European Headache School
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MEDICATION OVERUSE HEADACHE

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Historical data

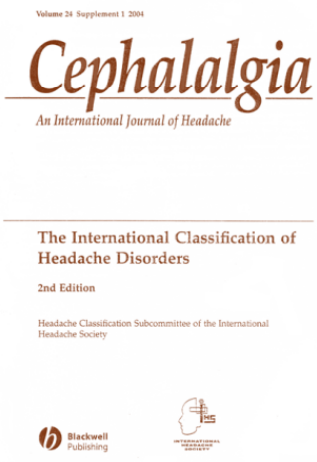
- **First cases were described in XVII century**
- **Wolfson i Graham first published in 1949. a case of ergotamine induced headache**
- **Kudrow in 1982. showed that analgesic withdrawal reduced headache frequency**
- **"rebound headache", "ergotamin headache", "medication-misuse headache", "painkiller headache"**

Classification

- International Classification of Headache Disorders, ICHD-I 1988. "drug induced headache"
- secondary headache induced by chronic substance use or exposure
- ergotamine and analgesics

Cephalalgia 1988; 8 (Suppl. 7): 1–96

International Classification of Headache Disorders ICHD-II 2004



"Medication overuse headache" MOH

Medication overuse was determined by frequency of drug intake (days per month), and not by total amount of taken medications

Cephalalgia 2004; 24 (Suppl. 1): 9-160

Medication overuse headache subtypes

8.2.1	Egotamine	≥ 10 days/m
8.2.2	Triptans	≥ 10 days/m
8.2.3	Aanalgesics	≥ 15 days/m
8.2.4	Opioids	≥ 10 days/m
8.2.5	Combination medication	≥ 10 days/m
8.2.6	Combination of acute medications*	≥ 10 days/m
8.2.7	Other drugs	
8.2.8	Probable MOH	

**Expert group, 2005.*

Medication overuse headache

ICHD-II 8.2

*Revised criteria *, 2006.*

A. Headache present on >15 days/month

B. Regular use for more than 3 months of acute medication

C. Headache has developed or markedly worsened during medication overuse

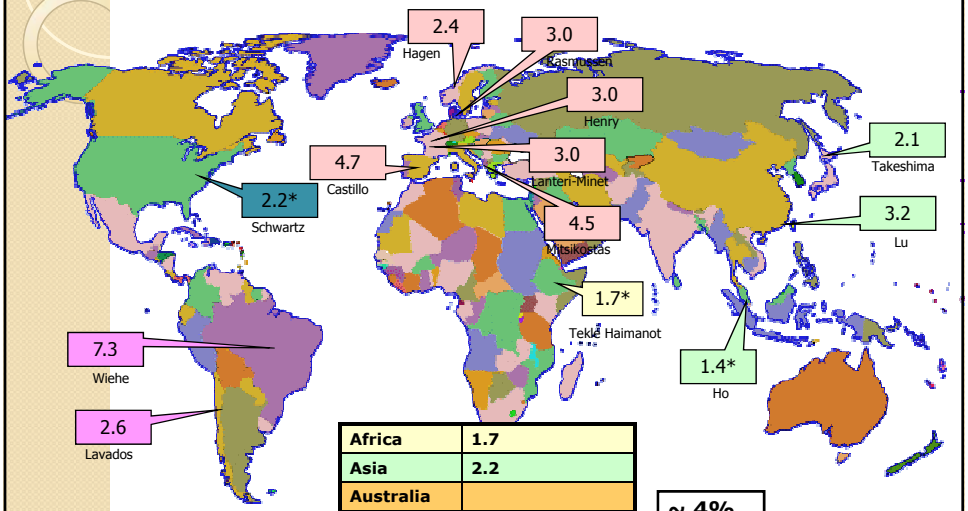
D. Headache resolves or reverts to its previous patterns within 2 months after discontinuation of medication

*** proposal of appendix criteria for MOH no longer requires the improvement of headache after withdrawal**

Is medication overuse cause of chronic headache or just a reflection of chronicfication?

