Received: 15 January 2022 | Accepted: 31 August 2022

DOI: 10.1111/head.14415

REVIEW ARTICLE

Is prednisone still a reasonable option in the treatment of withdrawal headache in patients with chronic migraine and medication overuse headache in the age of CGRP antibodies? A narrative review

Katharina Kaltseis MD[1] | Till Hamann MD[2] | Charly Gaul MD[3] | Gregor Broessner MD[1]

[1]Department of Neurology, Headache Outpatient Clinic, Innsbruck Medical University, Innsbruck, Austria

[2]Department of Neurology, Headache Center North-East, University Medical Center Rostock, Rostock, Germany

[3]Headache Center Frankfurt, Frankfurt, Germany

Correspondence
Gregor Broessner, Department of Neurology, Innsbruck Medical University, Anichstraße 35, 6020 Innsbruck, Austria.
Email: gregor.broessner@i-med.ac.at

Abstract

Objective: Along with the development of novel migraine therapies as the monoclonal antibodies against calcitonin gene-related peptide (CGRP) and its receptor, the question arises if the treatment of chronic migraine (CM) and medication overuse headache (MOH) must be reconsidered. Have previous therapeutic approaches, including glucocorticoids, lost their role in the management of this debilitating disorder? In this narrative review, we present an overview of the available treatment options in CM and MOH in light of CGRP antibodies as well as an evaluation of the role of glucocorticoids in withdrawal therapy.

Background: Chronic migraine and medication overuse continues to be a difficult to treat condition. To date, potent treatment options are scarce and algorithms for advising patients with MOH are often still based on expert consensus rather than evidence-based medicine. For years and probably due to lack of effective alternatives, glucocorticoids have been used in MOH, especially to alleviate withdrawal symptoms caused by detoxification. Small case series report positive effects of steroids in this respective patient group; however, randomized controlled trials did not show a consistent benefit, although this may be due to methodological limitations. Because of these discrepancies, their role in MOH has been under debate ever since.

Methods: We searched the electronic database PubMed for articles up to June 1, 2022 on the use of glucocorticoids in CM and MOH.

Conclusion: Despite popular use in clinical practice, there is currently still no scientific evidence for the efficacy of glucocorticoids in patients with CM and MOH. Treatment with monoclonal antibodies achieved high transition rates from medication overuse to non-overuse. However, further research is needed to evaluate the additional benefit of these new agents.

KEYWORDS
calcitonin gene-related peptide antibodies, chronic migraine, glucocorticoids, medication overuse, prednisone

Abbreviations: CGRP, calcitonin gene-related peptide; CM, chronic migraine; ICHD-3, International Classification for Headache Disorders, 3rd edition; mAbs, monoclonal antibodies; MeSH, medical subject headings; MMD, mean migraine days; MO, medication overuse; MOH, medication overuse headache; po, per os, by mouth; RCT, randomized controlled trials.

INTRODUCTION

Medication overuse headache (MOH) is the fourth most common headache disorder.[1] Its prevalence in the general population is estimated about 1%–2%.[2] According to the International Classification for Headache Disorders, 3rd edition (ICHD-3) MOH is defined as a headache that is present on at least 15 days/month and evolves from a regular overuse of acute headache medication (on ≥10 days/month for opioids, triptans, ergotamines, or combination analgesics and on ≥15 days/month for non-opioid analgesics) for more than 3 months.[3] Usually, patients with a pre-existing primary headache develop MOH—therefore, the ICHD-3 recommends coding for both the diagnosis of the pre-existing headache plus the diagnosis of MOH.[3]

Despite the high incidence and the imminent health risks that are entailed with an excessive use of analgesics and non-steroidal anti-inflammatory drugs, current treatment guidelines vary considerably among tertiary headache centers. National and international headache societies like the International Headache Society, the European Headache Federation, the German Migraine and Headache Society, the European Academy of Neurology, as well as the American Headache Society promote a multidisciplinary approach and recommend withdrawing the overused remedies plus potentially initiating a preventive medication.[3-6] Various prophylactic treatment options such as onabotulinumtoxinA[7] and topiramate[8] have been investigated in randomized controlled trials (RCTs) in MOH. The latest and most comprehensive review of the treatment of MOH by Diener et al. suggests a three-step treatment plan: (1) education, (2) withdrawal, and (3) start of a preventive drug and non-medical therapy.[9] Another systematic review and meta-analysis on the effectiveness of different treatment approaches in patients with MOH was published in 2017 by de Goffau et al.[10] and included RCTs until the November 1, 2015. In short, the final assessment comprised 16 trials, but no benefit of prophylactic treatment versus placebo could be found. However, clinical trials of the monoclonal antibodies were not available or rather completed before the data were reviewed. Therefore, no data on the use of calcitonin gene-related peptide (CGRP) antibodies in patients with MOH could be included in this review. But, recently published studies demonstrated the efficacy of CGRP antibodies in this subpopulation, which will be discussed later in this review.[11-14]

Patients who undergo a "cold detoxification," thus abruptly stopping their overused medication, frequently experience withdrawal symptoms like autonomic dysfunction and nausea. The discontinuation can temporarily even worsen the preexisting headache. Recommendations for the treatment of withdrawal symptoms vary considerably between studies and headache centers; however, in this context, corticosteroids (i.e., prednisone, prednisolone, and methylprednisolone) are used, although scientific evidence is scarce. Possible modes of actions of corticosteroids include anti-inflammatory effects and the inhibition of cyclo-oxygenase-II, but remain elusive.[15] Although small case series report positive effects, RCTs did not show a benefit regarding the reduction of headache days or days with acute medication use between cortisone and placebo.[10] Due to these discrepancies, the role of steroids in MOH has been under debate ever since.[1]

Herein we present an up-to-date review of the available treatment options in MOH in the light of CGRP antibodies as well as the role of glucocorticoids in withdrawal therapy. Can we finally offer adequate treatment for this difficult-to-treat patient group and establish guidelines?

