Clinical features, pathophysiology, and treatment of medication-overuse headache

Lancet Neurol 2010; 9: 391–401

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Abstract

- Medication-overuse headache (MOH)
- Definition:
  Headache Induced by the overuse of analgesics, triptans, or other acute headache compounds.
- Prevalence of MOH:0.7% to 1.7%.
- Most patients with MOH have migraine and overuse triptans or simple analgesics.
- Pathophysiology of MOH is unknow.

- Genetic susceptibility has been postulated.
- Treatment of MOH
  - > Abrupt withdrawal therapy and then initiation of an appropriate preventive drug therapy.
  - >No clear evidence on which method of withdrawal therapy is the most efficacious.
  - >Withdrawal symptoms can be treated with steroid.
- MOH can severely affect the quality of life of patients, it needs to be recognized early to enable appropriate treatment to be initiated.

Introduction

- MOH is a chronic disorder that results from the overuse of analgesics, triptans, or other acute headache compounds.
- MOH have a severe effect on the quality of life of patients and can have a high economic burden on society.
- 1951 : Chronic headache in patients with migraine or tension-type headache who were overusing ergotamine compounds was reported; withdrawal of these substances led to fewer occurrences of this chronic headache (call ergotamine headache).

- In a second study, the authors confirmed this finding and extended it to the overuse of combinations with barbiturates and caffeine.
- 1980s, MOH caused by simple analgesics and by combined analgesics were published, and MOH was recognized as a general problem of treatment for all headache subtypes.
- MOH has become one of the major challenges in headache treatment.
- In recent years studies have shown that MOH has a distinct clinical picture and a clear biological basis.

Epidemiological and socioeconomic aspects

- Prevalence:
  >Similar across different countries.
  6-month prevalence of MOH in Germany: 1·0%; F (74%); M (26%); mean age 53 In other countries, the prevalence rates were similar (average 1·1 %)
  Among patients aged older than 65 years, the prevalence rates
  1·0% in Taiwan
  1·7% in Italy

	Period	Prevalence (%)	Female sex (%)	Mean age (years)
Taiwan[7]	1 year	1·1	62	45±15
Norway[8]	..	0·9	66	..
Spain[9]	..	1·4	92	45
Netherlands[10]	1 year	0·7	72	43±8
Norway[11]	1 year	1·7	76	..
Germany[6]	6 months	1·0	74	53

..=data not available

Table 1: Prevalence rates and demographic features of medication-overuse headache in population-based studies

- Incidence
  - >No specific population-based studies.
  - >One study on episodic migraineurs (n=532), the 1-year incidence of chronic headache was 14%, with a higher risk for patients who had a higher headache frequency at baseline and for patients taking greater amounts of analgesics

    Neurology 2004; 62; 788-790
  - >Patients in headache clinics or centers of tertiary care
    - *. patients with MOH form the largest group, together with migraine and tension-type headache.
    - *. Europe 30%, USA:50% present MOH

- Patients with MOH
  - >Low income
  - >Lower education level

    (Cephalagia 2002;22:672-79)
  - >Poorer quality of life

    (Cephalagia 2006;26:1443-50)

Clinical picture

- First classification and diagnostic criteria: 1988 by International Headache Society (IHS).
  - >Drug-induced headache
  - > Differentiated between only ergotamine-induced and analgesic abuse headaches.
- 2004 IHS classification (ICHD-II)
  - -.Some subtype were missing
  - -.Headache feature of MOH can not be defined in general.
- 2005 new diagnostic criteria –panel 1
- 2006 second revision to MOH criteria of (ICHD-II)-panel 2

Panel 1: Current diagnostic criteria for medication-overuse headache, as proposed by the International Headache Society[25]

Medication-overuse headache (8.2)

Diagnostic criteria

A Headache* present on ≥15 days per month fulfilling criteria C and D

B Regular overuse† for ≥3 months of one or more drugs that can be taken for acute or symptomatic treatment of headache‡

C Headache has developed or markedly worsened during medication overuse

D Headache resolves or reverts to its previous pattern within 2 months after discontinuation of overused medication§

Subtypes of medication-overuse headache

Ergotamine-overuse headache (8.2.1)

Ergotamine intake on ≥10 days per month on a regular basis for >3 months

Triptan-overuse headache (8.2.2)

Triptan intake (any formulation) on ≥10 days per month on a regular basis for >3 months

Analgesic-overuse headache (8.2.3)

Intake of simple analgesics on ≥15 days per month on a regular basis for >3 months

Opioid-overuse headache (8.2.4)

Opioid intake on ≥10 days per month on a regular basis for >3 months

Combination analgesic-overuse headache (8.2.5)

Intake of combination analgesic medications¶ on ≥10 days per month on a regular basis for >3 months

