Pathophysiology, prevention, and treatment of medication overuse headache

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Regular or frequent use of analgesics and acute antimigraine drugs can increase the frequency of headache, and induce the transition from episodic to chronic headache or medication overuse headache. The 1-year prevalence of this condition in the general population is between 1% and 2%. Medication overuse headache is more common in women and in people with comorbid depression, anxiety, and other chronic pain conditions. Treatment of medication overuse headache has three components. First, patients need education and counselling to reduce the intake of medication for acute headache attacks. Second, some patients benefit from drug withdrawal (discontinuation of the overused medication). Finally, preventive drug therapy and non-medical prevention might be necessary in patients at onset of treatment or in patients who do not respond to the first two steps. The optimal therapeutic approach requires validation in controlled trials.

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See Online for appendix

Introduction

Medication overuse headache is a chronic secondary headache disorder attributed to the frequent or regular use of analgesics or acute antimigraine drugs in patients with a primary headache disorder. According to the current classification of the International Headache Society (ICHD-3),[1] medication overuse headache is defined as a headache occurring for 15 or more days per month in a patient with a pre-existing primary headache disorder that develops because of regular overuse of medication for acute or symptomatic headache (use for ≥10 days per month or ≥15 days per month, depending on the medication) for more than 3 months, or when the symptoms are not better described by another ICHD-3 diagnosis. The term medication overuse is used to describe the frequent intake of headache medication in a person with a primary headache disorder without causing an increase in headache frequency.

The use of medication for the treatment of primary headache episodes has been associated with an increase in the frequency and intensity of headache attacks.[2] The frequent use of analgesics for other indications (eg, chronic low back pain) can also increase the frequency of headaches in people with migraine.[3] Although the link between frequent medication use and increased headache frequency is well established in the general population and clinic-based studies,[4] the causal link between the frequent use of analgesics or specific antimigraine drugs and the development of medication overuse headache can be difficult to show in individual cases. According to our clinical experience, some patients with migraine who overuse acute medications do not develop chronic headache. Additionally, some individuals use frequent acute medication in response to increasingly frequent headaches. The overuse of acute medication, therefore, does not necessarily cause medication overuse headache.

Medication overuse headache is a condition that affects about 60 million people worldwide and is among the top 20 causes of disability worldwide[5] with substantial socioeconomic consequences.[6–9] The costs of this condition are three times higher than those of migraine and include costs associated with sick leave, lost productivity, increased medication use, and frequent health-care use.[6] Diagnosing medication overuse headache in population studies is challenging because of recall bias and other International Classification of Headache Disorders third edition (ICHD-3) diagnosis might be consistent with the symptoms described. Therefore, its estimated prevalence varies among studies, from between 0·5% and 7·2%, with a median of 1–2%, depending on the country, the nature of the study sample, the research methods, and the definition of the condition (appendix).[10] For example, a cross-sectional study[11] in Denmark with 129 150 adults found a prevalence of 1·8%, whereas smaller studies from Russia and Iran noted higher prevalences of up 7·2%.[12] Worldwide, women have this condition more commonly than men (ratio 4:1).[12] The peak prevalence of medication overuse headache is reached when patients are aged between 50 and 60 years;[12] in children, prevalence ranges between 0·3% and 1%.[13] Low socioeconomic position,[11] stress, obesity, physical inactivity, and daily smoking are associated with an increased risk of medication overuse headache (table 1).[20]

This Personal View summarises challenges and advances in understanding of the pathophysiology, primary and secondary prevention, withdrawal, and treatment of medication overuse headache. Primary prevention is of major importance to prevent the transition from frequent migraine to medication overuse headache. Treatment of this condition includes education and, in selected patients, withdrawal of the overused medication. The relapse after successful withdrawal is still high, warranting an improved follow-up of patients after withdrawal of drugs to treat acute migraine attacks.

Primary prevention

Although research on preventing medication overuse headache in the clinic is available, the scientific evidence on how primary prevention should be initiated is scarce.[21] The non-existence of studies on how awareness campaigns

	Odds ratio (95% CI)	Comment
Metabolic syndrome[14]	5·3 (1·6–24·6)	Obesity is the most important risk factor.
Regular intake of tranquilizers[15]	5·2 (3·0–9·0)	Avoid or withdraw tranquilizers
Anxiety disorder or depression[15]	4·7 (2·4–9·0)	Screening is advised
Physical inactivity[15]	2·7 (1·2–6·3)	Recommend exercise
Intake of opioids more than 10 days per month[16,17]	2·3 (1·3–3·9)	Might lead to addiction
Female sex[16]	1·9 (1·4–2·6)	..
Low educational level	1·9 (1·2–3·0)	..
Chronic musculoskeletal disease[15]	1·9 (1·4–2·7)	..
Smoking[15,16]	1·8 (1·2–2·5)	Smoking cessation education is advised
Age (<50 years)[16]	1·8 (1·3–2·4)	..
Gastrointestinal disease[15]	1·6 (1·1–2·2)	..
Intensity of headache[18]	1·5 (1·0–2·1)	..
Intake of aspirin more than 15 days per month[17]	0·5 (0·3–0·9)	Protective effect
Intake of ibuprofen more than 15 days per month[16]	0·7 (0·5–1·0)	Protective effct

Data from Denmark,[18] Norway,[15] USA,[16,17] and China.[14] Adapted from Diener and colleagues (2018).[18]

Table 1: **Risk factors associated with medication overuse headache that might help to identify people at risk**

should be designed to reach out to the general health-care system represents a gap in public health efforts (panel).