SEARCH STRATEGY AND SELECTION CRITERIA

The aim of this narrative review was to provide an up-to-date overview of the current treatment options, the role of glucocorticoids, guidelines as well as expert opinions in chronic migraine (CM), and medication overuse. We performed a systematic search of the electronic database PubMed up to June 1, 2022 using following medical subject headings (MeSH): (glucocorticoids [MeSH] OR methylprednisolone [tiab] OR prednisolone [tiab] OR prednisone [tiab]) AND (chronic migraine) AND (medication-overuse [MeSH] or medication-overuse-headache [tiab] or MOH [tiab] or medication-overuse headache [tiab] or medication overuse headache [tiab]). Language was restricted to English. Studies on non-human species were excluded. RCTs as well as observational studies were included in this review. Publications were largely selected from the last 20 years.

THE ROLE OF GLUCOCORTICOIDS IN WITHDRAWAL HEADACHE IN CM AND MOH

In 2017, de Goffau et al. published a systematic review and meta-analysis on the effectiveness of different treatment options for patients with medication overuse.[10] Altogether, 16 trials (RCTs, crossover studies, and cluster randomized trials) until November 1, 2015 comprising a total of 1105 patients were included. Three trials evaluated the effectiveness of prednisone (60–100 mg/day po [per os, by mouth]) compared to placebo[15-17] and one trial compared celecoxib to prednisone[18] during medication withdrawal. All trials gradually tapered prednisone every 5–6 days. There was no difference in the prednisone versus placebo group and no difference in prednisone versus celecoxib group with respect to acute medication, headache days, or headache intensity. Statistically, most of these studies were underpowered with low number of patients <50 per treatment group.

In a randomized, single-blinded, placebo-controlled study, Cevoli et al.[19] assessed the efficacy of methylprednisolone and paracetamol in the treatment of MOH. Fifty-seven patients were randomized into three groups with 19 participants in each cohort: group A received 500 mg methylprednisolone intravenously once daily, group B a cumulative dose of 4 g paracetamol per day, and group C placebo. These bridging therapies were carried on for 5 days during withdrawal. The outcome was evaluated at two follow-up

visits 1- and 3-months post-detoxification. No significant difference could be shown at any endpoint—headache intensity decreased significantly after detoxification irrespective of the bridging strategy.

In a retrospective non-randomized study including 94 patients, Paolucci et al.[20] compared the headache frequency and drug consumption after 3 months in patients who received a bridging therapy with a daily intravenous administration of 125 mg methylprednisolone and 10 mg diazepam for 5 days during withdrawal with patients who underwent detoxification without bridging. After 5 days both groups received a prophylactic treatment. Overall, patients obtaining a bridging therapy reported fewer headache days and significantly less acute medication intake after 3 months. However, these findings are limited by the retrospective design and small sample size.

Krymchantowski et al. conducted several studies investigating prednisone as a treatment option in withdrawal headache in patients with CM and MOH. Two studies were non-randomized[21,22] and one was a prospective randomized open-label trial.[23] All patients had to withdraw overused acute medication abruptly. In the first study, 400 patients were included and prescribed prednisone 60 mg and ranitidine 300 mg per day for 6 days, reducing the steroid dosage by half every second day. On day 7, prophylactic treatment (atenolol, amitriptyline, flunarizine, propranolol) was started. During the treatment with prednisone, 85% of the participants noted a decrease in headache frequency and only 12% reported withdrawal symptoms, such as nausea or autonomic dysfunction, in the first 2 weeks after discontinuing acute medication. In their other non-randomized study, 149 patients were included. One hundred one patients (67.8%) received a bridging therapy during detoxification, which consisted of either 5 days (60 mg for 3 days; 40 mg for 2 days; $n = 57$) or 7 days (60 mg for 3 days; 40 mg for 3 days; 20 mg for 1 day; $n = 44$) with prednisone. No outcome differences were observed at any the follow-up visits at 2, 4, and 8 months.

The WASH-OUT program is a multicenter, randomized, single-blind prospective study conducted in 10 Italian hospitals, which started in 2020 and is ongoing.[24] Patients with MOH were advised to abruptly stop overused drugs and received a new preventive medication. If patients were still overusing medication 12 weeks after initiation of the new preventive therapy, they were eligible to participate in the WASH-OUT program and were allocated to a 5-day bridging therapy with either 10 mg diazepam daily intravenously or 10 mg diazepam and 125 mg methylprednisolone daily intravenously during withdrawal. In an interim analysis, almost half of the patients met the inclusion criteria for bridging therapy. After 1 month, no significant difference between the diazepam and the methylprednisolone group in monthly migraine days or days with acute medication intake could be detected.

DETAILED CORTISONE REGIMEN FOR MOH IN THREE DIFFERENT TERTIARY HEADACHE CENTERS

In the tertiary headache center, in Innsbruck, Austria, patients with CM and MOH were advised to abruptly withdraw all overused acute medication. In addition, oral therapy with methylprednisolone (starting dose 80 mg po daily; the dose is then halved and tapered down every 5 days) is initiated. If the patient has already failed several withdrawal attempts or is overusing opioids, an inpatient withdrawal using methylprednisolone (as described above) including intravenous rescue medication plus sedatives (if necessary) is conducted. A detailed regime for all three headache centers detailed in this section is outlined in Table 1.

