD-3 headache diagnosis better accounts for the symptoms.

overuse of acute headache medication for >3 months (common)

- To receive a diagnosis of MOH, a patient must have been overusing acute medication for >3 months for symptomatic management of a primary headache disorder (almost always migraine and/or TTH).[1]
  - The overuse of acute/symptomatic medication is accompanied by a transition from an episodic to a chronic pattern of headache.[5] [6]
- Overuse is defined by:[1]
  - Use of simple analgesics on ≥15 days per month (acetaminophen, aspirin, or other nonsteroidal anti-inflammatory drug [NSAID], alone or in any combination), *or*
  - Use of an triptan, opioid, or ergot derivative on ≥10 days per month, *or*
  - Use of a combination of analgesics from different classes on ≥10 days per month.
- Common medications associated with MOH are triptans, ergot derivatives, simple analgesics (including acetaminophen or aspirin and other NSAIDs), opioids, barbiturates, or benzodiazepines.[27]
  - A cross-sectional survey of 13,649 US adults with migraine found that medication overuse was more common in those using triptans, opioids, and barbiturates and less likely in those using NSAIDs.[2]
  - Some evidence suggests that MOH develops over a shorter period when triptans, opioids, or combination analgesics are overused compared with simple analgesics.[27] [32]
  - Bear in mind that the individual may be overusing >1 medication.[27] If the patient is using multiple drug classes for acute, symptomatic treatment of the underlying headache, they can be diagnosed with MOH if acute medication is being used on ≥10 days/month, even if no individual drug class is being overused.[1]
- Be aware that MOH can develop in a patient with an episodic primary headache who uses pain medication for a different condition such as arthritis (rather than for the primary headache disorder).[27]
- Only make a diagnosis of MOH if, in addition to overuse of acute medication, the patient also meets the other two criteria set out in the 2018 International Classification of Headache Disorders (ICHD-3):[1]
  - Headache on ≥15 days per month on a background of a preexisting primary headache disorder

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- No other ICHD-3 headache diagnosis better accounts for the symptoms.

Other diagnostic factors

normal neurologic exam (common)

- An unremarkable neurologic exam is an important prerequisite for diagnosing MOH.[10]
-
  - Any motor weakness or sensory deficit should prompt suspicion for a brain tumor.[40]

absence of red flag symptoms and/or signs (common)

- Check for any red flags in the history or on examination that should raise suspicion of an alternative cause of secondary headache. These include:[40] [41]
-
  - Abnormal neurologic symptoms: could be suggestive of a variety of conditions that need to be ruled out, such as brain tumor, brain abscess, spontaneous intracranial hypotension, cerebral venous sinus thrombosis.
  - Headache aggravated by postural changes or Valsalva maneuver: may be a feature of intracranial hypertension or hypotension.
  - Systemic symptoms or features, such as fever or weight loss. Fever could indicate a secondary headache attributable to infection, particularly if the patient has a history of HIV or other immunosuppression. Weight loss might be a symptom of malignancy.
  - A history of cancer: potential for brain metastasis.
  - Papilledema on ophthalmologic exam (idiopathic intracranial hypertension [also known as pseudotumor cerebri] or brain tumor).
  - Visual field defect (pituitary tumor).
  - Neck tenderness with limited range of motion (cervical myofascial pain syndrome).
  - Localized pain, induration, tenderness, or erythematous nodules over or along both temporal arteries (giant cell arteritis, especially if >50 years of age).
  - Jaw tenderness (temporomandibular joint disorder).
  - Joint hypermobility (spinal cerebral spinal fluid leak).
  - Orthostatic tachycardia (postural orthostatic tachycardia syndrome).
  - Pregnancy or puerperium: exclude preeclampsia, cerebral sinus thrombosis, hypothyroidism, anemia, gestational diabetes.

Risk factors

Strong

migraine as the underlying primary headache disorder

- Migraine is by far the most common underlying primary headache condition, affecting around 80% of adults with MOH.[27] [28]
- Up to 90% have a history of either episodic migraine and/or tension-type headache as the preexisting headache disorder.[2] [3] [4]

female sex

- MOH is more common in women than in men. A prospective longitudinal study of 25,596 individuals in Norway with an 11-year follow-up found female sex was associated with a 1.9-fold increased risk of

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MOH compared with male sex (95% CI 1.4 to 2.6), and an epidemiologic survey of 44,300 randomly selected women in Sweden reported a female-to-male ratio of 2.8:1.[4] [16]

use of opioid, barbiturate, triptan, or ergot derivative

- Studies have shown that individuals who use simple analgesics as acute medication for their primary headache are at lower risk of developing MOH than those who use opioids, barbiturates, triptans, or ergot derivatives.[2] [3][4][29]
- In one US-based longitudinal study of 8219 individuals with episodic migraine who were followed for 5 years, the use of opioids or barbiturates was associated with a higher risk of transitioning to chronic migraine (odds ratio [OR] for barbiturate use compared with acetaminophen use: 2.06, 95% CI 1.3 to 3.1; OR for opioid use compared with acetaminophen: 1.98, 95% CI 1.4 to 2.2).[3]
- A prospective longitudinal 11-year follow-up study of 25,596 individuals in Norway found a fivefold increased risk for developing MOH among individuals who at baseline had reported regular use of tranquilizers compared with those who had not (OR 5.2, 95% CI 3.0 to 9.0).[4]
- Other studies have found that frequent use of opioids was associated with a 2.3-fold increased risk for MOH (95% CI 1.3 to 3.9).[2] [29]
- Another longitudinal study of 13,649 US adults with migraine found that, compared with those not overusing medications, patients with medication overuse were more likely to be taking triptans (31.3% vs. 14.2%), opioids (23.8% vs. 8.0%), barbiturates (7.8% vs. 2.7%), or ergot derivatives (3.1% vs. 0.6%).[2]

anxiety and/or depression

- Depression and anxiety are strong independent risk factors for chronification of the primary headache, which can lead in turn to medication overuse. They are the most frequent comorbidities among patients with MOH.[9] [17] [30] A prospective longitudinal 11-year follow-up study of 25,596 individuals in Norway found a twofold increased risk of MOH among individuals who at baseline had Hospital Anxiety and Depression Scale (HADS) scores ≥11 compared with those whose scores were ≤7. There was a 4.7-fold increased risk of MOH among those who had a combination of HADS scores ≥11 together with chronic musculoskeletal and gastrointestinal complaints (OR 4.7, 95% CI 2.4 to 9.0).[4]

Weak

chronic musculoskeletal disease

- A prospective longitudinal 11-year follow-up study of 25,596 individuals in Norway found that chronic musculoskeletal disease alone was associated with a 1.9-fold increased risk of MOH (95% CI 1.4 to 2.7).[4]
- Note that MOH can develop in a patient with an episodic primary headache who uses pain medication for a condition such as arthritis (rather than for the primary headache disorder).[27]

chronic gastrointestinal disease

- A longitudinal 11-year follow-up study of 25,596 individuals in Norway found that gastrointestinal disease alone was associated with a 1.6-fold increased risk of MOH (95% CI 1.1 to 2.2).[4]

low-level education

- In a prospective longitudinal study of 25,596 individuals in Norway, over the 11-year follow-up period low-level education was found to be a risk factor for developing MOH. Low educational level was associated with a 1.9-fold increased risk (95% CI 1.2 to 3.0) when compared with high educational level.[4]

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Tests

1st test to order

Test	Result
clinical diagnosis • The diagnosis of MOH is clinical.[1] • If you suspect MOH based on the history, ask the patient to keep a headache diary or calendar.[10] [30] This is a key tool to quantify headache frequency, intensity, and use of acute medication and thereby confirm that the diagnostic thresholds for MOH have been reached.[1] • Make a diagnosis of MOH if the patient meets all three of the criteria set out in the 2018 International Classification of Headache Disorders (ICHD-3):[1] • 1. Headache on ≥15 days per month on a background of a preexisting primary headache disorder. 2. Regular overuse for >3 months of acute treatments (at any dose) for the preexisting headache disorder. Overuse is defined by: use of simple analgesics on ≥15 days per month (acetaminophen, aspirin, or other nonsteroidal anti-inflammatory drug [NSAID], alone or in any combination); *or* use of a triptan, opioid, or ergot derivative on ≥10 days per month; *or* use of a combination of analgesics from different classes on ≥10 days per month. 3. No other ICHD-3 headache diagnosis better accounts for the symptoms. • There are no specific neuroimaging studies, blood tests, or biomarkers needed to confirm the diagnosis. Such tests are only indicated if there are red flags or other symptoms or signs that indicate the need to rule out an alternative diagnosis.[45]	**fulfills the ICHD-3 criteria**