Initiatives and tools that can reinforce the general public's desire for autonomy and control over their own health might be valuable for those with medication overuse headache. A Danish survey[29] tested the general knowledge of this condition before and after a national awareness campaign that targeted the general public (1000 individuals). For the public, the researchers used a variety of media outlets and materials, including newspapers, radio, television, online videos, online news, online quiz, and printed campaign materials (posters, leaflets, and cards). The messages were kept simple: overuse of acute medications can make headaches worse, use of analgesics or other symptomatic acute migraine medication should be limited to a maximum of 2 days per week, and further advice and treatment should be discussed with a general practitioner (GP). Overall the campaign was received by more than 10% of the total population, and the survey showed a significant increased knowledge about medication overuse headache from 31% to 38% after the campaign. Towards the goal of autonomy, an electronic headache calendar might promote self-monitoring of both headache and medication use, and should be evaluated for the potential to reduce acute medication intake and to prevent medication overuse headache.

The clinical benefits of educating patients about this condition have been shown in the general population, primary care, and headache specialty settings. In a Norwegian prospective cohort study of 109 individuals from the general population with chronic primary headache and medication overuse, a brief intervention that included information about the relationship between medication overuse and chronic headache was associated with substantial reductions in medication intake and headache frequency at follow-up (1·5 years after intervention).[30] A pragmatic study conducted within GP offices in Norway randomised 60 patients to usual care versus a brief intervention of patient education about medication overuse headache and development of an agreed upon plan for reducing the overused medication.[19] Compared with those receiving usual care, at 6 months postrandomisation, patients who participated in the intervention had significantly lower headache frequency (16·5–24·6 headache days per month *vs* 22·7–25·3 headache days per month) and fewer medication days (10·7–21·9 medication days per month *vs* 21·1–23·9 medication days per month). In an Italian study of 100 patients with medication overuse headache identified at a headache specialty clinic, a 15-min education session that included advice to discontinue the overused medications was added to the standard treatment. Patients had 24 headache days per month at baseline and used symptomatic medication on 22 days per month on average. The education session resulted in 79% of patients successfully reverting to a non-medication overuse pattern and 69% having more than a 50% reduction in headache frequency at 2 months.[31] Finally, a 90-min in-person didactic education session that included a review of this condition was delivered to 152 adult participants awaiting their initial appointment within the Center for Headache at the University of Toronto (ON, Canada). The educational programme resulted in a significant reduction in the proportion of patients who had medication overuse at the time of their initial appointment (53% *vs* 39%).[32] In conclusion, these studies show that education and advice can be very effective treatments for patients with this condition. A significant proportion of patients are able to reduce the intake of acute medication to treat migraine attacks. A possible confounding factor not accounted for in the analyses of these studies could be that preventive drug therapy might have been started in a subgroup of patients.

Withdrawal and preventive treatment

Chronic headache and medication overuse headache often revert to episodic headache when preventive medication is initiated and the intake of acute medications limited. In some cases, however, there might be only minimal or no improvement. The treatment outcomes of 175 patients who were diagnosed with medication overuse headache (with a combination of migraine and tension type headache as the primary headache) and treated in the Danish Headache Centre in 2002 and 2003 have been studied.[33] During the first 2 months after withdrawal, no preventive medication was offered. Approximately

45% of patients showed a reduction in headache frequency by more than 50%, whereas 48% did not improve in terms of headache frequency and 7% had an increase in headache frequency after drug withdrawal. 80 of 88 patients with no improvement 2 months after drug withdrawal subsequently responded to pharmacological or non-pharmacological prevention (eg, physiotherapy or psychological treatment). This prevention resulted in a 26% decrease in headache frequency measured from the end of withdrawal to dismissal. At discharge, 47% of patients were on preventive treatment.

A small study in Denmark compared complete cessation of acute medication with restricted intake in patients with medication overuse headache and migraine, tension-type headache, or both, in a prospective, out-patient setting.[34] Patients were randomised to a 2-month period of either no acute medication (programme A, n=35) or acute medication restricted to 2 days per week (programme B, n=37). Withdrawal was followed by appropriate preventive drug treatment if indicated. 59 patients completed drug withdrawal with a 18% drop-out proportion at 6-month follow-up, which was similar in both groups. Monthly headache days were significantly reduced after 6 months to a greater extent in programme A (46%) compared with programme B (22%). Significantly more patients reverted to episodic headache in programme A than programme B (70% *vs* 42%). Migraine days per month were significantly reduced by 7·2 days in programme A and 3·6 days in programme B, after 6 months. The authors concluded that a 2-month complete cessation of acute medication is successful and more effective in reverting chronic to episodic headache compared with reduced medication intake. Both withdrawal programmes reduced the frequency of headache and migraine, and effectively treated more than 80% of the patients who completed detoxification from medication overuse headache. The authors recommended that withdrawal should be considered as the standard of care for medication overuse headache before initiation of pharmacological prevention. However, most patients initiated preventive treatment after withdrawal in the two groups (74% in programme A and 85% in programme B). Therefore, it remains unclear whether drug withdrawal alone could result in similar long-term outcomes.

The COMOESTAS multicentre and open-label study involved 492 of 694 patients with medication overuse headache (89% migraine), from seven different countries. Prophylactic drugs were started in parallel with medication withdrawal and a frequency reduction of 44% in headache days occurred within the first month of the study, and maintained and further increased to 60% after 6 months.[7,35] In this study, 68% of those patients who completed the protocol reverted to episodic headache, and both coexisting depression, anxiety, and quality of life were markedly improved. The costs of medication and health-care service use were also reduced.[36] These findings show that successful treatment of medication overuse headache has extensive benefits for the individual and health-care system.