Since antibodies targeting CGRP or its receptor were approved, the therapeutical approach toward MOH has, however, changed. If a patient with CM and MOH is suitable for monoclonal antibody (mAB) therapy, treatment with a CGRP antibody is initiated and patients are advised to reduce acute medication but without strict withdrawal. In Austria, patients are eligible for therapy with a CGRP antibody if at least three previous attempts with standard of care preventive medications (beta-blockers, antiseizure medication, calcium channel blockers, onabotulinumtoxinA, or tricyclic antidepressants) of adequate duration showed either (1) no effect; (2) side effects that led to treatment discontinuation, or (3) pre-existing contraindications to their use.

In an outpatient headache center (Kopfschmerzzentrum Nord-Ost in Rostock, Germany) patients with MOH are advised to withdraw the overused medication. Simultaneously, a treatment with a prophylactic medication and prednisolone 80 mg is initiated. After 7 days, prednisolone is tapered down by 20 mg every other day. Patients with CM and MOH are treated with mABs. In Germany, however, patients only qualify for the treatment with mAbs if all other standard of care prophylactic medications prove to be ineffective.

In Frankfurt, Germany, patients overusing analgesics, triptans, or both are advised to abruptly withdraw their overused medication. In patients without co-existing psychiatric disorders, the preferred setting is an outpatient withdrawal, with the opportunity of daily

TABLE 1 Glucocorticoid regime in three tertiary headache centers.

Headache center	Glucocorticoid	Dose (mg)	Application	Tapering	Treatment duration	Setting
Innsbruck	Methylprednisolone	80	po	Halved every 5 days	20 days	Outpatient
Rostock	Prednisolone	80	po	Tapered 20 mg every other day after 7 days	13 days	Outpatient
Frankfurt	Prednisolone	100	po	–	3–5 days	Outpatient

Abbreviation: po, per os, by mouth.

appointments in the first week if needed. Only a short course of oral prednisolone (100 mg per day over 3 days without tapering) is used as a standard. In case of significant headaches on day three, the cortisone therapy is extended up to 5 days. All patients are advised to take metoclopramide 10 mg (up to 3 times per day) in case of nausea and amitriptyline 10–25 mg for relief of headache, withdrawal headache, vegetative symptoms, or sleep disturbances. Patients withdrawing from combination analgesics or opioids are more vulnerable to withdrawal complications and are therefore preferentially treated as inpatients. This is in line with published data comparing withdrawal of different substances.[25] Those patients frequently need intravenous therapy with antiemetics and replacement of intravenous volume in case of frequent vomiting. Therefore, prednisolone is usually administered intravenously for 5 days. Based on our clinical experiences, there is no beneficial effect of steroids in patients overusing opioids, such as tramadol, tilidine/naloxone, or codeine. However, it is important to mention that opioids and opioid-containing combinations are not recommended for treatment of primary headaches in Germany.[26] In addition and considering individual previous prophylactic treatment and somatic or psychiatric comorbidities, preventive treatment with topiramate, tricyclic antidepressants (e.g., amitriptyline), onabotulinumtoxinA, or a mAb targeting CGRP or its receptor is started.

WITHDRAWAL STRATEGIES AND PREVENTIVE MEDICATION IN CM AND MOH

Withdrawal

In general, there are two types of withdrawal settings, either inpatient or outpatient. The former might be better suited for patients with psychiatric comorbidities, previous unsuccessful withdrawal attempts, history of substance abuse, or patients overusing opioids or a combination of substances.[27] de Goffau et al. did not find a significant difference between inpatient and outpatient withdrawal regarding the number of responders nor headache days. However, the reduction of days with acute medication use was significantly higher in patients undergoing inpatient withdrawal.[10] Availability of headache-specific inpatient or day care clinics and reimbursement issues are important limitations in the real-world scenario. Two of the studies included in the meta-analysis by de Goffau et al. compared different therapeutic approaches in patients with MOH: One group received only the advice to withdraw the overused medication; one group received a structured outpatient withdrawal program including oral prednisone for the first 8 days and the implementation of a preventive therapy on day 1; and the third group received a similar procedure as group two, only in an inpatient setting and with additional intravenous antiemetic and fluid replacement therapy. Results showed no significant differences among the groups regarding reduction of headache days or days with the intake of acute medication.[28,29]

Carlsen et al.[30] investigated "cold detoxification" (i.e., abrupt stop) versus restricting the overused medication to 2 days/week and observed considerable differences between those approaches in an RCT. At the 6-month follow-up visit, patients who underwent the cold detoxification program had significantly fewer headache days/month compared to the patients who only reduced their analgesic intake (46% vs. 22%, $p = 0.005$). In addition, 70% of the "detox" patients reverted to episodic migraine compared to 42% in the other group. The COMOESTAS project, a multinational study for the management of medication overuse headache, found similar results: 6 months after abruptly discontinuing the overused medication, 71% of the patients remained non-overusers and reported <15 headache days/month.[31] These results are in line with the findings of Nielsen et al., who concluded that abrupt withdrawal might be the most effective approach not only to reduce migraine and/or headache days, but also to mitigate disability in patients with MOH.[32,33]