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Other tests to consider

Test	Result
MRI brain • Neuroimaging is not needed for patients who meet the ICHD-3 diagnostic criteria for MOH and have no red flags in their history or examination.[1] [45] • MRI (either without contrast, or both without and with contrast) is the recommended test for most patients with secondary headache who have one or more red flags (e.g., history of cancer; headache aggravated by postural changes or Valsalva maneuver; papilledema).[45] It is also recommended for any child with a secondary headache.[45]	**normal in MOH; otherwise may indicate an alternative cause for the secondary headache**
CT brain • Neuroimaging is not needed for patients who meet the ICHD-3 diagnostic criteria for MOH and have no red flags in their history or examination.[1] [45] • CT without contrast may be appropriate if intracranial hypertension is suspected or there are other red flags (e.g., neurologic deficits, or a history of cancer or immunocompromise).[45]	**normal in MOH; otherwise may indicate an alternative cause for the secondary headache**
CRP/erythrocyte sedimentation rate (ESR) • Laboratory tests are not needed for patients who meet the ICHD-3 diagnostic criteria for MOH and have no red flags in their history or examination.[1] [45] • Check inflammatory markers (CRP and ESR) if there are any red flags to indicate suspicion for giant cell arteritis or systemic infection.	**normal in MOH; if elevated, may indicate an alternative diagnosis (e.g., giant cell arteritis, infection)**
lumbar puncture (LP) • Tests are not needed for patients who meet the ICHD-3 diagnostic criteria for MOH and have no red flags in their history or examination.[1] [45] • High opening cerebrospinal fluid (CSF) pressure may suggest the presence of idiopathic intracranial hypertension (also known as pseudotumor cerebri), while low CSF pressure may indicate intracranial hypotension. • May also be considered if an infective cause is suspected.	**normal in MOH; otherwise may indicate an alternative cause for the secondary headache**
cerebrospinal fluid (CSF) culture • Tests are not needed for patients who meet the ICHD-3 diagnostic criteria for MOH and have no red flags in their history or examination.[1] [45] • If there is suspicion for a systemic or central nervous system infection, culture and microscopy of CSF may identify the infecting microorganism.	**normal in MOH; otherwise may indicate an alternative cause for the secondary headache**

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Differentials

Condition	Differentiating signs / symptoms	Differentiating tests

Chronic primary headache disorder	• Chronic headache that does not fulfill all the diagnostic criteria for MOH as set out in the 2018 International Classification of Headache Disorders (ICHD-3):[1]
	•
	  • Headache on ≥15 days per month on a background of a preexisting primary headache disorder.
	  • Regular overuse for >3 months of acute treatments (at any dose) for the preexisting headache disorder. Overuse is defined by: use of simple analgesics on ≥15 days per month (acetaminophen, aspirin, or other nonsteroidal anti-inflammatory drug [NSAID], alone or in any combination); *or* use of a triptan, opioid, or ergot derivative on ≥10 days per month; *or* use of a combination of analgesics from different classes on ≥10 days per month.
	  • No other ICHD-3 headache diagnosis better accounts for the symptoms.
	• Note that a diagnosis of chronic migraine or chronic tension-type headache (TTH) also requires headache on ≥15 days per month.[1] If the patient also meets the criteria for MOH, both diagnoses should be given in the first instance. After withdrawal of the overused drug, the
		• Diagnosis is clinical. A headache diary is key for distinguishing different ICHD-3 headache disorders.

DIAGNOSIS

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Condition	Differentiating signs / symptoms	Differentiating tests
	diagnosis of the chronic primary headache disorder is only retained if the headache fails to revert to an episodic pattern.[1]	
Idiopathic intracranial hypertension (pseudotumor cerebri)	• Headache type varies substantially between patients but in most cases has a migraine phenotype. Transient visual obscuration, pulsatile tinnitus, or horizontal diplopia. Papilledema may be present on ophthalmologic examination.[46]	• Brain MRI/magnetic resonance venogram (MRV): usually show transverse sinus stenosis, empty sella, posterior globe flattening, distended optic nerve sheath. • Lumbar puncture at spinal L3/L4: indicates an opening pressure of ≥25 cm H_2O.[47]
Spontaneous intracranial hypotension and/or cerebrospinal fluid (CSF) leak	• Orthostatic headache that is relieved by lying down. May have neurologic symptoms.	• Brain MRI: diffuse pachymeningeal enhancement or other findings suggestive of low CSF pressure (e.g., brain sag, venous engorgement).[48] • CT myelogram: may show CSF leak, and even CSF-venous fistula.[48]
Sphenoid sinusitis	• Nonspecific frontal/vertex headache.	• CT sinus: diffuse mucosal thickening, opacification of the affected sinus(es).
Cervicogenic headache	• Cervical joint tenderness or reduced range of motion are common but not specific. Cervical flexion rotation can be limited.[49]	• Usually a clinical diagnosis, although imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck may support the diagnosis.[49] • Facet or joint blockade may sometimes be used to confirm the diagnosis.[49]
Persistent headache attributed to traumatic brain injury/whiplash	• Trauma in the history.	• Diagnosis is usually clinical, based on ICHD-3 criteria. • Brain MRI: may or may not show structural lesion.
Cerebral venous sinus thrombosis	• Altered mental status, seizure, focal weakness/numbness.[50]	• MRI/magnetic resonance venogram (MRV): may include direct visualization of an acute thrombus or indirect signs (e.g., diffuse cerebral edema). A lack of flow is seen on MRV.[51] [52]

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Condition	Differentiating signs / symptoms	Differentiating tests
Space-occupying lesion in the brain	• Visual change, seizure, cognitive/behavior change, focal weakness/ numbness.[40]	• MRI brain: shows enhancing or nonenhancing mass with or without perifocal edema.
Chronic meningitis	• Photophobia, meningismus, cranial nerve palsy.	• Cerebrospinal fluid (CSF) chemistry: shows elevated protein, decreased glucose, elevated white blood cell counts, and positive microbiology/virology test.[53]

Criteria

International Classification of Headache Disorders, 3rd edition (ICHD-3)[1]

Under ICHD-3, the diagnostic criteria for MOH are:

- Headache occurring on ≥15 days/month in a patient with a preexisting headache disorder, *and*
- Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache, *and*
- Not better accounted for by another ICHD-3 diagnosis.

Overuse of the acute or symptomatic drug is defined as any one of:

1. Regular intake of ergotamine on ≥10 days/month for >3 months.
2. Regular intake of one or more triptans, in any formulation, on ≥10 days/month for >3 months.
3. Regular intake of acetaminophen on ≥15 days/month for >3 months.
4. Regular intake of one or more nonsteroidal anti-inflammatory drugs (NSAIDs) other than aspirin (acetylsalicylic acid) on ≥15 days/month for >3 months.
5. Regular intake of aspirin (acetylsalicylic acid) on ≥15 days/month for >3 months.
6. Regular intake of any other nonopioid analgesic on ≥15 days/month for >3 months.
7. Regular intake of one or more opioids on ≥10 days/month for >3 months.
8. Regular intake of one or more combination-analgesic medications (nonopioid analgesics with opioids, butalbital, and/or caffeine) on ≥10 days/month for >3 months.
9. Regular intake of any combination of ergotamine, triptans, nonopioid analgesics, and/or opioids on a total of ≥10 days/month for >3 months without overuse of any single drug or drug class alone.
10. Regular intake of any combination of ergotamine, triptans, nonopioid analgesics, and/or opioids on ≥10 days/month for >3 months. The identity, quantity, and/or pattern of use or overuse of these classes of drug cannot be reliably established.
11. Regular overuse, on ≥10 days/month for >3 months, of one or more medications other than those described above, taken for acute or symptomatic treatment of headache.