Patients with medication overuse headache might not need to be withdrawn of acute headache medication to respond to preventive medication.[37] A 1-year open-label, multicentre study[37] was done in 56 patients with this condition. Patients were randomly assigned to receive prophylactic treatment without withdrawal, to undergo a standard out-patient withdrawal programme without prophylactic treatment, or to no specific treatment, with a 5-month follow-up. The primary outcome, change in

Panel: **Education interventions for medication overuse headache**

Campaigns

Lifting the burden: the Global Campaign against headache, a UK-based charity that works in coordination with WHO, has been the leading actor to increase awareness about the most common headache disorders.[22,23] Another campaign is the Russian *Yekaterinburg* initiative, which educated general practitioners (GPs), pharmacists, and the general public about headache and appropriate treatment.[24]

Education of the public

In a UK study of 485 undergraduate students and their social contacts who were taking analgesics for headache (85% of the cohort) or other pain conditions, only 23% were aware that medication overuse headache could be a side effect of regular analgesic use.[21] A concerted campaign for a more appropriate use of acute medications for headache should be implemented through the involvement of key stakeholders, including the public, patients, pharmacies, and health-care professionals. The risk of adverse events from frequent acute medication consumption, such as the risk for gastrointestinal and renal toxicity from excessive use of nonsteroidal anti-inflammatory drugs (NSAIDs) and combination analgesics, should be discussed. Patients should understand that the use of acute medications to treat conditions other than headache, such as taking NSAIDs or opioids for back pain, can contribute to medication overuse headache if they have a primary headache as well.

Education of GPs

Involvement of GPs has been successfully implemented in Norway, where 25 486 people from a waiting list were screened for medication overuse headache and 50 GPs were offered a 1-day introduction to headache. The GPs were then invited to conduct a randomised controlled study with a brief intervention (9–10 min) with written and verbal information about the condition to the patients; these patients were followed up after 3 months and 6 months by structured interview about headache days and medication use. This brief intervention against medication overuse headache proved to have a great impact and long-lasting effect in most patients. Chronic headache reverted to episodic headache in 50% of the patients who received the short intervention.[19,25] In the future, increased awareness of medication overuse headache among the general population and GPs should improve primary prevention of medication overuse and, consequently, the resultant headaches.

Education of pharmacists

Pharmacists have an important role in health promotion and education about the correct use of medication.[26,27] Their role is crucial in recognising warning signs, such as increasing use of analgesics and symptomatic acute migraine medications and increased headache frequency, which might indicate medication overuse headache, and consequently advising their clients to consult a GP. Hedenrud and colleagues[28] documented that the existing knowledge was insufficient among pharmacy staff in Sweden, but with proper education they would be well positioned to influence both primary and secondary prevention of this condition.

headache frequency (days per month), was significantly different between the three groups. The prevention group had the greatest decrease in headache frequency from baseline compared with the withdrawal group. This group had also a significantly more pronounced reduction in the total headache index (ie, the product of number of headache days per month, headache intensity, and headache hours) at months 3 and 12 compared with the withdrawal group. At month 12, significantly more patients in the prevention group had a more than 50% reduction in monthly headache frequency compared with the withdrawal group (53% *vs* 25%). 60 patients were invited after 4 years to a follow-up investigation to determine long-term outcomes and 50 (83%) participated.[38] At follow-up, the mean number of headache days and acute headache medication days, per month, were significantly reduced compared with baseline (6·5 days *vs* 9·5 days). However, the difference between the treatment groups was no longer evident after 4 years. 16 (32%) people were considered responders (>50% reduction in headache frequency) but 17 (34%) people still met the criteria for a medication overuse headache diagnosis at the end of the trial.

Two similarly designed randomised, placebo controlled, multicentre studies of patients with chronic migraine in the USA and in the EU investigated the safety and efficacy of topiramate for the treatment of this condition in patients with and without medication overuse.[39] A post-hoc analysis in the subset of patients with medication overuse in the US trial showed no difference in reducing migraine and its frequency between topiramate and placebo; however, the EU trial did show a significant reduction. Key differences were evident between the patient populations in the two studies. In the US trial, 115 (38%) of 306 patients versus 46 (78%) of 59 patients in the EU trial reported using acute medications for migraine fulfilling the criteria for medication overuse during the 28-day prospective baseline period. In the US trial, the most commonly overused medications were non-steroidal anti-inflammatory drugs (NSAIDs), triptans, simple and combination analgesics, and opioids. In the EU trial, the most frequently overused medications were triptans (61%). Butalbital-containing analgesics were allowed in the US trial, but no butalbital-containing analgesics were prescribed in the EU trial. Therefore, the treatment benefit appears to be reduced in patients who overuse opioids or barbiturates.

The use of onabotulinumtoxinA (botox) was investigated in patients with chronic migraine in two placebo-controlled trials.[40,41] Patients were prospectively stratified according to whether they overused acute medications or not. This stratification was based on patient-reported frequencies of acute medication use during the 28-day baseline period and not based on a diagnosis of medication overuse headache (ICHD-2 8.2). The subgroup of patients with medication overuse in the two trials has been assessed in secondary analyses. Of 1384 patients, 904 (65%) were assigned to the medication overuse stratum. Most of the patients overused triptans or a combination of analgesics. Very few patients (1·7%) overused opioids. For the subgroup of patients with medication overuse, botox was superior to placebo for most efficacy endpoints.[42] In a separate 2-year open-label prospective study[43] in 172 patients with medication overused headache, treatment with botox reduced the frequency of headache significantly from 22·2 days per month at baseline to 5·7 days per month after 12 months and 4·1 days per month after 24 months. A randomised study in the Netherlands investigated the add-on efficacy of botox to ambulant withdrawal therapy in the treatment of medication overuse headache. They randomly assigned 179 adults to botox injections (155 units) or placebo (saline, with 17·5 units of botox in the forehead to maintain participant masking).[44] In weeks 9 to 12 after injection, the number of headache days was reduced by 26·9% in the botox group (n=90) and by 20·5% (n=89) in the placebo group, a non-significant difference. This study was small compared with the PREEMPT studies[40,41] and had a shorter observation time, and the small amount of botox injected into the forehead might exert biological activity.