According to the COMOESTAS project, a longer history of CM (7.7 ± 9.1 vs. 4.5 ± 6.2 years; $p = 0.032$) poses a risk factor for relapsing. This finding underlines the necessity of an early intervention in patients with episodic migraine to avoid chronification. A study currently conducted by Diener et al. specifically addresses this topic—by implementing a feedback system via a mobile software application, the development or relapse of MOH in patients with episodic or CM could be prevented.[9]

Another study by Carlsen et al. enrolled 120 patients in a prospective, longitudinal, open-label randomized trial to compare three treatment approaches: withdrawal plus preventive treatment, preventive treatment without withdrawal, and withdrawal with optional preventive treatment. The combination of withdrawal plus preventive medication might be 30% more effective in treating MOH than withdrawal or implementing preventive medication alone.[4] However, recently published data of the Medication Overuse Treatment Study, a prospective, longitudinal RCT enrolling 720 patients with CM and MOH arrived at different results. Participants were randomly assigned to one of two treatment groups. In the first group, patients were started on a preventive migraine medication and had to switch their overused acute medication to an alternative with a maximum use of 2 days/week. In the second group, the participants received a preventive migraine medication as well; however, they did not have to discontinue their overused acute medication and did not have a limited intake frequency. The authors could not detect a statistically significant difference regarding the reduction of headache days in patients starting preventive migraine medication with or without switching the overused acute medication suggesting that starting a preventive medication without withdrawing the symptomatic medication is not inferior to starting a preventive migraine medication and withdrawing.[34] Nevertheless, patients with a high baseline frequency of days using acute medication (>23 days per 4 weeks) achieved better outcomes in switching the overused symptomatic medication.[34]

These findings support the consensus of headache societies, that withdrawing the overused medication is still an adequate treatment approach for MOH and that adherence to abstinence should be encouraged.

Preventive medication

de Goffau et al.[10] identified five trials that evaluated the effectiveness of preventive medication (valproate, nabilone, onabotulinumtoxinA, topiramate, and amitriptyline) compared to placebo or ibuprofen.[35-39] There was neither a significant difference in the reduction of headaches days or days with acute medication intake between topiramate and valproate nor a significant difference in the outcome parameters for onabotulinumtoxinA versus placebo. However, a statistically significant difference between amitriptyline and placebo was detected.

OnabotulinumtoxinA

Onabotulinumtoxin injection according to the "PREEMPT" protocol is an approved and well-established treatment for CM.[7,40] Several studies investigated the potency of onabotulinumtoxinA in CM and MOH recently.[41-51] In their double-blind, RCT, Pijpers et al.[52] included 179 patients with CM and MOH. Patients with continuous headaches without headache-free days as well as patients with moderate and severe depression were enrolled and randomly assigned to receive either onabotulinumtoxinA according to the PREEMPT protocol or placebo prior to acute medication withdrawal. To prevent unblinding, the placebo group received low-dose onabotulinumtoxinA instead of saline in the seven injection sites on the forehead. At the 12-week follow-up assessment no additional benefit of onabotulinumtoxinA as add-on therapy before medication withdrawal could be found. Accordingly, Schiano di Cola et al. indicated a lower response rate to treatment with onabotulinumtoxinA in patients with MOH and psychiatric comorbidities.[48]

Topiramate and flunarizine

Two randomized, placebo-controlled, parallel-group, multicenter studies tested topiramate in patients with CM. Diener et al. enrolled 46 patients with an additional diagnosis of MOH. Treatment with topiramate significantly reduced the mean monthly migraine days compared to placebo ($p = 0.03$), however it failed statistical significance regarding the reduction of days with intake of acute medication ($p = 0.07$).[8] In a post hoc analysis of the study by Silberstein et al. enrolling 306 subjects, topiramate did not significantly reduce the mean migraine days compared to placebo in a subset of patients with CM and MOH ($p = 0.059$).[53,54]

Lai et al. compared the efficacy of flunarizine to topiramate in patients with CM in a randomized, open-label, blinded-endpoint trial, with a sample size of 62 participants (31 patients per treatment group).[55] The subgroup analysis for patients with CM and MOH showed a significant reduction in days of acute medication intake and a reduction in the number of tablets taken in the flunarizine group ($n = 15$), but not in the topiramate group ($n = 14$). However, these results must be interpreted with great caution due to the small sample size and the low target dose of topiramate with only 50 mg/day.

Propranolol

Silberstein et al.[56] evaluated the add-on effect of propranolol to topiramate in the treatment of patients with CM in a randomized, placebo-controlled trial. Altogether 171 patients (with and without medication overuse) were enrolled and received either topiramate (up to 100 mg/day) and propranolol (up to 240 mg/day) or topiramate (up to 100 mg/day) and placebo. The trial was terminated early as the primary endpoint (adding propranolol significantly reduces the headache rate) was not achieved.

CGRP antibodies

Currently, there are four mABs against CGRP or the CGRP receptor: erenumab being the only fully human anti-CGRP receptor monoclonal antibody whereas fremanezumab, galcanezumab, and eptinezumab are all humanized mAbs that selectively bind to the CGRP ligand. The latter is administered quarterly intravenously while all others are applied subcutaneously either monthly (fremanezumab, glacanezumab), every 4 weeks (erenumab), or quarterly (fremanezumab, triple dose). For all four mABs post hoc analysis of phase 2 or phase 3 studies on the efficacy in a subset of patients with CM and MOH have been published. The studies were conducted under standardized, randomized, placebo-controlled conditions and considered similar outcome parameters in an observational period of 12 weeks: reduction of mean migraine days (MMD), ≥50% responder rates, reduction of acute migraine-specific medication use days, and transition from medication overuse to non-overuse. The results are illustrated in Table 1. In addition, the patient population across all studies is comparable due to the homogeneous age and gender distribution (mean age 43.2 years and 85.3% women). For the evaluation of erenumab, we used the subgroup analysis of a randomized, phase 2 trial in CM patients,[11] for fremanezumab the subgroup analysis of the phase 3 HALO CM study,[13] for galcanezumab the subgroup analysis of the phase 3 REGAIN study,[12] and for eptinezumab the subgroup analysis of the phase 3 PROMISE-2 study.[14] An overview of the study endpoints and results is depicted in Table 2.