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Approach

Key points

- Education and advice for patients and family members is the first step in managing medication overuse headache (MOH) and may be sufficient on its own to resolve the condition in some patients.
- Withdrawal from the overused acute medication is an important element of treatment and can be abrupt for ergot derivatives, triptans, and simple analgesics but involves gradual tapering for opioids, barbiturates, or benzodiazepines. Symptomatic treatment for withdrawal symptoms may be needed.
- Initiation of a preventive regimen is typically used to facilitate withdrawal from the overused medication.
- Patients with complex MOH require a multidisciplinary approach that includes behavioral interventions and pain coping strategies. Consider inpatient treatment for any patient withdrawing from opioids, barbiturates, or benzodiazepines.
- Some acute headache medications, such as calcitonin gene-related peptide (CGRP) antagonists or antiemetics, probably do not lead to MOH and should be considered part of the treatment regimen for adults.

Managing MOH involves a multifaceted approach that includes:[10] [27]

- **Patient and family education**, including information on the importance of reducing the frequency of the overused medication. In uncomplicated MOH, this may be sufficient on its own.
- **Withdrawal of the overused medication**, supported by symptomatic management of any short-term breakthrough headaches that occur during the withdrawal period.
- Use of appropriate **preventive medication** targeting the underlying primary headache.
- **Behavioral interventions** to address any psychological or medical comorbidities and to maintain adherence to treatment.

Various strategies for managing MOH are used in practice, and there is limited evidence to support the benefits of one over another.[10]

- There are few double-blind randomized controlled trials specifically looking at different management options for MOH.[10] [27] Hence, the selection of treatment regimen is determined less by the strength of evidence and more by individual patient characteristics including comorbidities and the patient's willingness to discontinue the overused medication.[10] [27]
- Evidence is even more scant regarding MOH in children, although the general principles are the same as for adults.[10]

Commonly used approaches are:[10] [27]

- Early discontinuation of the overused medication(s) (either abrupt or tapered) without preventive medication.
- Early discontinuation of the overused medication(s) (either abrupt or tapered) supported by concurrent preventive medication.
- Preventive medication together with restricted frequency of use of the overused medication(s).

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- Preventive treatment without actively restricting use of the overused medication(s). In practice, this strategy is generally reserved for patients who are reluctant to withdraw from the acute medication, although evidence suggests it is noninferior to a combination approach.[54]

Bear in mind that the evidence on the relative benefits of these different management strategies is mixed.[10] [27]

- A multicenter open-label study involving 694 patients from seven countries found that starting preventive medication in parallel with withdrawal of the overused acute medication led to a 44% reduction in headache days in the first month, increasing to 60% after 6 months. Some 68% of the 492 participants who completed the protocol reverted from MOH to an episodic headache pattern.[55]
- An open-label randomized trial of 120 patients that compared withdrawal of the overused medication alone, preventive medication alone, and a combined strategy of withdrawal plus preventive medication found no difference in reduction of monthly migraine days, acute medication use, or headache intensity.[56] However, secondary outcome analysis showed higher rates of reversion from chronic to episodic migraine and greater chance of MOH resolution in the group who had a combination of withdrawal plus preventive medication (74% and 97%, respectively) compared with the preventive medication alone group (60% and 74%) or the withdrawal alone group (42% and 89%).[56]
- A subsequent, larger pragmatic randomized trial involving 720 participants found that preventive medication alone (with no limitation of the overused medication) was noninferior to the combination of preventive medication plus withdrawal of the overused medication.[54]

Tailoring management to the individual patient: a practical approach

A review by US and European experts has recommended a practical approach to selecting the most appropriate approach for the individual patient.[10]

- If the patient has **uncomplicated MOH and is willing to attempt withdrawal** of the overused medication, the recommended approach is a combination of education, discontinuation of the causative medication, and early use of preventive medication.
- If the patient has **uncomplicated MOH and is unwilling to attempt withdrawal** of the causative medication, education plus early preventive medication alone can be used. If this approach fails, withdrawal of the causative medication becomes necessary.
- If the patient has **complex MOH**, multidisciplinary specialist care is needed, with withdrawal of the overused medication, aggressive use of preventive medication, pain management therapy, and behavioral interventions to support lifestyle change. Complex MOH is defined by the presence of one or more of: use of an opioid, barbiturate, benzodiazepine, or sedative; significant psychiatric comorbidity; a substance misuse or addiction disorder; a history of relapse following previous treatment for MOH. For more detail, see *Complex cases*, below.

Note that local protocols for MOH are an additional factor that may determine the strategy.

Patient education

Patient education is an essential first step in managing medication overuse and may be sufficient on its own to bring about reduction in use of the acute medication and resolution of the MOH in some patients.[1] [27] [30]

- **Advice on its own** is an appropriate initial treatment approach in patients with uncomplicated MOH (i.e., they overuse triptans or simple analgesics, do not have a major psychiatric comorbidity, and have not relapsed after previous successful treatment for MOH).[27] The advice can be provided by a primary care physician, trained headache nurse, or neurologist.[27] In some patients,

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this may be sufficient to revert the headache pattern from chronic to episodic (i.e., <15 headache days/month).
- Advice alone is not appropriate for patients with complex MOH (i.e., they overuse an opioid, barbiturate, or sedative, and/or have experienced previous MOH relapse, and/or have a psychiatric comorbidity).[27] These patients need specialist referral, ideally for multidisciplinary management.[27]

When providing education, ensure the patient understands the concept of MOH and how the frequent use of acute medications can lead to more frequent headaches that become chronic over time.[6] [10]

- Explain that MOH is treatable and that restricting or withdrawing the overused medication is a key element.
- Use open conversation but take care to avoid using language that could be perceived as blaming the patient for excessive use of acute medications.[10]
- Evidence from randomized trials suggests that a primary care-based education intervention can be highly effective for uncomplicated MOH.[57] [58][59]

Ensure the patient is forewarned that the headache may worsen when the acute medication is reduced or terminated, but reassure them that this is transient.[10] [60]

Withdrawal/discontinuation of overused medication

Withdrawal of the causative medication(s), or severely restricting its use, is an important element in management of MOH and can lead many patients to revert from chronic to episodic headache.[27] [30]

- Advise the patient that aiming for complete withdrawal is often more effective than limited ongoing use of the overused medication(s).[61] [62]

There is no clear consensus on the optimum timing of discontinuation and whether this should be abrupt or gradual.[10] [27] [62]

- Uncertainty also remains as to whether, in what circumstances, and at what stage of withdrawal preventive medications should be used.[27]
- After medication withdrawal, the improvement in headache frequency may be gradual and can take up to 12 weeks.[30]

Tailor the speed of the withdrawal plan to the individual patient's circumstances.[10]

- **Abrupt discontinuation** is probably safe and effective for ergot derivatives, triptans, or simple analgesics (including acetaminophen, aspirin, and other nonsteroidal anti-inflammatory drugs [NSAIDs]).[27] In practice, any need for tapering is decided based on the patient's individual characteristics.
- **Gradual taper** is recommended for withdrawing opioids, barbiturates, or benzodiazepines.[27] [63] In some situations, long-acting opioids or phenobarbital may be needed as a transition.[27] This is important for reducing the risk of withdrawal symptoms.[10]

Ensure the patient is prepared for a transient worsening of symptoms prior to the start of withdrawal.[64]

- Withdrawal symptoms can last for 2-10 days (average 3.5 days) and can include withdrawal headache, nausea, vomiting, arterial hypotension, tachycardia, sleep disturbance, anorexia, and anxiety.[27] [30]
- In practice, it is important to encourage the patient to identify the most suitable time to attempt withdrawal (e.g., during a period of leave from work) and to pre-warn their family and friends.

