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Comparison of 3 Treatment Strategies for Medication Overuse Headache
A Randomized Clinical Trial

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IMPORTANCE Medication overuse headache (MOH) is a disabling, globally prevalent disorder representing a well-known and debated clinical problem. Evidence for the most effective treatment strategy is needed.

OBJECTIVE To compare 3 treatment strategies for MOH.

DESIGN, SETTING, AND PARTICIPANTS This open-label, randomized clinical trial with 6 months of follow-up was conducted in the tertiary sector at the Danish Headache Center, Glostrup, from October 25, 2016, to June 28, 2019. Of 483 patients with MOH referred during the inclusion period, 195 met the criteria consisting of migraine and/or tension-type headache, 18 years or older, eligibility for outpatient treatment, no severe physical or psychiatric disorder, no other addiction, and not pregnant or breastfeeding. Of these, 75 refused participation and 120 were included. Data were analyzed from July 3 to September 6, 2019.

INTERVENTIONS Random assignment (1:1:1 allocation) to 1 of the 3 outpatient treatments consisting of (1) withdrawal plus preventive treatment, (2) preventive treatment without withdrawal, or (3) withdrawal with optional preventive treatment 2 months after withdrawal.

MAIN OUTCOMES AND MEASURES The primary outcome was change in headache days per month after 6 months. Predefined secondary outcomes were change in monthly migraine days, use of short-term medication, pain intensity, number of responders, patients with remission to episodic headache, and cured MOH.

RESULTS Of 120 patients, 102 (mean [SD] age, 43.9 [11.8] years; 81 women [79.4%]) completed the 6-month follow-up. Headache days per month were reduced by 12.3 (95% CI, 9.3-15.3) in the withdrawal plus preventive group, by 9.9 (95% CI, 7.2-12.6) in the preventive group, and by 8.5 (95% CI, 5.6-11.5) in the withdrawal group (P = .20). No difference was found in reduction of migraine days per month, use of short-term medication, or headache intensity. In the withdrawal plus preventive group, 23 of 31 patients (74.2%) reverted to episodic headache, compared with 21 of 35 (60.0%) in the preventive group and 15 of 36 (41.7%) in the withdrawal group (P = .03). Moreover, 30 of 31 patients (96.8%) in the withdrawal plus preventive group were cured of MOH, compared with 26 of 35 (74.3%) in the preventive group and 32 of 36 (88.9%) in the withdrawal group (P = .03). These findings corresponded to a 30% (relative risk, 1.3; 95% CI, 1.1-1.6) increased chance of MOH cure in the withdrawal plus preventive group compared with the preventive group (P = .03).

CONCLUSION AND RELEVANCE All 3 treatment strategies were effective, but based on these findings, withdrawal therapy combined with preventive medication from the start of withdrawal is recommended as treatment for MOH.

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Supplemental content

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Medication overuse headache (MOH) is a prevalent disorder representing a well-known, difficult clinical problem. Globally, more than 60 million people are affected. Moreover, MOH is a disabling condition causing a considerable burden for individuals and socioeconomic challenges for society.[1-4] Several times, MOH has been ranked in the top 20 disorders causing years of life lost due to disability by the Global Burden of Disease studies.[1,5]

Medication overuse headache is characterized by escalating headache frequency and progressive use of short-term medication, resulting in chronic headache intractable to treatment. Medication overuse often occurs in patients with chronic headache and is considered one of the most important factors for the shift from episodic to chronic headache.[6-8] Medication overuse may also be a consequence of a poorly treated preexisting headache.[6] Identifying the best treatment strategy to decrease problems for these severely affected patients is of crucial importance. This topic is subject to debate,[1,9,10] and at present, several treatment strategies are considered for patients with MOH.

In European guidelines, education about MOH followed by preventive medication and withdrawal is recommended.[10,11] Withdrawal reverts chronic headache to episodic form in approximately 70% of patients.[12-14] According to Danish guidelines, withdrawal involves complete discontinuation of analgesics for 2 months. Pharmacological preventive therapy is only initiated if needed after the withdrawal period.[15] In other headache centers, preventive therapy is initiated simultaneously with gradual discontinuation of the overused medication.[16] Also, treatment with topiramate, onabotulinumtoxinA, and CGRP monoclonal antibodies (CGRP mAbs) without withdrawal has been proven effective in patients with chronic migraine and medication overuse.[17-20]

The aim of the present study was to compare 3 treatment strategies for MOH: withdrawal with preventive treatment from start (withdrawal plus preventive strategy); preventive treatment without withdrawal (preventive strategy); and withdrawal with postponed optional preventive treatment (withdrawal strategy). Our hypothesis was that the 2 withdrawal strategies (withdrawal plus preventive and withdrawal) would reduce headache days per month more than the preventive strategy. Furthermore, we hypothesized that the 2 withdrawal strategies would result in the same reduction of headache days per month, demonstrating no need for early start of preventive treatments.

Key Points

Question Which treatment is the most effective for medication overuse headache?

Findings This randomized clinical trial of 120 patients with medication overuse headache compared treatments consisting of withdrawal and preventive medication, preventive medication, and withdrawal alone. Withdrawal and preventive medication achieved the best results with a mean reduction of 12.3 headache days per month.

Meaning Given these findings, the use of withdrawal and preventive medication from the start of withdrawal is recommended for treatment of medication overuse headache.