Medication-overuse headache attributed to the combination of acute medications (8.2.6)

Intake of any combination of ergotamine, triptans, analgesics, and/or opioids on ≥10 days per month on a regular basis for >3 months without overuse of any single class alone‖

Headache attributed to other medication overuse (8.2.7)

Regular overuse** for >3 months of a medication other than those described above

Probable medication-overuse headache (8.2.8)

A Headache fulfilling criteria A, C, and D for 8.2

B Medication overuse fulfilling criterion B for any one of the subforms 8.2.1 to 8.2.7

C One or other of the following:

1 Overused medication has not yet been withdrawn

2 Medication overuse has ceased within the last 2 months but headache has not yet resolved or reverted to its previous pattern

Panel 2: Appendix criteria for medication-overuse headache (for research and clinical trial purposes only)[26]

Medication-overuse headache (appendix 8.2)

Diagnostic criteria:

A Headache present on ≥15 days per month

B Regular overuse for >3 months of one or more acute/symptomatic treatment drugs as defined under subforms of 8.2:

1 Ergotamine, triptans, opioids, or combination analgesic medications on ≥10 days per month on a regular basis for >3 months

2 Simple analgesics or any combination of ergotamine, triptans, analgesics, or opioids on ≥15 days per month on a regular basis for >3 months without overuse of any single class alone

C Headache has developed or markedly worsened during medication overuse

Snydromatic feature

- Headache leading to MOH
  - >migraine in most case
  - >Start early in life
  - >Women (95%)

    (Neurology 2004;62:1338-42)

- Risk factors for development of MOH
  - >Female
  - >Lower level of education
  - >Married
  - >Have migraine remission during pregnancy
  - >Higher use of health-care resources
  - >Unemployed
  - >Polypharmacy (sedative-hypnotics, anti-hypertensives)

(Headache 47. 65-72.2007)

- Mean number of monthly drug:10 to 180 average 50.
- Recommendation of expert:

  Not to count the number of drug units per month but the number of days permonth with intake of acute drug.
- MOH mainly occurs in patients with prinary headache.

  migraine and tension-type headache, cluster headache.
- Exception to the rule

  post-traumatic headache

  some secondary headache

- Patients with other pain disorder such as rheumatic disease and no headache disorder
  - -.Do not develop chronic headache
  - -.If these patient have a susceptibility to migraine, the can develop chronic daily headache.
- Triptans and combined analgesics have the highest risk of inducing MOH.

Comorbidities

- MOH more comorbid disorders than do episodic headache types (except allergies and thyroid function disorders, which are more common in episodic headaches).
- Subclinical obsessive-compulsive disorder, anxiety and mood disorders more frequent in MOH than episode migraine.
- Increased risk of mood disorders, anxiety, and disorders associated with the use of psychoactive substances other than analgesics in patients with MOH

- This risk was significantly more frequent even before the transformation from migraine into MOH.
- The comorbidity with psychiatric disorders is not only occurs in patients with migraine but also occurs in patients with tension-type headache.

- According to (DSM-IV), the overuse of analgesics and acute migraine drugs fulfils the criteria of substance abuse disorder in two-thirds of all patients with MOH.
- . High prevalence of smokers and individuals with a BMI more than 30 among patients with MOH.
- Sleeping problems are also more common

Types of medications overused

- All acute drugs for the treatment of headache could cause MOH (ie, ergotamine derivatives, barbiturates, triptans, simple and combined analgesics, opioids, benzodiazepines, and possibly also caffeine).
- whether simple analgesics and dihydroergotamine are able to induce MOH is still debated

- Untill the beginning of the 1980s, only ergotamine derivatives were thought to cause MOH, then analgesics, particularly combined analgesics, were identified as a cause of MOH.
- Nowadays, triptans are the most frequent drug taken by patients who develop MOH.
- Calcitonin gene-related peptide antagonists in the acute treatment of migraine attacks has been suggested to not cause MOH.
- The range of compounds taken (not necessarily overused) by patients with MOH varies widely

- In a Spanish study, for example, of 4855 people aged 14 years or over, most patients had taken paracetamol (54%), and others had taken caffeine (49%), ergotamine (38%), propyphenazone (35%), aspirin (18%), codeine (13%), and triptans (3%).
- Triptans and ergotamine derivatives are more likely to induce MOH than are simple analgesics.

- Contradictory results: whether ergotamine derivatives or triptans need a shorter duration to induce MOH and whether smaller amounts of ergotamine derivatives or triptans are sufficient to cause MOH.
- The headache features of MOH caused by ergotamine derivatives are more severe than those caused by triptans.
- The combination of triptan and analgesic overuse causes higher headache frequency and intensity and more accompanying symptoms than the overuse of triptans alone.