A systematic review of treatment strategies for medication overuse headache[45] showed that the evidence to support early withdrawal of overused medications alone was scarce because of the absence of controlled studies. The addition of prophylactic medication to early discontinuation led to a better outcome than early discontinuation alone. For patients with chronic migraine and medication overuse headache, randomised controlled trials support the use of botox and topiramate without early discontinuation of overused medication. The scientific evidence, however, is limited since data were obtained from post-hoc analyses. The authors concluded that discontinuation of the overused medication with the addition of prophylactic medication was the best approach on the basis of their appraisal of the available evidence.

Further support of the potential efficacy of prophylactic treatment without acute medication withdrawal comes from studies with fremanezumab, a fully humanised monoclonal antibody that selectively targets calcitonin gene-related peptide (CGRP). In a placebo-controlled trial,[46] fremanezumab reduced the frequency and severity of headaches in patients with chronic migraine and medication overuse headache. Silberstein and colleagues[47] assessed the effect of fremanezumab versus placebo on medication overuse and acute headache medication use in patients with chronic migraine and medication overuse headache. In this phase 3 study, fremanezumab treatment was associated with a reduction in overuse of acute medications and a corresponding decrease in days using acute medications. Fremanezumab significantly reduced the frequency of headache of at least moderate severity without withdrawal in patients with medication overuse at baseline by 4·7 days in the group who received quarterly

injections and 5·2 days in those who received monthly injections, compared with a 2·5 days reduction in the placebo group. Additionally, the proportion of patients who had a greater than 50% reduction in monthly average headache frequency over a 3-month period was significantly higher in the quarterly (35%) and monthly (39%) fremanezumab dose groups compared with a 14% response in the placebo group.

In a study evaluating the efficacy of erenumab, a fully human monoclonal antibody targeting the canonical CGRP receptor, monthly migraine days were reduced by 6·6 days versus 4·2 days for placebo after 12 weeks in 667 patients with chronic migraine, 41% of whom had medication overuse.[48] Erenumab led to an improvement in quality of life. These data might support the use of erenumab in patients with chronic migraine, including those with medication overuse headache.[49] The role of monoclonal antibodies against CGRP or the CGRP-receptor in this condition remains to be finally determined by dedicated randomised placebo-controlled trials.

In conclusion, prophylactic therapy without withdrawal might lead to a reduction in headache or migraine frequency and acute medication consumption in the absence of deliberate withdrawal (discontinuation) and is a reasonable approach in patients overusing analgesics or triptans. Prophylactic therapy without previous withdrawal might be an appropriate option for patients that are expected to be, or have been shown to be, difficult to withdraw without simultaneous effective prophylactic therapy. Patients who do not manage out-patient withdrawal might require in-patient withdrawal. In patients overusing opioids or butalbital containing analgesics and in those with substantial comorbidities (eg, major psychiatric disease, epilepsy, major medical conditions) in-patient withdrawal might be necessary (figure 1). Most drugs used and recommended for the prevention of episodic migraine have not been investigated for the treatment of medication overuse headache. They also have an unfavourable profile of adverse events which explains the high drop-out rate. Botox and anti-CGRP therapies have a very good tolerability profile and show a very low drop-out rate.

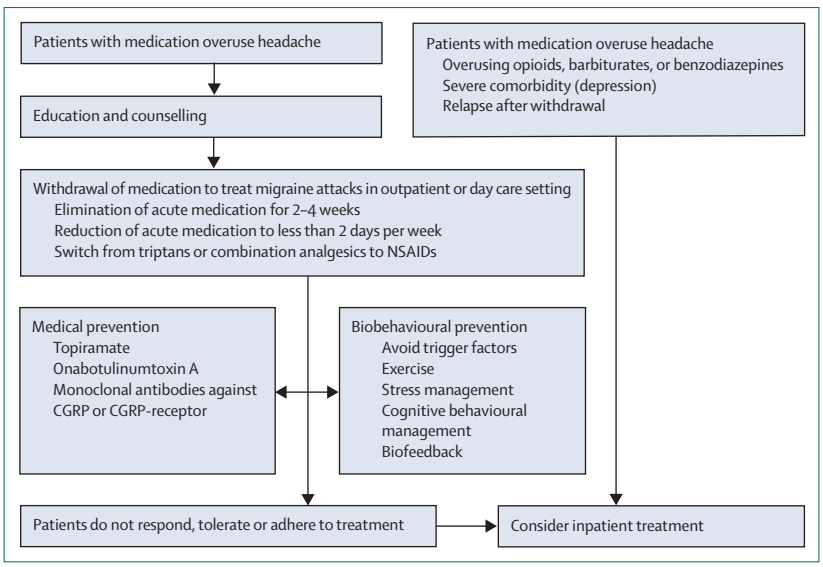

Figure 1: **Proposed treatment path for patients with medication overuse headache**
NSAID=non-steroidal anti-inflammatory drug. CGRP=calcitonin gene-related peptide.

Treatment of withdrawal symptoms

The utility of bridging therapy is still a subject of debate. Moreover, it is not known which bridging therapy is best at the time that acute medication is withdrawn. Similarly, it remains undetermined whether a preventive drug started during withdrawal is effective in preventing or minimising the intensity of withdrawal symptoms.

A large open-label observational trial[50] in 400 patients with chronic daily headache and medication overuse showed that treatment with 60 mg prednisone for 2 days, followed by tapering down by 20 mg every other day, reduced rebound headache and withdrawal symptoms. The study, however, had no control group. This evidence was strengthened by a retrospective study[51] evaluating whether a bridging therapy consisting of a 5-day intravenous infusion of methylprednisolone and diazepam leads to a significant reduction in headache frequency and drug consumption in patients with medication overuse headache compared with patients without such a standardised protocol. After 3 months, the intervention group showed a significantly greater reduction in monthly headache frequency (9·4 days *vs* 3·0 days) and symptomatic drug consumption (19·7 days *vs* 6·5 days) than the control group.