Provide an alternative acute medication (with limited frequency of use) for breakthrough headaches that occur during withdrawal.

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- Symptomatic treatment ("rescue" or **bridging medication**) is often required to mitigate the symptoms of breakthrough headache that occur when the overused medication is withdrawn.[9] [10] There is no trial evidence to guide selection of bridging medication; hence, recommendations are based on expert consensus.[6]
- For breakthrough headache, select a medication from a different drug class from the overused medication (e.g., an analgesic if triptans are overused, and vice versa).[10] [27]
- Other options for bridging therapy during withdrawal are medications recommended for acute migraine (e.g., prochlorperazine or metoclopramide, diphenhydramine, valproate). Note that valproate must not be used in pregnancy or in women of childbearing potential unless they are following a pregnancy prevention program and specific conditions are met.[27] Systemic corticosteroids are sometimes used for more severe withdrawal symptoms, although the evidence to support this is not strong.[10] [27] For more information on rescue therapy options in pregnant and nonpregnant adults, see Migraine headache in adults or Tension-type headache .

Advise the patient to stay off the withdrawn medication for at least 2 weeks and ideally 1 month.[6]

- Once the MOH has been successfully treated, the previously overused medication can be reintroduced, but ensure a reduced frequency of use to avoid relapse.

Preventive treatment

Preventive medication that **targets the underlying headache disorder** is an important part of the management plan for many patients with MOH.[10] [27]

- In principle, preventive medication can be used: before withdrawal of the overused medication; from the start of withdrawal as part of a combination strategy; or after withdrawal is complete.[10]
- In practice, the combination approach is often taken, with initiation of a preventive regimen used to facilitate withdrawal from the overused medication(s).

A preventive regimen alone may be the best available option if the patient has uncomplicated MOH and is unwilling to discontinue the overused medication.[9] [10]

- This has been found to be noninferior to preventive medication with acute medication withdrawal.[54]

Ongoing long-term use of the preventive medication, supported by regular follow-up consultations, is important to reduce the risk of relapse into renewed overuse of acute headache medication.[10]

Preventive medication options for migraine

The goal of preventive medication is to target the underlying headache disorder, which is usually migraine or tension-type headache (TTH).[10]

Use one of the following preventive medication options first line in patients with migraine as the underlying primary headache disorder:[6] [27] [33]

- **Topiramate.** Topiramate is recommended as a first-line option for chronic migraine by the American Headache Society.[33] Subgroup analysis of results from two multicenter randomized controlled trials in patients with migraine and MOH who did not discontinue the overused medication concluded that topiramate was likely effective.[65] However, its use can be limited by adverse effects.[10] Note that topiramate should not be used during pregnancy or in women of childbearing potential as it may cause fetal harm.[27]

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- **OnabotulinumtoxinA.** The American Headache Society recommends onabotulinumtoxinA as a first-line option for chronic migraine.[33] It was found to be more effective than placebo in reducing headache days in subgroup analysis of two trials in patients with migraine and MOH who did not discontinue the overused acute medication.[66] However, it did not show any added benefit over acute medication discontinuation alone in one randomized trial.[67] Note that onabotulinumtoxinA should generally be avoided in pregnancy unless essential as there are limited data in pregnant women.
- **Calcitonin gene-related peptide (CGRP) antagonists.** Therapies that target CGRP are recommended by the American Headache Society as a first-line option for migraine prevention.[33] Protocols vary, so check local guidance.
    - Oral CGRP antagonists (also known as gepants) - atogepant or rimegepant. These are small molecule CGRP antagonists that are taken orally. Atogepant has been shown to be associated with fewer monthly migraine days and fewer acute medication use days compared with placebo in people with migraine who overuse acute medications.[68] [69]
    - CGRP antagonist monoclonal antibodies - these include erenumab, fremanezumab, and galcanezumab (all administered subcutaneously) or eptinezumab (administered intravenously). All four have been found to result in fewer monthly migraine days and lower acute medication use compared with placebo in patients with migraine who overuse acute medications.[70] [71] [72] [73] They also have good tolerability, suggesting the possibility of a major role in treatment of MOH, particularly when combined with withdrawal of the overused acute medication.[27] [74] [75]
    - Note that use of CGRP antagonists should be avoided in pregnancy due to a lack of data.

A meta-analysis of randomized controlled trials that evaluated the relative efficacy of the above medications in patients with MOH against a background of migraine found that:[76]

- Studies assessing CGRP antagonist monoclonal antibodies included 1982 patients and showed a significant benefit compared with placebo, with a mean reduction of 2.68 migraine days per month (95% CI -3.46 to -1.91) and a 2.90 times higher likelihood (95% CI 2.23 to 3.78) of a ≥50% reduction in migraine or headache days from baseline.
- Studies assessing onabotulinumtoxinA included 1139 patients and showed a mean reduction in headache frequency of 1.92 days per month (95% CI -2.68 to -1.16) compared with placebo, although there were uncertainties regarding the likelihood of a ≥50% reduction in migraine or headache days.
- There was insufficient evidence available to determine the efficacy of topiramate for this purpose.

Other oral preventive medications, such as beta-blockers, tricyclic antidepressants, valproate, and candesartan (an angiotensin-II receptor antagonist), are also widely used in clinical practice but have not been well studied in MOH and so lack supporting evidence.[10] [27]

- Most patients who need preventive medication as part of specialist MOH management have already failed preventive therapy with beta-blockers, valproate, or amitriptyline.[27]

Nerve blockade, noninvasive neuromodulation devices, and acupuncture may also be considered.[10]

- One small study found that repeated sessions of occipital nerve blockade with lidocaine resulted in better outcomes than acute medication withdrawal alone in patients with MOH associated with triptan overuse.[77]

For more detail on preventive approaches to migraine, see Migraine headache in adults .

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Preventive medication options for tension-type headache (TTH)

No evidence is available from controlled trials to inform the most appropriate preventive approach for MOH against a background of TTH.[6]

If the patient's underlying primary headache disorder is TTH, target the preventive regimen at that.

- **Amitriptyline**, started at a low dose and titrated up to an effective dose, is the most commonly used pharmacologic option, although its use should be avoided during pregnancy if at all possible.[6] [78] [79]
- **Mirtazapine and venlafaxine** are second-line options but should also be avoided during pregnancy.[79]

There is evidence to support the effectiveness of relaxation training and cognitive behavioral therapy (CBT) in prevention of chronic TTH and some evidence to suggest benefit from acupuncture.[6] [78] [79]

For more detail, see Tension-type headache .

Complex cases

A holistic, multimodal approach is needed for individuals with complex MOH.

- Complex MOH is often defined by one or more of: overuse of opioids, barbiturates, benzodiazepines, or other sedatives; the presence of psychiatric or substance abuse comorbidity; a history of relapse following previous treatment for MOH.[10] [27]
- In addition to an aggressive preventive medication regimen, these patients will likely benefit from additional interventions, such as behavioral interventions to address any anxiety, depression, and suicidality together with pain coping strategies.
    - Overuse of pain medication has a strong behavioral element, and discontinuation involves substantial changes in behavior and lifestyle.[10]
    - One trial involving 179 patients with uncomplicated MOH found that, compared with minimal behavioral support, maximal behavioral intervention - which consisted of intensive contact with a headache nurse for education, motivational interviewing, and value-based activity planning - significantly reduced acute medication use days, although there was no change in monthly migraine days.[80]
    - Biofeedback and mindfulness have also shown promising results as add-ons to preventive medication.[81] [82]
    - Acupuncture and neuromodulation techniques have limited evidence but may also be used.[10]

Setting of care

Patients with uncomplicated MOH (i.e., those who are overusing simple analgesics, triptans, or ergot derivatives and do not have significant comorbidities) can be successfully managed by primary care physicians.[27]

- Withdrawal of triptans, ergot derivatives, and simple analgesics can be undertaken in outpatient settings.[10]

Patients with complex MOH are ideally managed by a specialist multidisciplinary team including neurologists or pain specialists and psychologists.[27]

Consider inpatient care, where available, if:

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- The patient is discontinuing long-term use of an opioid, barbiturate, or benzodiazepine.[10] [27] [83] Careful monitoring of metabolic parameters, blood pressure, fluid balance, and sedation is generally required during withdrawal.[27]
- The patient has been overusing acute medications from multiple drug classes.
- The patient has had a prior attempt at medication withdrawal that either failed or resulted in a relapse of MOH.[6] [27] [60] [83]
- The patient has a significant psychiatric or substance misuse comorbidity.[6] [10] [83]

Management of children and adolescents

There is limited high-quality evidence to inform management of MOH in children and adolescents.[10] In practice, the same general treatment strategies used for adults with MOH can be applied to children and adolescents. Education on the importance of reduction of acute medication is a vital aspect of care, and an emphasis on behavioral support is important.[10] [84]

Medication withdrawal

Withdrawal of the overused medication is recommended.[85]

- The few studies published on MOH in children with migraine show a response rate to drug withdrawal (i.e., a >50% reduction in headache frequency) that varies between 40% and 77%.[35] [86] [87] [88]
- If bridging therapy is needed for withdrawal symptoms, depending on the overused acute medication, options might include a simple analgesic (acetaminophen or an NSAID) or a triptan.[89] [90] Daily use of naproxen for one month to support withdrawal of the overused medication has been suggested as a reasonable strategy.[85] For more detail on bridging therapy options, see acute management in Migraine headache in children .
- If conventional approaches to bridging therapy fail, one group has suggested the following alternative strategies for children and adolescents with MOH:[85]
    - Occipital nerve blockade (with a mix of local anesthetic and corticosteroid)[85]
    - Hospital admission for a short course of intravenous dihydroergotamine if both simple analgesia (e.g., naproxen) and occipital nerve blockade prove to be insufficient as bridging therapies to support withdrawal from the overused medication.[85]

Prevention of the underlying headache

Nonpharmacologic preventive strategies are preferred to long-term medication whenever possible. Trigger avoidance is recommended, and behavioral therapies such as cognitive behavioral therapy (CBT) or biofeedback are options.[79] [84] Neuromodulation devices have also shown promising early results.[90]

- Triggers to avoid often include inadequate hydration, skipping meals, poor sleep, and insufficient physical activity.[90]

Evidence is scarce to support **preventive medication for chronic migraine** in children.[84]

- Most randomized controlled trials have failed to demonstrate any benefit over placebo.[91] Agents that can be considered include propranolol (though not in children with asthma), topiramate (with appropriate cautions over adverse effects), and amitriptyline combined with CBT (with caution around the risk of suicidal thoughts and behavior).[84] A cautious approach is required, with

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decision-making shared with patients and caregivers and regular monitoring of benefit versus potential harm, because evidence is limited and often conflicting.[91]

- Oral preventive medications can be poorly tolerated, and onabotulinumtoxinA and CGRP antagonists are not licensed for use in children in most countries.[10]
- For more detail on preventive medications, see Migraine headache in children .

Evidence to support the use of preventive medication is even scarcer for children with **chronic TTH**.

- Low-dose amitriptyline is sometimes used.[92] [93] [94]

Management of pregnant patients

The same broad principles apply to management of MOH in pregnancy as in any other adult patient, with education, withdrawal of the overused medication, and an effective preventive strategy for the primary headache disorder all important.

Nonpharmacologic strategies are preferred wherever possible. If medication is needed either as part of bridging therapy or the preventive strategy for the underlying headache, the safest available medication at the lowest dose for the shortest duration is recommended.

Note that the American College of Obstetricians and Gynecologists has published specific recommendations for management of headaches in pregnancy and postpartum.[95]

For more detail on acute and symptomatic management options in pregnancy, see Migraine headache in adults or Tension-type headache .

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Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
adults: uncomplicated		
	1st	withdrawal from/reduction of acute medication ± rescue medication
with migraine as underlying disorder	adjunct	pharmacologic preventive therapy
	adjunct	occipital nerve blockade
	adjunct	nonpharmacologic preventive therapy
with tension-type headache as underlying disorder	adjunct	pharmacologic preventive therapy
	adjunct	nonpharmacologic preventive therapy
adults: complex		
	1st	multidisciplinary care and consider hospital admission
children and adolescents		
	1st	withdrawal from/reduction of acute medication ± rescue medication
	adjunct	nonpharmacologic preventive therapy
with migraine as underlying disorder	adjunct	pharmacologic preventive therapy
with tension-type headache as underlying disorder	adjunct	pharmacologic preventive therapy

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Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

adults: uncomplicated

adults: uncomplicated — **1st** — **withdrawal from/reduction of acute medication ± rescue medication**

» Withdrawal of the causative medication(s), or severely restricting its use, is an important element in management of MOH and can lead many patients to revert from chronic to episodic headache.[27] [30]

- Advise the patient that aiming for complete withdrawal is often more effective than limited ongoing use of the overused medication(s).[61] [62]

» Patient education is an essential first step in managing medication overuse, and may be sufficient on its own to bring about reduction in use of the acute medication and resolution of the MOH in some patients.[1] [27] [30]

- Advice on its own is an appropriate initial treatment approach in patients with uncomplicated MOH (i.e., they overuse triptans, simple analgesics, or ergot derivatives; do not have a major psychiatric comorbidity; and have not relapsed after previous successful treatment for MOH).[27] The advice can be provided by a primary care physician, trained headache nurse, or neurologist.[27]
- When providing education, ensure the patient understands the concept of MOH and how the frequent use of acute medications can lead to more frequent headaches that become chronic over time.[6] [10]
- Evidence from randomized trials suggests that a primary care-based education intervention can be highly effective for uncomplicated MOH.[57] [58] [59]
- Ensure the patient is forewarned that the headache may worsen when the acute medication is reduced or terminated, but reassure them that this is transient.[10] [60]

» Patients with uncomplicated MOH can be successfully managed by primary care physicians.[27]

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- Withdrawal of triptans, ergot derivatives, and simple analgesics can be undertaken in outpatient settings.[10]
- Abrupt discontinuation is probably safe and effective for ergot derivatives, triptans, or simple analgesics (including acetaminophen, aspirin, and other nonsteroidal anti-inflammatory drugs [NSAIDs]).[27] In practice, any need for tapering is decided based on the patient's individual characteristics.
- After medication withdrawal, the improvement in headache frequency may be gradual and can take up to 12 weeks.[30]

» Ensure the patient is prepared for a transient worsening of symptoms prior to the start of withdrawal.[64]

- Withdrawal symptoms can last for 2-10 days (average 3.5 days) and can include withdrawal headache, nausea, vomiting, arterial hypotension, tachycardia, sleep disturbance, anorexia, and anxiety.[27] [30]
- In practice, it is important to encourage the patient to identify the most suitable time to attempt withdrawal (e.g., during a period of leave from work) and to pre-warn their family and friends.

» Provide an alternative acute medication (with limited frequency of use) for breakthrough headaches that occur during withdrawal.

- Symptomatic treatment ("rescue" or "bridging" medication) is often required to mitigate the symptoms of breakthrough headache that occur when the overused medication is withdrawn.[9] [10] There is no trial evidence to guide selection of bridging medication; hence, recommendations are based on expert consensus.[6]
- For breakthrough headache, select a medication from a different drug class from the overused medication (e.g., an analgesic if triptans are overused, and vice versa).[10] [27]
- Other options for bridging therapy during withdrawal are medications recommended for acute migraine (e.g., prochlorperazine or metoclopramide, diphenhydramine, and valproate). Note that valproate must not be used in pregnancy or in women of childbearing potential unless they are following a

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pregnancy prevention program and specific conditions are met.[27] Systemic corticosteroids are sometimes used for more severe withdrawal symptoms, although the evidence to support this is not strong.[10] [27] For more information on rescue therapy options in pregnant and nonpregnant adults, see Migraine headache in adults or Tension-type headache .

» Advise the patient to stay off the withdrawn medication for at least 2 weeks and ideally 1 month.[6]

- Once the MOH has been successfully treated, the previously overused medication can be reintroduced, but ensure a reduced frequency of use to avoid relapse.