Complications of MOH

- MOH can lead to several somatic complications, most of which are caused by the side-effects of the overused drugs.
- Most of the problems in patients with MOH have been described for ergotamine overuse.
  sensory neuropathy, slowing of central cognitive processing, and decreased distensibility or changes in the arterial vessel wall structure of the brain-supplying arteries. Distress.

Pathophysiology

Neurophysiology

- Mean blood flow velocity was increased in patients with ergotamine-overuse headache compared with patients with simple analgesic-overuse headache and healthy control individuals. (Funct Neurol 2008;23:83-86)
- Increase latencies of SSR.

  (cephalalgia 1998;18:216-221)
- Experimental electrical peripheral pain stimulation causes central sensitisation in patients with MOH

Genetic factors

- The risk of MOH is increased threefold if there is a family history of MOH or other substance abuse such as drug or alcohol abuse.
- The risk of developing drug overuse or substance abuse is increased fourfold if another family member has had MOH.
- The Val66Met polymorphism in brain-derived neurotrophic factor, which is related to behavioral disorders and substance abuse, is associated with increased analgesic drug consumption in patients with MOH.

- This finding suggests that MOH is, at least in part, a substance abuse disorder rather than just a complication of the underlying idiopathic headache disorder.
- Allele 10 of the dopamine transporter gene (SLC6A3; also known as DAT1) was significantly under-represented in patients with MOH compared with patients with episodic migraine.
- The different genotypic and allelic distributions of the known polymorphisms of several 5-HT receptor genes do not seem to have a role in the genetic susceptibility to MOH.

Endocrine and neurotransmitter function

- Increased concentrations of orexin A and corticotrophin-releasing factor have been detected in the CSF of patients with MOH and, to a lesser extent, in patients with chronic migraine.
- The CSF glutamate was significantly lower in patients with MOH who overused triptans compared with patients with migraine who did not overuse triptans, although concentrations were significantly higher compared with healthy control individuals.

- Endocrinological stimulation tests patients with MOH had reduced growth hormone and thyroid stimulating hormone responses, and adrenocorticotropic hormone and cortisol concentrations were increased.
- 5-HT_2 Receptors were upregulated, more dense on platelet membrane.
- The platelet content of 5-HT was low, suggesting that suppression of 5-HT uptake induced by medication overuse might be one mechanism that underlies MOH
- Increased activity of the serotonin transporter mechanisms in these patients compared with controls. (J headache pain 2008; -: 109-12.)

- MOH have shown
  decreased β-endorphin and opioid concentrations,
  increased norepinephrine turnover, and
  increased inositol phosphate production in platelets.

Functional imaging

- PET study

  After withdrawal therapy 3 weeks, the earlier hypometabolism of the bilateral thalamus, anterior cingulate gyrus, insula/ventral striatum, and right inferior parietal lobe normalised in patients with MOH.
- This finding is also known from other types of drug dependency and again suggests that MOH might be a consequence of a susceptibility to substance abuse.

Psychological mechanisms

- It has also been assumed that MOH is a subtype of drug addiction. Most of drugs taken by patients with MOH contain substances with psychotropic effects. (barbiturates, opoids, caffeine).
- However, there is no evidence for true addiction to triptans or to simple analgesics.
- Therefore, this mechanism can not fully explain the development of MOH.

Withdrawal treatment

Withdrawal procedure

- No study has compared abrupt withdrawal treatment with tapered withdrawal.
- Most headache specialists are in favor of abrupt discontinuation of pain medication because this is thought to be associated with fast resolution of the drug-induced pain-coping behavior.

- Tapered withdrawal might be recommended for opioids, barbiturates and, in particular, benzodiazepines to reduce withdrawal symptoms.
- Withdrawal symptoms are
  Worsening of the headache, nausea, vomiting, arterial hypotension, tachycardia, sleep disturbances, restlessness, anxiety, and nervousness.
- The withdrawal headache last between 2 and 10 days, but can persist for up to 4 weeks. triptans (mean 4·1 days) ergotamine (mean 6·7 days) or NSAIDs (mean 9·5 days).

- Non-pharmacological approaches for treatment of MOH are important tools.
- Combination of short-term psychodynamic psychotherapy and pharmacological therapy has had better outcomes than has pharmacological therapy alone.
- Inpatient withdrawal and outpatient withdrawal treatment

  both methods significant decrease in headache days per month after 12 months and a reduction in migraine disability scores without superiority of one method.