A placebo-controlled, randomised, double-blind study investigated oral prednisolone during the first 6 days after medication withdrawal. 97 patients were recruited; 49 received prednisolone (60 mg initially with dose reduction until day 6) and 48 received placebo tablets. No significant effect was measured for a combined primary endpoint of calculated mean headache, based on number of days with headache and mean intensity for the first 6 days after withdrawal.[52] In a separate small proof-of-concept study,[53] nine patients with medication overuse headache received either placebo or 100 mg prednisone for 5 days. The duration of withdrawal headache was significantly lower in the prednisone group than in the placebo group. In another prospective double-blind, placebo-controlled, parallel-group multicentre trial, 96 consecutive patients with medication overuse headache were randomised to withdrawal treatment with either 100 mg prednisone or placebo for 5 days.[54] Withdrawal symptoms, headache severity, and intake of rescue medication were documented for 2 weeks after randomisation. Patients treated with prednisone had similar hours of moderate or severe headache than patients receiving placebo. However, patients requested less rescue medication within the first 5 days. These results suggest a potential role for corticosteroids to treat withdrawal

symptoms in patients with medication overuse headache but further placebo-controlled trials are needed.

In a comparative trial, 97 patients with medication overuse headache were randomised to treatment with either celecoxib or prednisone for 10 days. Patients treated with celecoxib experienced lower headache intensity during the first 3 weeks after withdrawal than those treated with prednisone. Headache frequency and the need for rescue medication intake were not significantly different between the two groups.[55] In another comparative, randomised, single-blinded, placebo-controlled trial,[56] which enrolled 83 consecutive patients with medication overuse headache who received intravenous methylprednisolone (500 mg), intravenous paracetamol (4 g), or intravenous placebo daily for 5 days during withdrawal therapy, no significant differences were observed in any endpoint for the three treatment groups.

The acute treatment of withdrawal headache or other withdrawal symptoms in patients with medication overuse headache is also debated. Early trials or case series recommended subcutaneous sumatriptan (6 mg)[57] or naproxen (500 mg)[58] for the treatment of acute headache during withdrawal in patients who did not overuse these drugs. In the USA, a variety of intravenous infusion protocols are used to treat the acute headache of patients with this condition.[59] However, these treatment protocols have not been specifically evaluated in the treatment of these patients during withdrawal. From our own clinical experience, the use of antiemetics and NSAIDs to treat withdrawal symptoms and headache during withdrawal therapy might be useful but is not (yet) supported by placebo-controlled trials.

Although most studies that have evaluated the role of in-patient treatment for headache included a substantial proportion of patients who overused acute medications, to our knowledge, no class 1, randomised controlled studies have evaluated the safety or efficacy of in-patient treatment. Moreover, the heterogeneous patient populations, and highly variable interventions and outcome measures make the interpretation of these studies very difficult. Nevertheless, in an evidence-based assessment of in-patient headache treatment studies done in the USA and reported during a meeting of the of the US Headache Guidelines Consortium,[60] 81% of patients achieved at least a 81% short-term (<6 months) and 61% long-term (>6 months) improvement. In-patient treatment might be indicated for patients with medication overuse headache for whom outpatient or day-care treatment programmes have been unsuccessful, and for those who overuse substantial daily amounts of opioid or butalbital-containing analgesics. In-patient treatment has the advantage of facilitating a drug taper under observation and an improved management of withdrawal symptoms.[60] Although in-patient treatment is more expensive, it should also be considered in the presence of comorbid or coexistent conditions that would make outpatient treatment unsafe (eg, in patients with severe depression).

Clinical evidence suggests that, regardless of the treatment setting, psychological counselling and behavioural interventions, including cognitive behavioural therapy and biofeedback assisted relaxation therapy, should be included in an interdisciplinary treatment approach to increase treatment adherence and favourable outcomes.[61]

Prevention of relapse

Withdrawal of, and reduction in, overused acute medication can reduce the frequency of migraine and headache but will not cure the underlying primary headache. Unfortunately, between 25% and 35% of patients will relapse and overuse acute medication again. A systematic review and meta-analysis[45] analysed the remission and relapse after discontinuation from 22 studies with a follow-up between 2 and 60 months (most studies 12 months). Relapse varied between 0% and 45%. The majority of studies showed a relapse between 25% and 35%. Relapses were more frequent in chronic tension-type headache compared with migraine as the original primary headache disorder. Other predictors of relapse were overuse of opioids versus triptans and comorbid psychiatric disorders. Depression was an important predictor of relapse.[62] The COMOESTAS study[35] investigated whether electronic-assisted monitoring, advice, and communication would improve the outcome over a follow-up of 6 months in a controlled, multicentre, multinational study conducted in six headache centres in Europe and Latin America. 663 patients with medication overuse headache were enrolled. Group 1 was monitored with an electronic diary with an alert system and a facilitated communication option, and group 2 with a paper headache diary. A significantly higher percentage of patients did not overuse medications in group 1 compared with group 2 (73% *vs* 64%). Long-term predictors of remission in patients treated for this condition include a lower number of initial headache days and efficient initial drug withdrawal.[63] An unresolved issue is whether the immediate initiation of preventive medication after drug withdrawal prevents relapse.[45,64] The combination of drug withdrawal with multidisciplinary educational programmes is effective in preventing relapse and is also cost-effective.[65,66]

In conclusion, patients at high risk of relapse after treatment of medication overuse headache should be identified on the basis of their risk profile and managed and monitored closely. Regular follow-up of these patients after treatment reduces the risk of relapse.