Chronic headache in adults
One year prevalence

Headache maps
Lifting the Burden of Headache



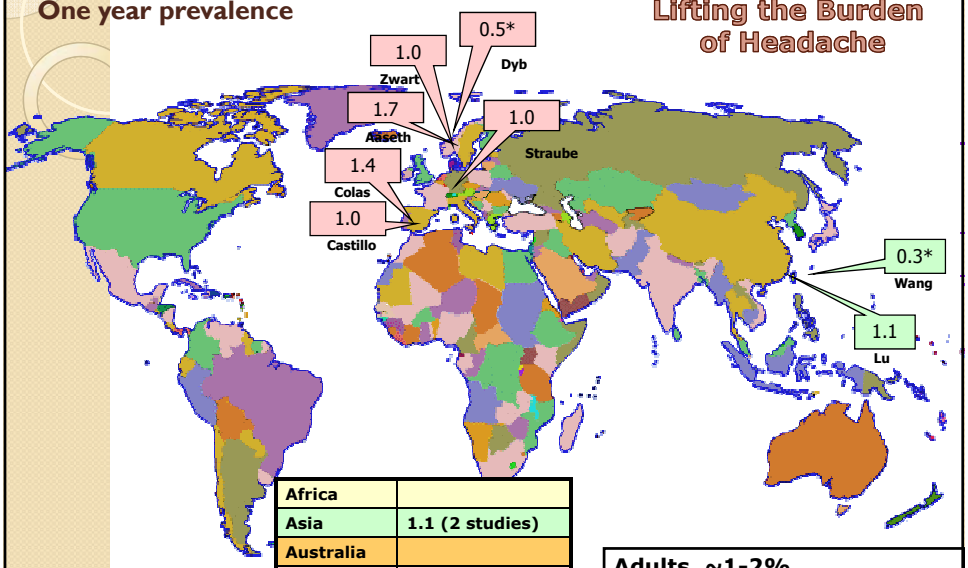
Africa	**1.7**
Asia	**2.2**
Australia	
Europe	**3.4**
N. America	**2.2**
S. America	**5.0**

~ 4%

MOH

One year prevalence

Headache maps
Lifting the Burden of Headache



Africa	
Asia	1.1 (2 studies)
Australia	
Europe	1.3 (6 studies)
N. America	
S. America	

Adults ~1-2%
Adolescents ~ 0.5%
Women in fifth decade~ 5%

*Adolescents

Medication overuse

- Population studies
- *Switzerland*

  4.4% of men i 6.8% women take analgesics at least once a week

  2.3% daily

  Gutzwiller et al. 1985.
- *Germany*

  1% of population takes 1-10 tablets of analgesics every day

  Schwarz et al. 1985.
- *Norway*

  5% of population uses analgesics on a daily basis

  Zwart et al. 2003.

Medication overuse

Triptans

Sumatriptan

5.1% of migraine patients takes an average of one or more doses per day

Gaist et al. BMJ 1998.

1% of patients accounted for 20% of the total consumption

Gaist et al. Eur J Clin Pharmacol 1996.

Triptans are used by 1.3% of Dutch population
10.4 % are overusers by ICHD-II criteria

Dekker et al. Cephalalgia 2011.

Medication overuse
cause or consequence?

- **Chronic daily headache study in patients who underwent total colectomy for ulcerative colitis**
- **19 % of all patients treated with opiates developed chronic daily headache, and all of them had a previous history of migraine!**
- **No patient without migraine history developed chronic headache**

Wilkinson et al. 2001.

Medication overuse
cause or consequence?

- **NSAIDs used daily in a large doses for rheumatoid arthritis do not induce chronic daily headache in a subjects who have no preexisting primary headache disorders**
- **In patients with migraine are strong risk factor for chronification**

Bahra et al. 2004.

✓ ***Even when the overused medication is used for reasons other than headache it may still be associated with development of chronic headache***

✓ ***Acute medication overuse induces chronic headache only in those with preexisting primary headache***

Risk factors

- **Primary headache**

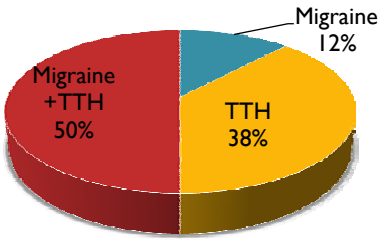
21% of patients suffering from TTH develops MOH

Schnider et al. Cephalalgia 1995.

Cluster headache patients with a personal or family history of migraine may also develop MOH

Paemeleire et al. Neurology 2006.