» Note that various strategies for managing MOH are used in practice. These include discontinuation of the overused medication without use of preventive medication; discontinuation supported by concurrent preventive medication; or initiation of preventive medication together with restricted frequency of the acute overused medication.[10] [27] Studies have produced varying conclusions; hence, there is limited evidence to support the benefits of one approach over another.[10] One review co-authored by US and European experts has recommended a combination of education, discontinuation of the overused medication, and early use of preventive medication for any patient with uncomplicated MOH who is willing to attempt withdrawal.[10]

- Local protocols for MOH are an additional factor that may determine the strategy.

»

Pregnant patients

» The same broad principles apply to management of MOH in pregnancy as in any other adult patient, with education, withdrawal of the overused medication, and an effective preventive strategy for the primary headache disorder all important.

» Nonpharmacologic strategies are preferred wherever possible. If medication is needed either as part of bridging therapy or as the preventive strategy for the underlying headache, the safest available medication at the lowest dose for the shortest duration is recommended.

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» Note that the American College of Obstetricians and Gynecologists has published specific recommendations for management of headaches in pregnancy and postpartum.[95]

» For more detail on acute and symptomatic management options in pregnancy, see Migraine headache in adults or Tension-type headache .

with migraine as underlying disorder — **adjunct** — **pharmacologic preventive therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» topiramate: 25 mg orally (immediate-release) once daily at bedtime for 1 week initially, increase gradually according to response, maximum 100-200 mg/day in 2 divided doses; 25 mg orally (extended-release) once daily for 1 week initially, increase gradually according to response, maximum 100-200 mg/day

OR

» onabotulinumtoxinA: consult specialist for guidance on dose

OR

» atogepant: 60 mg orally once daily

OR

» rimegepant: 75 mg orally/sublingually once daily on alternate days

OR

» erenumab: 70-140 mg subcutaneously once monthly

OR

» fremanezumab: 225 mg subcutaneously once monthly; 675 mg subcutaneously every 3 months

OR

» galcanezumab: 240 mg subcutaneously as a single loading dose, followed by 120 mg once monthly

OR

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» eptinezumab: 100-300 mg intravenously every 3 months

» Preventive medication that targets the underlying headache disorder is an important part of the management plan for many patients with MOH.[10] [27]

- In principle, preventive medication can be used: before withdrawal of the overused medication; from the start of withdrawal as part of a combination strategy; or after withdrawal is complete.[10]
- In practice, the combination approach is often taken, with initiation of a preventive regimen used to facilitate withdrawal from the overused medication(s).
- A preventive regimen alone may be the best available option if the patient has uncomplicated MOH and is unwilling to discontinue the overused medication.[9] [10] This has been found to be noninferior to preventive medication with acute medication withdrawal.[54]

» The goal of preventive medication is to target the underlying headache disorder.[10] Use one of the following preventive medication options first line in patients with migraine as the underlying primary headache disorder:[6] [27] [33]

- **Topiramate.** Topiramate is recommended as a first-line option for chronic migraine by the American Headache Society.[33] Subgroup analysis of results from two multicenter randomized controlled trials in patients with migraine and MOH who did not discontinue the overused medication concluded that topiramate was likely effective.[65] However, its use can be limited by adverse effects.[10] Note that topiramate should not be used during pregnancy or in women of childbearing potential as it may cause fetal harm.[27]
- **OnabotulinumtoxinA.** The American Headache Society recommends onabotulinumtoxinA as a first-line option for chronic migraine. It was found to be more effective than placebo in reducing headache days in subgroup analysis of two trials in patients with migraine and MOH who did not discontinue the overused acute medication.[66] However, it did not show any added benefit over

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acute medication discontinuation alone in one randomized trial.[67] Note that onabotulinumtoxinA should be avoided in pregnancy unless essential as there are limited data in pregnant women.

- **Calcitonin gene-related peptide (CGRP) antagonists.** Therapies that target CGRP are recommended by the American Headache Society as a first-line option for migraine prevention.[33] Protocols vary, so check local guidance.
    - Oral CGRP antagonists (also known as gepants) - atogepant or rimegepant. These are small molecule CGRP antagonists that are taken orally. Atogepant has been shown to be associated with fewer monthly migraine days and fewer acute medication use days compared with placebo in people with migraine who overuse acute medications.[68] [69]
    - CGRP antagonist monoclonal antibodies - these include erenumab, fremanezumab, and galcanezumab (all administered subcutaneously) or eptinezumab (administered intravenously). All four have been found to result in fewer monthly migraine days and lower acute medication use compared with placebo in patients with migraine who overuse acute medications.[70] [71] [72] [73] They also have good tolerability, suggesting the possibility of a major role in treatment of MOH, particularly when combined with withdrawal of the overused acute medication.[27] [74] [75]
    - Note that use of CGRP antagonists should be avoided in pregnancy due to a lack of data.

» A meta-analysis of randomized controlled trials that evaluated the relative efficacy of the above medications in patients with MOH against a background of migraine found that:[76]

- Studies assessing CGRP antagonist monoclonal antibodies included 1982 patients and showed a significant benefit compared with placebo, with a mean reduction of 2.68 migraine days per month (95% CI -3.46 to -1.91) and a 2.90 times

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higher likelihood (95% CI 2.23 to 3.78) of a ≥50% reduction in migraine or headache days from baseline.

- Studies assessing onabotulinumtoxinA included 1139 patients and showed a mean reduction in headache frequency of 1.92 days per month (95% CI -2.68 to -1.16) compared with placebo, although there were uncertainties regarding the likelihood of a ≥50% reduction in migraine or headache days.
- There was insufficient evidence available to determine the efficacy of topiramate for this purpose.

» Ongoing long-term use of the preventive medication, supported by regular follow-up consultations, is important to reduce the risk of relapse into renewed overuse of acute headache medication.[10]

» For more detail on preventive strategies, see Migraine in adults .

adjunct **occipital nerve blockade**

Treatment recommended for SOME patients in selected patient group

» One small study found that repeated sessions of occipital nerve blockade with lidocaine resulted in better outcomes than acute medication withdrawal alone in patients with MOH associated with triptan overuse.[77]

adjunct **nonpharmacologic preventive therapy**

Treatment recommended for SOME patients in selected patient group

» Noninvasive neuromodulation devices and acupuncture may also be considered as part of the preventive management approach.[10]

with tension-type headache as underlying disorder

adjunct **pharmacologic preventive therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» amitriptyline: 10-25 mg orally once daily at bedtime initially, increase gradually according to response, maximum 150 mg/day

Secondary options

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» mirtazapine: 15 mg orally once daily at bedtime initially, increase gradually according to response, maximum 30 mg/day

OR

» venlafaxine: 37.5 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 150 mg/day

» Preventive medication that targets the underlying headache disorder is an important part of the management plan for many patients with MOH.[10] [27]

- In principle, preventive medication can be used: before withdrawal of the overused medication; from the start of withdrawal as part of a combination strategy; or after withdrawal is complete.[10]
- In practice, the combination approach is often taken, with initiation of a preventive regimen used to facilitate withdrawal from the overused medication(s).
- A preventive regimen alone may be the best available option if the patient has uncomplicated MOH and is unwilling to discontinue the overused medication.[9] [10] This has been found to be noninferior to preventive medication with acute medication withdrawal.[54]

» If the patient's underlying primary headache disorder is tension-type headache (TTH), target the preventive regimen at that.

- No evidence is available from controlled trials to inform the most appropriate preventive approach for MOH against a background of TTH.[6]
- Amitriptyline, started at a low dose and titrated up to an effective dose, is the most commonly used pharmacologic option, although its use should be avoided during pregnancy if at all possible.[6] [78] [79]
- Mirtazapine and venlafaxine are second-line options but should also be avoided during pregnancy.[79]

» Ongoing long-term use of preventive medication, supported by regular follow-up consultations, is important to reduce the risk of relapse into renewed overuse of acute headache medication.[10]

» For more detail on preventive strategies for TTH, see Tension-type headache .