Pathophysiology

Genetic predisposition has been hypothesised to be involved in the pathophysiology of medication overuse headache. The angiotensin converting enzyme (ACE) insertion or deletion polymorphism,[67] the BDNF mutation Val66Met,[68] or polymorphisms in catechol-O-methyltransferase (*COMT*) and serotonin transporter (*SLC6A4*) genes[69] have been suggested as genetic risk factors in

	Number of participants	Control group	Study design and follow up	Results*	Comments
Structural imaging					
Voxel-based morphometry[82]	29 patients	Not available	Cross-sectional study; no follow-up	Grey matter increase in the midbrain, thalamus, and striatum; and grey matter decrease in frontal regions	MIDAS and HADS-anxiety subscale scores correlated positively with the grey matter increase of the midbrain periaqueductal grey matter
Voxel-based morphometry[83]	38 patients	Patients who do not respond to medication	Longitudinal study; MRI before and at least 3 months after detoxification	Decreased volumes of left hemisphere temporal gyri and occipital middle gyrus	In patients with clinical improvement after detoxification, these grey matter changes are resolved
Volumetry[84]	27 patients	27 controls (age-matched and gender-matched to the treatment group)	Cross-sectional study; no follow-up	Decreased number of reconstructed fibres passing through the left hippocampus	Grey matter volume of the orbitofrontal cortex was predictive of the response to medication overuse treatment
Cortical thickness and gyrification[85]	29 patients	29 controls (age-matched and gender-matched to the treatment group)	Cross-sectional study; no follow-up	Reduced cortical thickness in the left prefrontal cortex; higher local gyrification in the fusiform cortex and medial temporal regions and occipital pool in patients with medication overuse headache	High gyrification in the right occipital is associated with poor response after detoxification
Diffusion tensor imaging[86]	13 patients with migraine without aura; 5 patients with migraine with aura	68 patients with migraine without aura without medication overuse headache; 17 patients with migraine with aura without medication overuse headache; 46 healthy controls	Cross-sectional study; no follow-up	Decrease of fractional anisotropy of white matter in patients with migraine without aura with medication overuse headache and patients with migraine with aura without medication overuse	Fractional anisotropy values were not associated with disease duration and frequency of migraine attacks
Functional imaging					
fMRI: decision making under risk design[85]	8 patients	8 patients who detoxified from mediation overuse headache; 8 patients with chronic migraine; 8 healthy controls	Longitudinal study; follow-up 6 months after detoxification	Dysfunctions within the lateral pain system (i.e. the right supramarginal gyrus, right inferior and superior parietal cortex), somatosensory cortex, inferior parietal lobe, supramarginal gyrus, midbrain, orbitofrontal cortex	After stopping medication overuse, functional changes were at least partly reversible within 6 months
fMRI: trigeminal nociception paradigm[87]	18 patients	18 patients who detoxified from mediation overuse headache; 18 healthy controls	Longitudinal study; follow-up before and 8 weeks after detoxification	Reduced activity in the pain matrix (operculum, insula, and spinal trigeminal nucleus) before detoxification; reduced functional connectivity of the orbitalfrontal cortex and cerebellum, which was regained after withdrawal	Orbitofrontal cortex seems to mediate between bottom-up and to downstream in headache processing
PET[88]	6 patients	68 healthy controls	Longitudinal study; follow-up 3 weeks after detoxification	Hypometabolism within the bilateral thalamus, orbitofrontal cortex, anterior cingulate gyrus, insula or ventral striatum, and right inferior parietal lobule;[76] additionally, hypermetabolism could be detected within the cerebellar	Almost all metabolic abnormalities resolved after stopping of medication overuse; hypometabolism of the orbitofrontal cortex persisted; the initial alterations seemed to be more pronounced in patients with medication overuse headache who overuse combination analgesics with ergotamine or caffeine containing drugs, or both

fMRI=functional MRI. HADS=Hospital Anxiety and Depression Scale. MIDAS=Migraine Disability Assessment. *Results report changes in patients with migraine overuse headache compared with controls.

Table 2: **Imaging modalities to assess structural and functional changes in patients with medication overuse headache**

humans, but clear causal links have yet to be established. A systematic review[70] reported 50 polymorphisms in 33 genes as risk factors for medication overuse headache susceptibility in humans. These genes were associated with serotonergic and dopaminergic transmission, drug dependence, metabolic pathways, oxidative stress, and CGRP pathways.

The exposure to acute medication seems to be the main cause for medication overuse headache because it is pathognomonic for the disorder itself. All acute medication, in principle, can cause this condition; however, some drugs for headache appear to lead to more frequent and faster symptoms than others. Patients overusing triptans for the treatment of migraine attacks are more prone to develop medication overuse headache compared with patients overusing simple analgesics.[71,72] Therefore, medication-specific mechanisms might be involved in the underlying pathophysiology.

Patients with migraine often have painful responses to normally innocuous sensory stimuli, including touch (allodynia), light (photodynia), and sound (phonodynia). Painful responses to usually innocuous stimuli suggest underlying neural amplification processes commonly referred to as sensitisation. Symptomatic acute pain-relieving medications (eg, triptans, opioids) can themselves elicit injury-free sensitisation characterised by increased evoked transmitter release, increased temporal summation, and expansion of receptive fields.[73] Additionally, sudden abstinence from acute medications can lead to withdrawal-induced headaches. After sustained exposure to morphine in rats, precipitation of withdrawal by microinjection of opioid antagonists within the rostral ventromedial medulla led to increased activity and expression of c-Fos in dura-sensitive spinal trigeminal nucleus caudalis neurons, as well as in the subnucleus reticularis dorsalis, an area associated with diffuse noxious inhibitory controls.[74] Sensitised states probably promote vulnerability to typical provocative stimuli associated with headache and migraine attacks, such as stress and nitric oxide donors. In rodents, a 7-day exposure to common migraine medications (including triptans) elicited persistent alterations in peripheral dural afferents, including increased expression of CGRP and neuronal nitric oxide synthase.[75] In triptan-sensitised animals, stress or nitric oxide donors produce allodynia, increased c-FOS expression in trigeminal nucleus caudalis, and increased blood concentrations of CGRP.[75] Sumatriptan-sensitised rats also show a lower threshold for cortical spreading depression.[76] These preclinical pathophysiological observations might explain the vulnerability of people with medication overuse headache to headaches triggered by a variety of environmental stimuli.