Primary headache



- **Patients with migraine and TTH are at greater risk for medication overuse**

Zeeberg et al. Neurology 2006.

Medications

- **Opioids and barbiturats are associated with migraine progression and MOH regardless of the initial frequency of headache**
- **Triptans and NSAIDs induce migraine progression and MOH in those with high frequency of migraine at baseline (10-14 days per month) but not overall**

American Migraine Prevalence and Prevention Study-AMPP

Bigal et al. Headache 2008.

Drugs that cause MOH

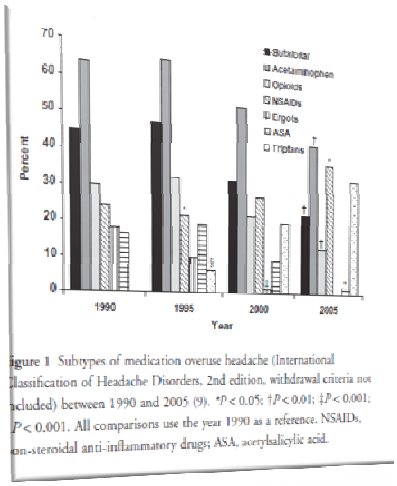


Figure 1 Subtypes of medication overuse headache (International Classification of Headache Disorders, 2nd edition, withdrawal criteria not included) between 1990 and 2005 (9). *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$; §$P < 0.001$. All comparisons use the year 1990 as a reference. NSAIDs, non-steroidal anti-inflammatory drugs; ASA, acetylsalicylic acid.

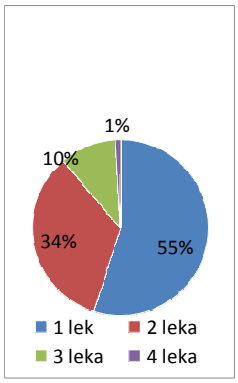
90% of patients take more than one specific drug

Diener et al. The Lancet Neurology, 2006.

Meskunas et al. Headache 2006.

Headache center, Neurology Clinic, Belgrade

The profile of overused medications in 240patients with MOH



Overuse of one drug
NSAID 25.8%
Combination medication 21.7%

Overuse of 2 or more different drugs
Combination medication 88.0%
NSAID 78.7%
Ergotamins 36.1%

Triptans 9%

Other risk factors

- Bihevioral factors
- Low socio-economic status
- Obesity
- Sleep disturbances
- Head trauma
- Smoking
- Coffee consumption
- Life without partner

Scher et al. Headache 2008.

Pathophysiology

- Unknown!
- Genetic predisposition
- "Down" regulation of receptors and enzymes
- Structural changes and impairment of the antinociceptive activity of PAG
- Orbitofrontal cortex dysfunction
- Central sensitization

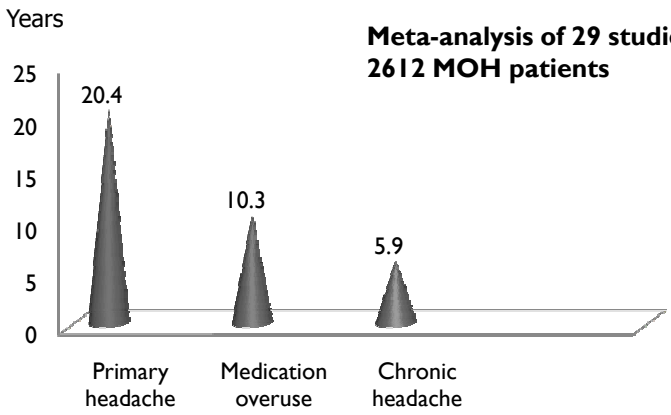
Bigal , Lipton 2009.

Clinical features

- Depend on primary headache type, and type of overused medication
- Patients who overuse analgesics and ergots typically develop daily tension type headache
- Triptans overuse result in to a significant increase in the frequency of migraine attacks (39.5%), or to the development of almost daily migraine-like (26.3%) or tension type (32.4%) headache
- Migraine transformation

Limmroth et al. Neurology 2002.

Duration of primary headache, medication overuse and chronic daily headache in patients with MOH



Meta-analysis of 29 studies with 2612 MOH patients

Diener, The headaches, 2nd edition, 1999.

Treatment

- MOH patients consult an average 5.5 physicians who prescribe 8.6 different therapies

Diener, The Lancet Neurology 2004.