- Outpatient treatment is the preferred method in most cases.
- Advantages of inpatient withdrawal are that it enables the close monitoring of medication intake and clinical state, immediate treatment of withdrawal symptoms, and treatment with intravenous drugs.
- Overuse of opioids, barbiturates, or benzodiazepines, psychological problems, severe medical comorbidities, severe withdrawal symptoms (eg, vomiting and status migrainous), or previous medication withdrawal failure are reasons for inpatient treatment

Treatment of withdrawal headache

- Studies of specific preventive therapies for MOH are not available.
- The choice of preventive drug in MOH should be based on the primary headache (migraine vs tension-type headache), the possible side-effects of the drugs, the comorbidities, and the patient's preference and previous therapeutic experiences.

- Positive effects of different substances, such as valproic acid and topiramate, in the prophylactic treatment of chronic daily headache with excessive medication intake.
- In patients with chronic migraine and MOH, reduction of the mean number of migraine days per month in patients treat with topiramate.
- Side effect 75% (topiramate), (37% placebo) .
- The reduction in headache occurrence was not large enough.

- Oral prednisolone during the first 6 days after medication withdrawal revealed no effect of the corticosteroid on a combined primary endpoint.
- 400 patients with chronic daily headache and who had medication overuse, treatment with 60 mg prednisone for 2 days that was tapered down by 20 mg every other day effectively reduced rebound headache and withdrawal symptoms.
- Duration of withdrawal headache was significantly lower in the prednisone group compared with the placebo group.

- These results suggest that corticosteroids might be effective for treatment of withdrawal symptoms in patients with MOH.

Prognosis after withdrawal therapy

- The prognosis of MOH depends on use of an appropriate withdrawal therapy.
- Relapse rate seems to be about 30% after 1 year, regardless of whether inpatient, outpatient, or advice-alone treatment was used.
- Relapse rate: Table 2

	Relapse rate	Follow-up	Type of withdrawal therapy
Andersson[108]	9%	6 months	Outpatient (n=44)
Tfelt-Hansen and Krabbe[107]	29%	1 year	Inpatient (n=40)
Ala-Hurula et al[106]	19%	3–6 months	Inpatient (n=23)
Isler[3]	16%	1–30 months	Inpatient (n=29), outpatient (n=75)
Henry et al[109]	33%	4–24 months	Inpatient (n=22)
Granella et al[110]	22%	6 months	Inpatient (n=21), outpatient (n=74)
Baumgartner et al[111]	24%	17 months	Inpatient (n=54)
Hering and Steiner[112]	4%	6 months	Outpatient (n=46)
Silberstein and Silberstein[113]	13%	24 months	Inpatient (n=50)
Pini et al[114]	38% 25%	4 months 4 months	Outpatient (total n=102) Inpatient
Schnider et al[115]	39%	5 years	Inpatient (n=38)
Suhr et al[116]	15% 25%	5·9 years 5·9 years	Outpatient (n=41) Inpatient (n=60)
Fritsche et al[117]	49%	2–4 years	Not specified (n=83)
Katsarava et al[118]	31% 41% 45%	6 months 1 year 4 years	Inpatient (total n=80) Inpatient (total n=80) Inpatient (total n=80)
Relja et al[119]	0%	3 months	Inpatient (n=101)
Rossi et al[120]	14% 23% 25%	1 year 1 year 1 year	Advice only (n=40) Outpatient detoxification (n=39) Inpatient (n=39)
Bøe et al[121]	30%	1 year	Outpatient (n=80)
Ghiotto et al[122]	23%	1 year	Inpatient (n=114)
Zidverc-Trajkovic et al[123]	40%	1 year	Inpatient and outpatient (n=240)

Table 2: Relapse rates after different types of withdrawal therapy in studies of medication-overuse headache

- Increase risk for relapse of MOH (Italian study)
  - >a long duration of migraine before MOH.
  - >a high frequency of migraine after withdrawal therapy.
  - >a high number of previous preventive treatments.
- The prognosis was better for patients who had migraine as the underlying primary headache disorder than for patients who had tension-type headache and for ergotamine or triptan withdrawal than for analgesic withdrawal.

MOH in children and adolescents

- Taiwan detected a 1-year prevalence of 0·3% in adolescents who overused analgesics available over the counter.
- 0·5% with a preponderance in females of 4:1 was found in Norwegian adolescents.
- Children also benefit from withdrawal therapy.

- At 1 month after withdrawal therapy, about 53% of all children had a reduction in headache frequency of more than 90% regardless of whether they were on preventive medication or not; the only predictor for a poor outcome after withdrawal therapy was a duration of MOH of longer than 2 years

Conclusions

- MOH is a common and disabling headache disorder that should be familiar to every neurologist.
- Patients with MOH should be referred to appropriate centers for withdrawal therapy.
- The relapse rate after successful withdrawal therapy is still consistently about 25–30%.

- MOH also emphasis the need for effective preventive strategies such as early initiation of prophylactic headache drugs and behavioral therapy.
- Increased public awareness about the need to restrict intake of acute headache medication should also contribute to primary prevention strategies.


Thank You