Electrophysiological investigations have shown neuronal hyperexcitability with increased stimulation response and a habituation deficit in patients with medication overuse headache. These alterations have been observed with different stimulation modes, such as sensory evoked cortical potentials,[77] cold pressor test,[78] somatosensory-evoked potentials,[79] and CO_2 laser-evoked potentials,[80] within cephalic and extracephalic stimulation regions.[77] Additionally, the hyperexcitability pattern in medication overuse headache seems to depend on the overused drug. Patients with this condition show an increased amplitude of somatosensory evoked potentials when stimulating the median-nerve, but patients who overuse triptans show lower amplitudes than patients overusing NSAIDs.[79] The observed differences could reflect triptan-induced changes in central serotoninergic transmission.

Central sensitisation of the trigeminal and somatic nociceptive system suggests that hyperexcitability is a reversible phenomenon in medication overuse headache. After withdrawal of triptans, NSAIDs, or combinations of both, or ergots in patients with this condition, all or most of the changes were reversible.[79,81]

Imaging studies with different modalities have shown structural, functional, and metabolic changes of the brain in patients with medication overuse headache (table 2).[89] These alterations involve all parts of the so-called central pain network, including areas that control the sensory discriminative, cognitive, attentional, and emotional processing of pain. The observed alterations are not specific to medication overuse headache and can also be observed in other headache and pain disorders.

Functional MRI of awake sumatriptan-sensitised rats showed differences in several resting state networks, including the default mode, autonomic, basal ganglia, salience, and sensorimotor networks that were accompanied by stress-induced CSD-like responses.[90] Pretreatment with fremanezumab, an anti-CGRP antibody, blocked pain-like behaviours in sumatriptan or opioid sensitised rats, thus indicating the potential involvement of CGRP in sensitisation.[91] Following sumatriptan sensitisation, stress-elicited allodynia in rats was also prevented by blockade of signalling at kappa opioid receptors (KOR) in the central nucleus of the amygdala.[22] Morphine-sensitised rats showed a loss of the diffuse noxious inhibitory controls response that was restored by KOR antagonists in the right central nucleus of the amygdala.[23] These observations suggest that in both humans and other animals, medications can increase vulnerability to pathways that trigger migraine by promoting sensitised states characterised by an alteration of descending pain modulatory pathways, which result in pain facilitation. In sensitised states, enhanced dynorphin and KOR signalling in amygdala circuits might promote pain resulting from environmental stimuli, suggesting possible ways to develop a preventive therapeutic intervention that might promote the remission of medication overuse headache by counteracting medication-induced transformation of episodic to chronic headache conditions (figure 2).

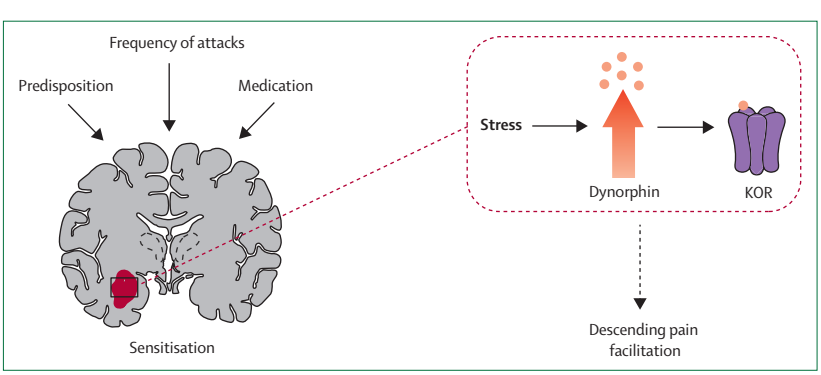

Figure 2: **Sensitised states during medication overuse headache**
In sensitised states, external or internal events (eg, stress, sleep) engage brain stress circuits and dynorphin signalling at kappa opioid receptors to promote dysregulation of descending modulatory pathways and pain. KOR= kappa opioid receptors

Conclusions and future directions

Medication overuse headache is a worldwide problem with an incidence of about 1–2%. In the past 10 years,

Search strategy and selection criteria

We searched MEDLINE for articles published in English from Jan 1, 1990, until March 31, 2019, with a focus on randomised controlled trials published since 2010 (but including earlier publications as appropriate), using the search terms "medication overuse", "medication overuse headache", "chronic migraine", and "chronic headache". We also considered reviews and meta-analyses. We did not exclude any retrieved papers.

progress has been made to understand the pathophysiology of this condition and to identify patients at risk and in treatment.