Taken together, these studies provide solid evidence that these new preventive treatments not only reduce the MMD per month but also seem to be effective in reducing days with acute migraine medication use even without additional or prior withdrawal of acute medication. Recently published real-life data corroborate the efficacy of mABs in this context.[57,58]

CONCLUSION

Currently, there is still no solid scientific proof for the efficacy of glucocorticoids in MOH. However, clinical experience indicates that glucocorticoids can contribute to alleviating headache intensity and withdrawal symptoms and thus may help patients to convert to non-overusers. The reason these positive results are not reflected in

TABLE 2 Key aspects of the four mAb studies on chronic migraine with medication overuse headache.

	Erenumab		Galcanezumab	Fremanezumab		Eptinezumab	
Target	CGRP receptor		CGRP	CGRP		CGRP	
Route of administration	sc		sc	sc		iv	
Dosage	70 mg/140 mg		120 mg	225 mg/675 mg		100 mg/300 mg	
Administration period	4 weeks		Monthly	Monthly/quarterly		Quarterly	
Observational period	12 weeks		12 weeks	12 weeks		12 weeks	
Randomization	3:2:2 (placebo/ 70 mg/140 mg)		2:1:1 (placebo/ 120 mg/240 mg[c])	1:1:1 (placebo/ 225 mg/675 mg)		1:1:1 (placebo/ 100 mg/300 mg)	
Female, *n* (%)	233 (85%)		591 (83%)	524 (89%)		376 (87.2%)	
Sample size[a]	274		708	587		431	
Age, mean, y	43.4		43.3	44.8		41.4	
MMD (BL)	19.0		20.0	17.3		16.7	
Days with acute medication (BL)	13.1		18.3	18.2		na	
Reduction of MMD from BL (days)[b]	70 mg	140 mg	120 mg	225 mg	675 mg	100 mg	300 mg
	−3.1	−3.1	−2.5	−2.4	−2.0	−3.0	−3.2
Reduction of days with acute medication from BL[b]	−3.3	−2.8	−2.8	−2.4	−1.8	na	na
50% RR[b]	18.7%	16.9%	13.3%	25.6%	21.0%	25.9%	27.4%
Transition from MO to non-MO[b]	na	na	18.3%	14.3%	8.9%	−1.7%	−10.7%
AE[b]	−12.3%	−14.2%	−7.7%	na	na	−10.0%	4.8%

Abbreviations: 50% RR, response rate—proportion of patients with a ≥50% reduction on the monthly average number of mean migraine days; AE, adverse event; BL, baseline; CGRP, calcitonin gene-related peptide; CM, chronic migraine; iv, intravenous; mAb, monoclonal antibody; MMD, mean migraine days; MO, medication overuse; MOH, medication overuse headache; na, not applicable; P, placebo; sc, subcutaneous.

[a]Only patients with the diagnosis of CM + MOH were considered.

[b]Placebo-adjusted values.

[c]Galcanezumab 240 mg was not included because it has not been approved for the treatment of migraine.

clinical trials may be due to methodological limitations: small sample size, inhomogeneous study design and patient population, short observational period, and missing control group.

In our three tertiary headache centers, glucocorticoids play an important role in the treatment of patients with MOH. Although different agents, dosing regimens, and tapering schemes are used, the therapeutic success justifies its use and can therefore be recommended by experts.

Apart from the controversy surrounding glucocorticoids, acute medication withdrawal might be the most important and effective tool in patients with CM and MOH. It is of utmost importance to promote patient education—people with migraine need to be advised in detail about the risks accompanying the frequent use of acute medication.

Neither treatment with onabotulinumtoxinA as add-on therapy to acute drug withdrawal nor propranolol as add-on therapy to treatment with topiramate showed a benefit in reducing migraine and/or headache days compared to placebo. Topiramate showed advantages in reducing migraine days; however, in this study flunarizine seemed to be more effective than topiramate in patients with CM and MOH. Further, the results must be interpreted with caution due to the small sample size and the low dose of topiramate.[59]

The CGRP receptor and CGRP ligand antibodies showed significant superiority over placebo in reducing headache days, migraine days, and days with acute medication in well designed and highly powered RCTs even without stratified detoxification. Thus, further studies will be needed to evaluate the additional benefit of antibodies in combination with acute withdrawal compared to a placebo group.

AUTHOR CONTRIBUTIONS

Study concept and design: Charly Gaul, Gregor Broessner. *Acquisition of data*: Katharina Kaltseis, Till Hamann. *Analysis and interpretation of data*: Katharina Kaltseis, Till Hamann, Charly Gaul, Gregor Broessner. *Drafting of the manuscript*: Katharina Kaltseis. *Revising it for intellectual content*: Till Hamann, Charly Gaul, Gregor Broessner. *Final approval of the completed manuscript*: Katharina Kaltseis, Till Hamann, Charly Gaul, Gregor Broessner.