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	adjunct	**nonpharmacologic preventive therapy** Treatment recommended for SOME patients in selected patient group » There is evidence to support the effectiveness of relaxation training and cognitive behavioral therapy (CBT) in prevention of chronic TTH and some evidence to suggest benefit from acupuncture.[6] [78] [79]
adults: complex		
	1st	**multidisciplinary care and consider hospital admission** » A holistic, multimodal approach is needed for individuals with complex MOH. Patients with complex MOH are ideally managed by a specialist multidisciplinary team including neurologists or pain specialists and psychologists.[27] » Complex MOH is defined by one or more of: overuse of opioids, barbiturates, benzodiazepines, or other sedatives; the presence of psychiatric or substance abuse comorbidity; a history of relapse following previous treatment for MOH.[10] [27] » Consider inpatient care, where available, if: • The patient is discontinuing long-term use of an opioid, barbiturate, or benzodiazepine.[10] [27] [83] Careful monitoring of metabolic parameters, blood pressure, fluid balance, and sedation is generally required during withdrawal.[27] • The patient has been overusing acute medications from multiple drug classes. • The patient has had a prior attempt at medication withdrawal that either failed or resulted in a relapse of MOH.[6] [27][60] [83] • The patient has a significant psychiatric or substance misuse comorbidity.[6] [10] [83] » A combined approach to withdrawal, bridging medication, and preventive medication is taken for complex MOH, using similar principles to those employed for uncomplicated MOH, with the choice of preventive regimen dependent on the underlying primary headache disorder. See the *Adults: uncomplicated* patient group for details. • A gradual taper is recommended for withdrawing opioids, barbiturates, or benzodiazepines.[27] [63] In some

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Acute

situations, long-acting opioids or phenobarbital may be needed as a transition.[27] This is important for reducing the risk of withdrawal symptoms.[10]

» In addition, patients with complex MOH will likely benefit from additional interventions, such as behavioral interventions to address any anxiety, depression, and suicidality together with pain coping strategies.

- Overuse of pain medication has a strong behavioral element, and discontinuation involves substantial changes in behavior and lifestyle.[10]
- One trial involving 179 patients with uncomplicated MOH found that, compared with minimal behavioral support, maximal behavioral intervention - which consisted of intensive contact with a headache nurse for education, motivational interviewing, and value-based activity planning - significantly reduced acute medication use days, although there was no change in monthly migraine days.[80]
- Biofeedback and mindfulness have also shown promising results as add-ons to preventive medication.[81] [82]
- Acupuncture and neuromodulation techniques have limited evidence but may also be used.[10]

children and adolescents

1st **withdrawal from/reduction of acute medication ± rescue medication**

» There is limited high-quality evidence to inform management of MOH in children and adolescents.[10] In practice, the same general treatment strategies used for adults with MOH can be applied to children and adolescents. Education on the importance of reduction of acute medication is a vital aspect of care, and an emphasis on behavioral support is important.[10] [84]

» Withdrawal of the overused medication is recommended.[85]

- The few studies published on MOH in children with migraine show a response rate to drug withdrawal (i.e., a >50% reduction in headache frequency) that varies between 40% and 77%.[35] [86] [87] [88]
- If bridging therapy is needed for withdrawal symptoms, depending

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on the overused acute medication, options might include a simple analgesic (acetaminophen or a nonsteroidal anti-inflammatory drug [NSAID]) or a triptan.[89] Daily use of naproxen for 1 month to support withdrawal of the overused medication has been suggested as a reasonable strategy.[85]

- For more detail on bridging therapy options, see acute management in Migraine headache in children or Tension-type headache .
- If conventional approaches to bridging therapy fail, one group has suggested the following alternative strategies for children and adolescents with MOH:[85]
  - Occipital nerve blockade (with a mix of local anesthetic and corticosteroid)[85]
  - Hospital admission for a short course of intravenous dihydroergotamine if both simple analgesia (e.g., with naproxen) and occipital nerve blockade prove to be insufficient as bridging therapies to support withdrawal from the overused medication.[85]

adjunct **nonpharmacologic preventive therapy**

Treatment recommended for SOME patients in selected patient group

» Nonpharmacologic preventive strategies are preferred to long-term medication whenever possible. Trigger avoidance is recommended, and behavioral therapies such as cognitive behavioral therapy (CBT) or biofeedback are options.[79] [84] Neuromodulation devices have also shown promising early results.[90]

- Triggers to avoid often include inadequate hydration, skipping meals, poor sleep, and insufficient physical activity.[90]

with migraine as underlying disorder

adjunct **pharmacologic preventive therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» propranolol hydrochloride: children <35 kg body weight: 10 mg orally once daily initially, increase gradually according to response, maximum 60 mg/day in 3 divided doses; children >35 kg body weight: 20-40 mg orally three times daily

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Acute

Secondary options

» topiramate: children ≥12 years of age: 25 mg orally (immediate-release) once daily at bedtime for 1 week initially, increase gradually according to response, maximum 100-200 mg/day in 2 divided doses; 25 mg orally (extended-release) once daily for 1 week initially, increase gradually according to response, maximum 100-200 mg/day

OR

» amitriptyline: children ≥2 years of age: 0.1 to 0.25 mg/kg orally once daily at bedtime initially, increase gradually according to response, maximum 2 mg/kg/day in 2 divided doses (or 75 mg/day)

» If nonpharmacologic approaches are ineffective, preventive medication may become necessary, although evidence is scarce to support this for chronic migraine in children.[84]

» Most randomized controlled trials have failed to demonstrate any benefit over placebo.[91] Agents that can be considered include propranolol (though not in children with asthma), topiramate (with appropriate cautions over adverse effects), and amitriptyline combined with CBT (with caution around the risk of suicidal thoughts and behavior).[84] A cautious approach is required, with decision-making shared with patients and caregivers and regular monitoring of benefit versus potential harm, because evidence is limited and often conflicting.[91]

» Oral preventive medications can be poorly tolerated, and onabotulinumtoxinA and calcitonin gene-related peptide (CGRP) antagonists are not licensed for use in children in most countries.[10]

» For more detail on preventive medications, see Migraine headache in children .

with tension-type headache as underlying disorder — **adjunct** — **pharmacologic preventive therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» amitriptyline: children ≥2 years of age: 0.1 to 0.25 mg/kg orally once daily at bedtime initially, increase gradually according to response, maximum 2 mg/kg/day in 2 divided doses (or 75 mg/day)

MANAGEMENT

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Acute

» If nonpharmacologic approaches are ineffective, preventive medication may become necessary, although evidence is very scarce to support this for tension-type headache in children. Low-dose amitriptyline is sometimes used.[92] [93] [94]

Primary prevention

MOH is, in principle, preventable. However, high-quality studies on different preventive strategies are lacking; hence, recommendations are based on expert experience.[27]

- One of the most important preventive strategies is to increase awareness among both health professionals and the wider population about the relationship between frequent use of medications to treat acute headache episodes and the risk of an increase in frequency of headache days, with a transition from episodic to chronic headache.[27] [30] This can help to reduce the risk of MOH associated with overprescribing of medications such as triptans, barbiturates, and opioids for preexisting headache disorders.[10]

It is important to develop a comprehensive plan for the underlying primary headache disorder that promotes early and optimal use of preventive and rescue medications, in combination with nonpharmacologic therapies and lifestyle modifications. This can reduce the need for acute medications and thereby lower the likelihood of individuals progressing from lower to higher headache frequency.[10] [30]

- Regular reassessment of the effectiveness and tolerability of the preventive strategy is important so that adjustments can be made as necessary to achieve optimal management of the primary headache.[10]

In particular, if a primary or secondary headache disorder is not adequately addressed, the headache may persist and perpetuate the overuse behavior. Among patients with migraine (which is the most common underlying headache disorder in MOH), the American Headache Society recommends the following to reduce the risk of MOH:[31]

- Instruct individuals to limit use of acute medication to an average of two headache days per week. Offer preventive treatment to any patient who exceeds this limit.
- If a patient continues to exceed this limit while taking preventive treatment, consider: increasing the dose of preventive medication; changing the acute or preventive therapy; or adding a second preventive treatment.
- Consider recommending use of an approved neuromodulatory device as this may reduce the use of acute medication.
- Be aware that repeated use of oral calcitonin gene-related peptide (CGRP) antagonists (also known as gepants) does not appear to be associated with development of MOH.