- Placebo- controlled double-blind trials for a specific treatment of MOH are almost completely missing
- Treatment effectiveness is generally estimated from the results of open-label trials, retrospective case reviews, and clinical observations

MOH treatment

Standard treatment protocol:

1. Withdrawal of the overused medication
2. Initiation of bridge (replacement) therapy to treat withdrawal symptoms
3. Initiation of preventive therapy
4. Nonpharmacological approach

The goals:

- Reducing a headache frequency
- Reducing medication overuse
- Improve responsiveness to acute and preventive therapy

Therapeutic dilemmas

- Should medication withdrawal be abrupt or gradual?
- What are the most effective therapeutic protocols for controlling withdrawal symptoms?
- Should patients receive replacement therapy?
- Should patients be managed in inpatient or outpatient settings?
- Should preventive treatment be started before, during or after withdrawal?
- What are the most effective preventive treatments?

Medication withdrawal

- Almost all patients have some benefit from the detoxification
- Goal: breaking the cycle of chronic daily headache and return to the previous episodic pattern
- Clinical experience shows that after successful detoxification, prophylactic therapy which was not previously effective becomes effective

Diener i Limmroth 2004

Medication withdrawal

- **Medication withdrawal symptoms precede clinical improvement**
- **Most pronounced in the first 4 days of detoxification**

Mathew et al. 1999.

- **Can persist 2-3 weeks**

Krymchantowski i Barbosa, 2000.

- **Worsening of headache, nausea, vomiting, arterial hypotension, tachycardia, sleep disturbances, restlessness, anxiety, nervousness, seizures and hallucinations**

Duration of the withdrawal symptoms

- **Shortest in patients overusing triptans (4,1 days)**
- **Ergots (6,7 days)**
- **NSAID (9,5 days)**

Katsarava et al. Neurology 2002.

Replacement strategies (bridge therapy)

- Treatment of withdrawal headache and associated symptoms
- Administered for short period up to 2 weeks
- Many different replacement strategies for treating medication withdrawal symptoms in MOH have been proposed and found to be effective, almost exclusively in uncontrolled, unblinded studies
- Dihydroergotamine, antiemetics, corticosteroids, NSAID, narcoleptics, valproic acid, lidocaine, triptans, fluids….

Replacement strategies (bridge therapy)

- No evidence-based recommendation can be made on the most effective replacement therapy
- By expert consensus, headache drugs and analgesics are not recommended for the treatment of headache during withdrawal therapy except single intravenous administrations in very severe cases
- Corticosteroids (at least 60 mg prednisone or prednisolone) and amitriptyline (up to 50 mg) are possibly effective in the treatment of withdrawal symptoms

good practice point recommendation

EFNS Guidelines, Eur J Neurol 2011

Corticosteroids

- **Prednisone 100 mg,** for 5 days significantly reduces the duration of withdrawal headache

Pageler et al. Cephalalgia, 2007.

- **Prednisone 60 mg** for 2 days, and tapering down by 20 mg every other day effectively reduced rebound headache and withdrawal symptoms

Krymchantowski et al.Cephalalgia, 2000.

- Oral prednisolone during the first 6 days after medication withdrawal revealed no effect on a intensity and duration of withdrawal headache

Boe MG et al. Neurology 2007.

Treatment of withdrawal headache

- A prospective, randomized, open–label study which evaluated 120 MOH patients without comorbid psychiatric illness and addictive habits indicated that **strong advice** to withdraw medications was equally effective as an outpatient or inpatient detoxification programmes with structured protocols

Rossi, Nappi, Cephalalgia 2006.

Is replacement therapy really necessary?

Outpatient/Inpatient withdrawal

- Outpatient and inpatient programmes could be equally effective
- Outpatient vs. inpatient strategy is not a significant predictor of the long-term success of withdrawal therapy

Pini 1996, Suhr 1999.

Inpatient withdrawal

- Patients who overuse benzodiazepines, codeine or barbiturate
- Patients with severe medical or psychiatric comorbidity
- Previous outpatient withdrawal failure

German Migraine and Headache Society, 1999.
EFNS Guidelines 2011.

Prophylactic treatment

- Goals: decrease attack frequency, intensity and duration, reduce acute medication intake, improve responsiveness to acute therapy
- When? Before, during or after withdrawal?
- After two-month drug withdrawal period, the introduction of prophylactic drug was necessary for less than 50% MOH patients

Zeeberg et al. Cephalalgia 2006.