CONFLICTS OF INTEREST

Katharina Kaltseis and **Till Hamann** declare no conflicts of interest. **Charly Gaul**: received honoraria for consulting and lectures within the past 3 years from Allergan Pharma, Lilly, Novartis Pharma, Hormosan Pharma, Grünenthal, Sanofi-Aventis, Weber & Weber, Lundbeck, Perfood, and TEVA. His research is supported by a grant of the German Research Foundation (DFG). He does not hold any stocks of pharmaceutical companies. He is honorary secretary of the German Migraine and Headache Society. **Gregor Broessner:**

has received honoraria for consulting and lectures within the past 3 years from Allergan, Abbvie, Grünenthal, Lilly, Novartis Pharma, and TEVA. He does not hold any stocks of pharmaceutical companies. He is past president of the Austrian Headache Society.

ORCID

Charly Gaul https://orcid.org/0000-0002-9362-3711

REFERENCES

1. Diener HC. How to treat medication-overuse headache: prednisolone or no prednisolone? *Neurology*. 2007;69:14-15. doi:10.1212/01.wnl.0000269324.27980.a9
2. Kristoffersen ES, Lundqvist C. Medication-overuse headache: epidemiology, diagnosis and treatment. *Ther Adv Drug Saf*. 2014;5:87-99. doi:10.1177/2042098614522683
3. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211.
4. Carlsen LN, Munksgaard SB, Nielsen M, et al. Comparison of 3 treatment strategies for medication overuse headache: a randomized clinical trial. *JAMA Neurol*. 2020;77:1069-1078. doi:10.1001/jamaneurol.2020.1179
5. Sacco S, Braschinsky M, Ducros A, et al. European Headache Federation Consensus on the definition of resistant and refractory migraine: developed with the endorsement of the European Migraine & Headache Alliance (EMHA). *J Headache Pain*. 2020;21:76. doi:10.1186/s10194-020-01130-5
6. Diener HC, Antonaci F, Braschinsky M, et al. European Academy of Neurology guideline on the management of medication-overuse headache. *Eur J Neurol*. 2020;27:1102-1116. doi:10.1111/ene.14268
7. Silberstein SD, Blumenfeld AM, Cady RK, et al. OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. *J Neurol Sci*. 2013;331:48-56. doi:10.1016/j.jns.2013.05.003
8. Diener HC, Bussone G, Van Oene JC, et al. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia*. 2007;27:814-823. doi:10.1111/j.1468-2982.2007.01326.x
9. Diener HC, Donoghue S, Gaul C, et al. Prevention of medication overuse and medication overuse headache in patients with migraine: a randomized, controlled, parallel, allocation-blinded, multicenter, prospective trial using a mobile software application. *Trials*. 2022;23:382. doi:10.1186/s13063-022-06329-2
10. de Goffau MJ, Klaver ARE, Willemsen MG, et al. The effectiveness of treatments for patients with medication overuse headache: a systematic review and meta-analysis. *J Pain*. 2017;18:615-627. doi:10.1016/j.jpain.2016.12.005
11. Tepper SJ, Diener HC, Ashina M, et al. Erenumab in chronic migraine with medication overuse: subgroup analysis of a randomized trial. *Neurology*. 2019;92:e2309-e2320. doi:10.1212/WNL.0000000000007497
12. Dodick DW, Doty EG, Aurora SK, et al. Medication overuse in a subgroup analysis of phase 3 placebo-controlled studies of galcanezumab in the prevention of episodic and chronic migraine. *Cephalalgia*. 2021;41:340-352. doi:10.1177/0333102420966658
13. Silberstein SD, Cohen JM, Seminerio MJ, et al. The impact of fremanezumab on medication overuse in patients with chronic migraine: subgroup analysis of the HALO CM study. *J Headache Pain*. 2020;21:114. doi:10.1186/s10194-020-01173-8
14. Diener HC, Marmura MJ, Tepper SJ, et al. Efficacy, tolerability, and safety of eptinezumab in patients with a dual diagnosis of chronic migraine and medication-overuse headache: subgroup analysis of PROMISE-2. *Headache*. 2021;61:125-136. doi:10.1111/head.14036