Awareness of medication overuse headache and education of patients, the public, GPs, and health-care workers (eg, pharmacists) are important for primary prevention. At-risk patients with frequent attacks of migraine or tension-type headache should be identified, educated on the systemic and headache progression risk of medication overuse and on strategies for reducing headache frequency (prophylactic medications, biologics, devices, and behavioural approaches), and optimised treatment of acute attacks should be initiated. Most patients can be managed by GPs or neurologists. Patients who relapse and those with excessive overuse of opioids or butalbital containing analgesics should be managed by a multidisciplinary team of neurologists, headache specialists, and psychologists. Discontinuation of the overused medication should be recommended to all patients and can be done on an out-patient basis, in a day-care setting, or an in-patient setting. The most appropriate setting and the abruptness of drug withdrawal will depend on the type of drug being overused, the degree of overuse, the presence of comorbid or coexistent disorders, and resource availability. Withdrawal might involve the complete cessation of acute medications or limiting acute medications to 2 days or less per week. Further research is required to determine whether changing from the overused medication to an alternative acute medication should be recommended. Prophylactic therapy should be considered either in combination with discontinuation or limitation of the overused medication or in patients who do not improve with education and withdrawal alone. Topiramate, botox, and anti-CGRP monoclonal antibodies might be effective in reducing headache and migraine frequency, and acute drug consumption, even in the absence of active drug withdrawal. Many aspects of the management of medication overuse headache need to be further investigated in properly designed and adequately powered randomised controlled trials.

Contributors

All authors contributed to the draft of the manuscript. HCD, DD, and TS edited the final draft. All authors approved the final version of the manuscript.

Declaration of interests

HCD received honoraria for participation in clinical trials, contribution to advisory boards, or oral presentations from Alder, Allergan, Amgen, Autonomic Technology, Bristol-Myers Squibb, CoLucid, Electrocore, Ipsen, Lilly, Medtronic, Merck Sharp & Dohme, Novartis, Pfizer, Schaper and Brümmer, Teva, and Weber & Weber; financial support for research projects was provided by Allergan, Electrocore, Merck Sharp & Dohme, and Pfizer; headache research at the Department of Neurology in Essen is supported by the German Research Council, the German Ministry of Education and Research, and the EU; has no ownership interest and does not own stocks of any pharmaceutical company; serves on the editorial boards of *Cephalalgia* and *The Lancet Neurology*; chairs the Clinical Guidelines Committee of the German Society of Neurology; and is member of the Clinical Trials Committee of the International Headache Society. DD reports personal fees from Allergan, Amgen, Alder, Arteaus, Pfizer, Colucid, Merck Sharp & Dohme, NuPathe, Eli Lilly and Company, Autonomic Technologies, Ethicon J&J, Zogenix, Supernus, Labrys, Boston Scientific, Medtronic, St Jude, Bristol-Myers Squibb, Lundbeck, Impax, MAP, electroCore, Tonix, Novartis, Teva, Alcobra, Zosano, ZP Opco, Insys, Ispen, Acorda, eNeura, Charleston Laboratories, Gore, Biohaven, Biocentric, Magellan, Theranica, Xenon, Dr Reddy's/Promius Pharma, Vedanta, CC Ford West Group, Foresight, Satsuma, Axsome, Impel, Neurolief, IntraMed, SAGE Publishing, Sun Pharma, Oxford University Press, American Academy of Neurology, American Headache Society, West Virginia University Foundation, Canadian Headache Society, Healthlogix, Universal Meeting Management, WebMD, UptoDate, Medscape/WebMD, Oregon Health Science Center, Albert Einstein University, University of Toronto, Starr Clinical, Decision Resources, Synergy, MedNet LLC, Peer View Institute for Medical Education, Medicom, Medlogix, Wolters Kluwer Health, Chameleon Communications, Academy for Continued Healthcare Learning, Haymarket Medical Education, Global Scientific Communications, Miller Medical, MeetingLogiX, Wiley Blackwell; other support from Dr Reddy's/Promius Pharma, Epien, GBS/Nocira, Second Opinion, Healint, NeuroAssessment Systems, Myndshft; holds equity (stock options) in Aural Analytics, Theranica, Healint, King Devick Technologies, Ontologics/Matterhorn, Nocira, Second Opinion, Aural Analytics, and Epien; is on the board of directors of King-Devick Technologies and Ontologics/Matterhorn, Aural Analytics, and Epien, outside the submitted work; and has a patent (number 17189376·1–1466:v; Botulinum toxin dosage regimen for chronic migraine prophylaxis). SE has received honoraria for participation in clinical trials, contribution to advisory boards, or oral presentations from Allergan, Johnson & Johnson, Lilly, Novartis, Reckitt Benckiser, and Teva; has no ownership interest and does not own stocks of any pharmaceutical company; serves on the editorial boards of Cephalalgia and European Journal of Pain; and is Honorary Secretary of the International Headache Society and Chair of the Headache Panel of the European Academy of Neurology. DH received honoraria for participation in clinical trials, contribution to advisory boards, or oral presentations from Alder, Allergan, Amgen, Autonomic Technology, Hormosan, Lilly, MSD, Novartis, and Teva; financial support for research projects provided by Allergan and Novartis; headache research at the Department of Neurology in Essen is supported by the German Research Council, the German Ministry of Education and Research, and the EU; and has no ownership interest and does not own stocks of any pharmaceutical company. RHJ has received honoraria, travel grants, and an unrestricted research grant from Autonomic Technologies, Allergan, and Novartis; conducted clinical trials for Eli Lilly, ElectroCore, and ATI; and is director in Lifting The Burden and trustee in International Headache Society. FP has received compensation for consulting from Amgen and Voyager; has stock options in BlackThorn and is an equity partner in Catalina Pharmaceuticals; has received research support from Teva, Ipsen, Lilly, Proximagen, Nektar, Hoba, Voyager, PeptideLogic, the US Department of Defense, the National Institutes of Health (NIH), and the Mayo Clinic; and serves on the Editorial Boards of Cephalalgia and Pain. RBL has received personal fees from Alder, Allergan, Amgen, Electrocore, eNeura, Boston Scientific, Bristol Meyers Squibb, Dr. Reddys, Eli Lilly, Teva, and Vedanta; has also received grant funding from Alder, Electrocore, Novartis, the Migraine Research Fund, the National Headache Foundation, and the NIH; and owns stock in eNeura

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