- Individualized preventive medication should be started at the first day of withdrawal treatment or even before if applicable

Level of recommendation C
EFNS Guidelines, Eur J Neurol 2011

Prophylactic treatment

- **Which drug? Previously ineffective prophylactic drug may be effective after detoxification**
- **The choice of the preventive agent in MOH should be based on the primary headache (e.g., migraine vs. tension-type headache), the possible side effects of the drugs, the comorbidities, and the patients preference and previous therapeutic experience**
- **Monotherapy with beta blockers, tricyclic antidepressants, antiepileptics, and calcium channel blockers**

Rossi et al. Cephalalgia, 2009.

Prophylactic treatment-TOP-CHROME

- **The aim of this study was to determine the efficacy and tolerability of topiramate in the prevention of chronic migraine**
- **82 patients, 78% met criteria for MOH**
- **Topiramate produced a significant reduction in the mean number of migraine days/month compared with placebo**
- **This randomized, double-blind, placebo-controlled trial demonstrated that topiramate is effective when used for the preventive treatment of chronic migraine, even in the presence of MOH!**

Diener et al. Cephalalgia 2007.

Is medication withdrawal really necessary?

- **The introduction of prophylactic therapy (beta blockers, valproate, angiotensin II blockers, tricyclic antidepressants) without a medication withdrawal is equally effective as detoxification for the reduction of headache frequency and headache disability in patients with MOH**

Hagen et al. Cephalalgia 2009.

- **PREEMPT: onabotulinum toxin A (155 U) is efficacious in the reduction of headache days in patients with chronic migraine and medication overuse**

Dodick et al. Headache 2010

Prognosis

- **The analysis of 17 studies (11000 patients) found a that 72.4% of patients have a favorable outcome 1-6 months after withdrawal treatment**

Diener HC et al. 2006

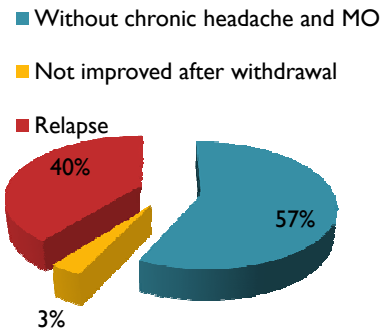
- **Studies with longer observation period of 4-6 years revealed 40% rate of relapse**

Evers i sar. 1999., Katzarava 2003.

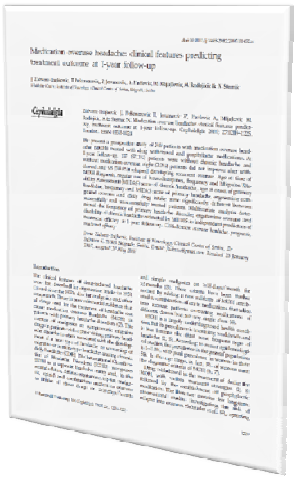
Headache center, Neurology Clinic, Belgrade

Evaluation of treatment outcome of 240 MOH patients at 1-year follow-up and detection of possible relapse predictors

- **57.1% patients were without chronic headache and without medication overuse**
- **3.3% patients did not improve after withdrawal**
- **39.6% patients relapsed developing recurrent overuse**

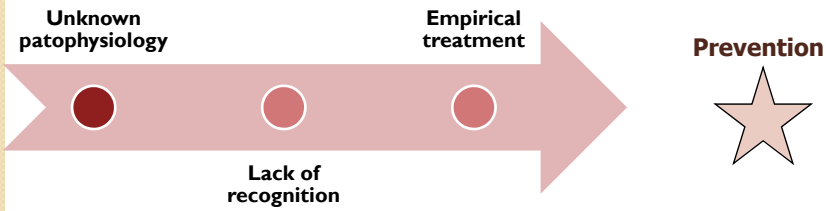


Multivariate analysis determined the frequency of primary headache disorder (p=0.008), ergotamine overuse (p=0.012) and disability of chronic headache estimated by MIDAS (p=0.045) as independent predictors of treatment efficacy at 1-year follow-up



Zidverc- Trajković et al. Cephalalgia 2007.

Summary...



Belgrade, May, 2012

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