Secondary prevention

There is a relatively high relapse rate after initially successful treatment for MOH, particularly in the first year.[27] In the absence of sufficient evidence to make strong recommendations, the European Academy of Neurology MOH guideline includes a good practice statement that regular follow-up is important and risk factors for relapse should be identified.[27]

For individuals identified as being at risk of relapse:[27]

- Use of a headache diary to monitor drug intake is probably effective in reducing relapse rates
- Short-term psychodynamic psychotherapy and/or mindfulness-based training can be considered and might possibly reduce early and late relapse rates

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- Ongoing treatment with preventive medication may be effective in preventing relapse.

Predictive factors that increase the risk of relapse of MOH include:[10]

- The presence of both migraine and tension-type headache as underlying headache disorders
- Longer duration of regular acute medication intake
- A higher number of acute treatments
- Overuse of opioids
- Lack of improvement after 2 months of withdrawal
- Smoking and/or alcohol consumption
- Poor sleep
- High levels of bodily pain.

Patient discussions

Ensure the patient is educated about the concept of MOH.

- This is an open, patient-centric process that begins with understanding the reason and context behind medication overuse.
- This is followed by education on the risk factors and consequences of medication overuse, and an explanation of the multidisciplinary treatment approach to MOH, involving pharmacologic and nonpharmacologic interventions.

The concept of medication overuse and its treatment can be uncomfortable for both healthcare providers and patients, as the advice to minimize or discontinue acute medications seems to contradict the objective of minimizing pain.

- Always emphasize that it is not the patient's fault for overusing acute medication.
- Avoid frightening the patient into stopping medications unsupervised or refraining from taking any acute medication at all.

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Monitoring

Monitoring

Follow-up monitoring of MOH is important because patients can have both short- and long-term relapses.[27] Ongoing use of the preventive medication, supported by regular follow-up consultations, is important to reduce the risk of relapse into renewed overuse of the acute headache medication.[10]

Focus the follow-up on both the underlying headache disorder and the MOH.

- Monitor adherence to the preventive medication and progress with withdrawal of the overused medication(s).[10]
- Ask the patient to keep a headache diary to evaluate the success of treatment. This can be used to assess the monthly number of headache days and intensity of symptoms, and the number of days on which acute medication is used and its effectiveness.[10] [27] [American Headache Society: weekly headache diary] (https://americanheadachesociety.org/wp-content/uploads/2018/05/Weekly_Headache_Diary.pdf) [National Headache Foundation: headache diary] (https://headaches.org/wp-content/uploads/2021/05/HEADACHE-DIARY.pdf)
- During clinic visits, be alert to any change in headache pattern, or the development of any red flag that may be suggestive of a new primary or secondary headache and that might require further investigation.

Complications

Complications	Timeframe	Likelihood
refractory headache	**variable**	**high**
Undiagnosed or untreated MOH may cause frequent or daily headache or worsening of headache, including increased frequency, intensity, and headache-related disability.[10]		
organ damage (e.g., liver toxicity, kidney injury, respiratory suppression) from overuse of specific medications	**variable**	**high**
Organ damage can occur depending on the medication that is overused. For example: • Overuse of acetaminophen may cause liver toxicity • Overuse of a nonsteroidal anti-inflammatory drug (NSAID) may lead to kidney injury • Overuse of opioids may induce respiratory suppression or hyperalgesia • Overuse of triptans or ergot derivatives may be associated with cardiovascular adverse effects.		

Prognosis

In general, the prognosis for patients with MOH is favorable. One systematic review found that 66% to 100% of patients were free of medication overuse at 2-6 months, and 60% to 83% at 1 year, with the best outcomes for those who had withdrawal therapy combined with preventive medication.[96]

- However, it also found that approximately 10% to 40% of patients experience relapse within 5 years after withdrawal, with most relapses occurring during the first year.

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FOLLOW UP

Predictive factors that increase the risk of relapse of MOH include:[10]

- The presence of both migraine and tension-type headache as underlying headache disorders
- Longer duration of regular acute medication intake
- A higher number of acute treatments
- Overuse of opioids
- Lack of improvement after 2 months of withdrawal
- Smoking and/or alcohol consumption
- Poor sleep
- High levels of bodily pain.

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Diagnostic guidelines

International

International classification of headache disorders, 3rd edition (https://ihs-headache.org/en/resources/guidelines) [1]

Published by: International Headache Society **Last published:** 2018

European Academy of Neurology guideline on the management of medication-overuse headache (https://www.ean.org/research/ean-guidelines/guideline-reference-center) [27]

Published by: European Academy of Neurology **Last published:** 2020

Treatment guidelines

International

International classification of headache disorders, 3rd edition (https://ichd-3.org) [1]

Published by: International Headache Society **Last published:** 2018

European Academy of Neurology guideline on the management of medication-overuse headache (https://www.ean.org/research/ean-guidelines/guideline-reference-center) [27]

Published by: European Academy of Neurology **Last published:** 2020

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Online resources

1. American Headache Society: weekly headache diary (https://americanheadachesociety.org/wp-content/uploads/2018/05/Weekly_Headache_Diary.pdf) *(external link)*

2. National Headache Foundation: headache diary (https://headaches.org/wp-content/uploads/2021/05/HEADACHE-DIARY.pdf) *(external link)*

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Key articles

- International Headache Society. 2018 International Headache Society international classification of headache disorders (ICHD), 3rd edition. 2018 [internet publication]. Full text (https://ichd-3.org)
- Ashina S, Terwindt GM, Steiner TJ, et al. Medication overuse headache. Nat Rev Dis Primers. 2023 Feb 2;9(1):5. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/36732518?tool=bestpractice.bmj.com)
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+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
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WC1H 9JR
UK

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Contributors:

// Authors:

Sait Ashina, MD, FAHS

Director
BIDMC Comprehensive Headache Center, Beth Israel Deaconess Medical Center, Assistant Professor of Neurology and Anesthesia, Department of Neurology and Anesthesia, Critical Care and Pain Medicine, Harvard Medical School, Boston, MA
DISCLOSURES: SA declares that he has received fees for consulting from Allergan, AbbVie, Eli Lilly, Impel NeuroPharma, Linpharma, Lundbeck, Satsuma, and Theranica. He has received fees for teaching from Eli Lilly and Teva. He has received unrestricted research grants from AbbVie, Eli Lilly, and NINDS, paid to his hospital/institution. SA also serves as Associate Editor for the journals Neurology Reviews, Frontiers in Neurology, and BMC Neurology, and is an advisory board member for the Journal of Headache.

Hsiangkuo Yuan, MD, PhD

Associate Professor of Neurology
Department of Neurology, Director of Clinical Research, Jefferson Headache Center, Thomas Jefferson University, Philadelphia, PA
DISCLOSURES: HY declares that he has received a grant from the National Institutes of Health (reference R44NS115460). He has served as a site investigator for Teva, AbbVie, Trillen, and Thermaquil. He has also served on advisory boards or as a consultant for Silva, Clexio Biosciences, and Pfizer.

// Peer Reviewers:

Benjamin Wakerley, FRCP, PhD

Consultant Neurologist
Headache Lead, University Hospital Birmingham NHS Foundation Trust, Honorary Clinical Associate Professor, University of Birmingham, Birmingham, UK
DISCLOSURES: BW declares that he has received speaking fees from AbbVie. He is the founder of Ceftronics Ltd and a creator of the CEFREF headache app.

Alyssa Ann LeBel, MD

Director
Chronic Headache Program, Boston Children's Hospital, Associate Professor of Anesthesia, Harvard Medical School, Boston, MA
DISCLOSURES: AAL declares that she has no competing interests.