15. Rabe K, Pageler L, Gaul C, et al. Prednisone for the treatment of withdrawal headache in patients with medication overuse headache: a randomized, double-blind, placebo-controlled study. *Cephalalgia*. 2013;33:202-207. doi:10.1177/0333102412462638
16. Pageler L, Katsarava Z, Diener HC, Limmroth V. Prednisone vs. placebo in withdrawal therapy following medication overuse headache. *Cephalalgia*. 2008;28:152-156. doi:10.1111/j.1468-2982.2007.01488.x
17. Bøe MG, Mygland A, Salvesen R. Prednisolone does not reduce withdrawal headache: a randomized, double-blind study. *Neurology*. 2007;69:26-31. doi:10.1212/01.wnl.0000263652.46222.e8
18. Taghdiri F, Togha M, Razeghi Jahromi S, Paknejad SMH. Celecoxib vs. prednisone for the treatment of withdrawal headache in patients with medication overuse headache: a randomized, double-blind clinical trial. *Headache*. 2015;55:128-135. doi:10.1111/head.12487
19. Cevoli S, Giannini G, Favoni V, et al. Treatment of withdrawal headache in patients with medication overuse headache: a pilot study. *J Headache Pain*. 2017;18:56. doi:10.1186/s10194-017-0763-9
20. Paolucci M, Altamura C, Brunelli N, et al. Methylprednisolone plus diazepam i.v. as bridge therapy for medication overuse headache. *Neurol Sci*. 2017;38:2025-2029. doi:10.1007/s10072-017-3098-z
21. Krymchantowski AV, Barbosa JS. Prednisone as initial treatment of analgesic-induced daily headache. *Cephalalgia*. 2000;20:107-113. doi:10.1046/j.1468-2982.2000.00028.x
22. Krymchantowski AV, Tepper SJ, Jevoux C, Valença M. Medication-overuse headache: protocols and outcomes in 149 consecutive patients in a tertiary Brazilian headache center. *Headache*. 2017;57:87-96. doi:10.1111/head.12970
23. Krymchantowski AV, Moreira PF. Out-patient detoxification in chronic migraine: comparison of strategies. *Cephalalgia*. 2003;23:982-993. doi:10.1046/j.1468-2982.2003.00648.x
24. Vernieri F, Pasqualetti P, Paolucci M, et al. Drug withdrawal along with bridge therapy with methylprednisolone and/or diazepam for treatment of medication overuse headache: a preliminary report from the WASH-OUT study. *Neurol Sci*. 2020;41:499-501. doi:10.1007/s10072-020-04675-0
25. Katsarava Z, Fritsche G, Muessig M, Diener HC, Limmroth V. Clinical features of withdrawal headache following overuse of triptans and other headache drugs. *Neurology*. 2001;57:1694-1698. doi:10.1212/wnl.57.9.1694
26. Totzeck A, Gaul C. The role of opioids in the treatment of primary headache disorders. *Schmerz*. 2014;28:135-140. doi:10.1007/s00482-013-1380-4
27. Diener H-C, Kropp P. Kopfschmerz bei Übergebrauch von Schmerz- oder Migränemitteln (Medication Overuse Headache = MOH), S1-Leitlinie, Deutsche Gesellschaft für Neurologie, Leitlinien für Diagnostik und Therapie in der Neurologie. 2022. Accessed Novemeber 02, 2022. https://www.dgn.org/leitlinien
28. Rossi P, Faroni JV, Tassorelli C, Nappi G. Advice alone versus structured detoxification programmes for complicated medication overuse headache (MOH): a prospective, randomized, open-label trial. *J Headache Pain*. 2013;14:10. doi:10.1186/1129-2377-14-10
29. Rossi P, Di Lorenzo C, Faroni J, et al. Advice alone vs. structured detoxification programmes for medication overuse headache: a prospective, randomized, open-label trial in transformed migraine patients with low medical needs. *Cephalalgia*. 2006;26:1097-1105. doi:10.1111/j.1468-2982.2006.01175.x
30. Carlsen LN, Munksgaard SB, Jensen RH, et al. Complete detoxification is the most effective treatment of medication-overuse headache: a randomized controlled open-label trial. *Cephalalgia*. 2018;38:225-236. doi:10.1177/0333102417737779
31. Bottiroli S, Allena M, Sances G, et al. Psychological, clinical, and therapeutic predictors of the outcome of detoxification in a large clinical population of medication-overuse headache: a six-month

follow-up of the COMOESTAS project. *Cephalalgia*. 2019;39:135-147. doi:10.1177/0333102418783317
32. Engelstoft IMS, Carlsen LN, Munksgaard SB, Nielsen M, Jensen RH, Bendtsen L. Complete withdrawal is the most feasible treatment for medication-overuse headache: a randomized controlled open-label trial. *Eur J Pain*. 2019;23:1162-1170. doi:10.1002/ejp.1383
33. Nielsen M, Carlsen LN, Munksgaard SB, Engelstoft IMS, Jensen RH, Bendtsen L. Complete withdrawal is the most effective approach to reduce disability in patients with medication-overuse headache: a randomized controlled open-label trial. *Cephalalgia*. 2019;39:863-872. doi:10.1177/0333102419828994
34. Schwedt TJ, Hentz JG, Sahai-Srivastava S, et al. Patient-centered treatment of chronic migraine with medication overuse: a prospective, randomized, pragmatic clinical trial. *Neurology*. 2022;98:e1409-e1421. doi:10.1212/WNL.0000000000200117
35. Descombes S, Brefel-Courbon C, Thalamas C, et al. Amitriptyline treatment in chronic drug-induced headache: a double-blind comparative pilot study. *Headache*. 2001;41:178-182. doi:10.1046/j.1526-4610.2001.111006178.x
36. Mei D, Ferraro D, Zelano G, et al. Topiramate and triptans revert chronic migraine with medication overuse to episodic migraine. *Clin Neuropharmacol*. 2006;29:269-275. doi:10.1097/01.WNF.000022888.49044.99
37. Sandrini G, Perrotta A, Tassorelli C, et al. Botulinum toxin type-A in the prophylactic treatment of medication-overuse headache: a multicenter, double-blind, randomized, placebo-controlled, parallel group study. *J Headache Pain*. 2011;12:427-433. doi:10.1007/s10194-011-0339-z
38. Sarchielli P, Messina P, Cupini LM, et al. Sodium valproate in migraine without aura and medication overuse headache: a randomized controlled trial. *Eur Neuropsychopharmacol*. 2014;24:1289-1297. doi:10.1016/j.euroneuro.2014.03.010
39. Pini LA, Guerzoni S, Cainazzo MM, et al. Nabilone for the treatment of medication overuse headache: results of a preliminary double-blind, active-controlled, randomized trial. *J Headache Pain*. 2012;13:677-684. doi:10.1007/s10194-012-0490-1
40. May A, Schulte LH. Chronic migraine: risk factors, mechanisms and treatment. *Nat Rev Neurol*. 2016;12:455-464. doi:10.1038/nrneurol.2016.93
41. Cheng F, Ahmed F. OnabotulinumtoxinA for the prophylactic treatment of headaches in adult patients with chronic migraine: a safety evaluation. *Expert Opin Drug Saf*. 2021;20:1275-1289. doi:10.1080/14740338.2021.1948531
42. Grazzi L. Onabotulinumtoxin a for chronic migraine with medication overuse: clinical results of a long-term treatment. *Neurol Sci*. 2017;38:141-143. doi:10.1007/s10072-017-2864-2
43. Aicua-Rapun I, Martínez-Velasco E, Rojo A, et al. Real-life data in 115 chronic migraine patients treated with onabotulinumtoxinA during more than one year. *J Headache Pain*. 2016;17:112. doi:10.1186/s10194-016-0702-1
44. Butera C, Colombo B, Bianchi F, et al. Refractory chronic migraine: is drug withdrawal necessary before starting a therapy with onabotulinum toxin type A? *Neurol Sci*. 2016;37:1701-1706. doi:10.1007/s10072-016-2662-2
45. Guerzoni S, Pellesi L, Baraldi C, et al. Increased efficacy of regularly repeated cycles with onabotulinumtoxinA in MOH patients beyond the first year of treatment. *J Headache Pain*. 2015;17:48. doi:10.1186/s10194-016-0634-9
46. Negro A, Curto M, Lionetto L, et al. A two years open-label prospective study of onabotulinumtoxinA 195 U in medication overuse headache: a real-world experience. *J Headache Pain*. 2015;17:1. doi:10.1186/s10194-016-0591-3
47. Rothrock JF, Adams AM, Lipton RB, et al. FORWARD study: evaluating the comparative effectiveness of onabotulinumtoxinA and topiramate for headache prevention in adults with chronic migraine. *Headache*. 2019;59:1700-1713. doi:10.1111/head.13653
48. Schiano di Cola F, Caratozzolo S, Liberini P, Rao R, Padovani A. Response predictors in chronic migraine: medication overuse and depressive symptoms negatively impact onabotulinumtoxinA treatment. *Front Neurol*. 2019;10:678. doi:10.3389/fneur.2019.00678
49. Grazzi L, Grignani E, Sansone E, Raggi A, D'Amico D, Andrasik F. Catastrophizing attitude changes after onabotulinumtoxin a treatment in chronic migraine. *Neurol Sci*. 2019;40:201-202. doi:10.1007/s10072-019-03816-4
50. Caronna E, Gallardo VJ, Hernández-Beltrán N, Torres-Ferrus M, Pozo-Rosich P. OnabotulinumtoxinA: an effective tool in the therapeutic arsenal for chronic migraine with medication overuse. *Front Neurol*. 2018;9:808. doi:10.3389/fneur.2018.00808
51. Guerzoni S, Pellesi L, Baraldi C, et al. Long-term treatment benefits and prolonged efficacy of onabotulinumtoxinA in patients affected by chronic migraine and medication overuse headache over 3 years of therapy. *Front Neurol*. 2017;8:586. doi:10.3389/fneur.2017.00586
52. Pijpers JA, Kies DA, Louter MA, van Zwet EW, Ferrari MD, Terwindt GM. Acute withdrawal and botulinum toxin a in chronic migraine with medication overuse: a double-blind randomized controlled trial. *Brain*. 2019;142:1203-1214. doi:10.1093/brain/awz052
53. Diener HC, Dodick DW, Goadsby PJ, et al. Utility of topiramate for the treatment of patients with chronic migraine in the presence or absence of acute medication overuse. *Cephalalgia*. 2009;29:1021-1027. doi:10.1111/j.1468-2982.2009.01859.x
54. Silberstein SD, Lipton RB, Dodick DW, et al. Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. *Headache*. 2007;47:170-180. doi:10.1111/j.1526-4610.2006.00684.x
55. Lai KL, Niddam DM, Fuh JL, et al. Flunarizine versus topiramate for chronic migraine prophylaxis: a randomized trial. *Acta Neurol Scand*. 2017;135:476-483. doi:10.1111/ane.12626
56. Silberstein SD, Dodick DW, Lindblad AS, et al. Randomized, placebo-controlled trial of propranolol added to topiramate in chronic migraine. *Neurology*. 2012;78:976-984. doi:10.1212/WNL.0b013e31824d5846
57. Scheffler A, Messel O, Wurthmann S, et al. Erenumab in highly therapy-refractory migraine patients: first German real-world evidence. *J Headache Pain*. 2020;21:84. doi:10.1186/s10194-020-01151-0
58. Cainazzo MM, Baraldi C, Ferrari A, Lo Castro F, Pani L, Guerzoni S. Erenumab for the preventive treatment of chronic migraine complicated with medication overuse headache: an observational, retrospective, 12-month real-life study. *Neurol Sci*. 2021;42:4193-4202. doi:10.1007/s10072-021-05105-5
59. Frank F, Ulmer H, Sidoroff V, Broessner G. CGRP-antibodies, topiramate and botulinum toxin type A in episodic and chronic migraine: a systematic review and meta-analysis. *Cephalalgia*. 2021;41:1222-1239. doi:10.1177/03331024211018137

How to cite this article: Kaltseis K, Hamann T, Gaul C, Broessner G. Is prednisone still a reasonable option in the treatment of withdrawal headache in patients with chronic migraine and medication overuse headache in the age of CGRP antibodies? A narrative review. *Headache*. 2022;62:1264-1271. doi: 10.1111/head.14415