Methods

Study Population

Patients with MOH referred to tertiary care at the Danish Headache Center (DHC), Glostrup, were invited to participate by the project team. Patients with an MOH diagnosis according to the *International Classification of Headache Disorders, Third Edition (Beta Version)* (*ICHD-3*β)[21] were eligible for inclusion. Headache days and medication use were ascertained from detailed history and a headache calendar with data from at least 1 month. Patients were considered eligible for outpatient treatment based on the type of medication overuse (without daily or almost daily use of opioids or barbiturates), personal resources, and motivation; capability of completing a headache calendar; being 18 years or older; and MOH arising from preexisting tension-type headache and/or migraine, including episodic and chronic forms, according to the *ICHD-3*β criteria. Patients were excluded if they had severe physical illness (eg, severe comorbid pain, uncontrolled diabetes, serious heart disease, cancer), psychiatric disorders (requirement of antidepressants or ongoing treatment by a psychiatrist or in a psychiatric clinic), or alcohol or drug addiction; if they were pregnant, breastfeeding, or planning pregnancy within 12 months; if they were unable to provide information about their medical history (including a linguistic barrier); or if they continued other preventive headache treatments. The regional ethics committee in the Capital Region approved the study, and all participants provided written informed consent. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Study Design

The study protocol is found in Supplement 1. In this prospective, longitudinal, open-label randomized clinical trial (RCT), patients with MOH were randomized 1:1:1 to the withdrawal plus preventive treatment group, preventive treatment group, or withdrawal group. All 3 strategies were outpatient treatments. Patients were followed up with visits at baseline and 2 and 6 months and by telephone at 1 and 4 months after initiation of treatment. A headache calendar was filled out continuously until the study was completed. The calendar was used to record days with headache and migraine, pain intensity, and days with short-term medication use.

Withdrawal Approach

The withdrawal plus preventive group and the withdrawal group received individual advice on withdrawal and MOH from trained headache nurses, followed by complete discontinuation of analgesics for 2 months (eTable 1 in Supplement 2). The preventive group received only brief information about withdrawal in connection with a description of the project, and no limit on the use of short-term medication was requested (eTable 1 in Supplement 2). Rescue medication (levomepromazine or promethazine hydrochloride;

maximum dosage, 75 mg/d) and antiemetics (tablet metoclopramide hydrochloride or domperidone; recommended dosage, 10 mg) were offered to all patients during withdrawal. After withdrawal, patients in the withdrawal plus preventive group and withdrawal group could use short-term medication as many as 9 days per month (or 14 days per month for simple analgesics alone), and the withdrawal group was offered preventive treatments.

Preventive Treatment

The withdrawal plus preventive group and preventive group received information about the specific preventive treatment that was chosen according to the existing guideline at the DHC (eTable 1 in Supplement 2).[15] In case of unacceptable adverse effects or lack of effect, preventive treatments were changed. Beneficial preventive treatment was continued throughout the study period. CGRP mAbs were not available at the time of the study.

Randomization

Patients were randomized in blocks of 9 using the Sealed Envelope applications.[22] Patients were stratified based on preexisting headache diagnoses, because patients with pure tension-type headache have been reported to have a possible poorer treatment response.[23,24] The randomization process was conducted by a project nurse from another research group at the DHC.

End Points

The primary outcome was change in headache days per month from baseline to 6 months in the 3 treatment strategies. The prespecified secondary outcomes were comparison of the 3 treatment strategies on the following parameters: (1) change in headache days per month from baseline to 1, 2, and 4 months; (2) change in migraine days per month from baseline to 1, 2, 4, and 6 months; (3) change in days per month with short-term medication use from baseline to 1, 2, 4, and 6 months; (4) change in total monthly headache intensity score ranging from 0 to 90 (30 days times a daily score of 0, indicating no pain; 1, mild pain; 2, moderate pain; or 3, severe pain) from baseline to 1, 2, 4, and 6 months; (5) number of patients with at least 50% reduction in headache days per month at 2 and 6 months; (6) number of patients reverting to episodic headache at 2 and 6 months; and (7) numbers of patients with medication overuse at 2 and 6 months and cured of MOH at 6 months. Cured MOH is defined as no longer fulfilling all 3 diagnostic *ICHD-3*β MOH criteria with headache on at least 15 days per month plus medication overuse.

Dropout rates, course of treatment, and self-reported adverse effects were documented. All end points were predefined in the trial protocol (Supplement 1). The number needed to treat based on cured MOH was predefined as an additional primary end point but was removed after statistical consultancy. A correct number-needed-to-treat calculation required a control group (not included), and a number needed to treat based on cured MOH would not provide any additional information, because cure rates and relative risks (RRs) already were reported.

Statistical Analysis

Data were analyzed from July 3 to September 6, 2019. R statistical software, version 1.1.463 (R Project for Statistical Computing), was used for statistical analyses.

Sample size was based on 1-way analysis of variance and the Cohen *d* statistic for comparison of 3 groups. The efficacy variable was reduction in headache days per month. The *F* value (0.35) was calculated based on estimates from previous literature and clinical experience (highest mean value, 14.0; lowest mean value, 6.0; SD between groups, 7.5; SD for the complete group, 10.5). The α error was set at 5% and power at 80% for a sample size of 102 patients. We assumed a dropout rate of approximately 15% and aimed to include 120 patients with MOH.

Continuous data were presented as mean with SD, standard error of the mean, or 95% CI or as median with range if the distribution was skewed. One-way analysis of variance was used for comparison of continuous outcomes. Model control, the *F* test, and the Levene test were conducted. In case of heterogeneity of variance, the Welch test was performed. Dichotomous variables were presented as percentages or numbers, and the χ^2 test was used for statistics. If a χ^2 test revealed a significant difference among the 3 groups, this difference was explored by relative risk (RR) with 95% CI and corrected for multiple testing by Bonferroni correction. $P \leq .05$ was considered as significant, and all *P* values were 2-tailed.

Results

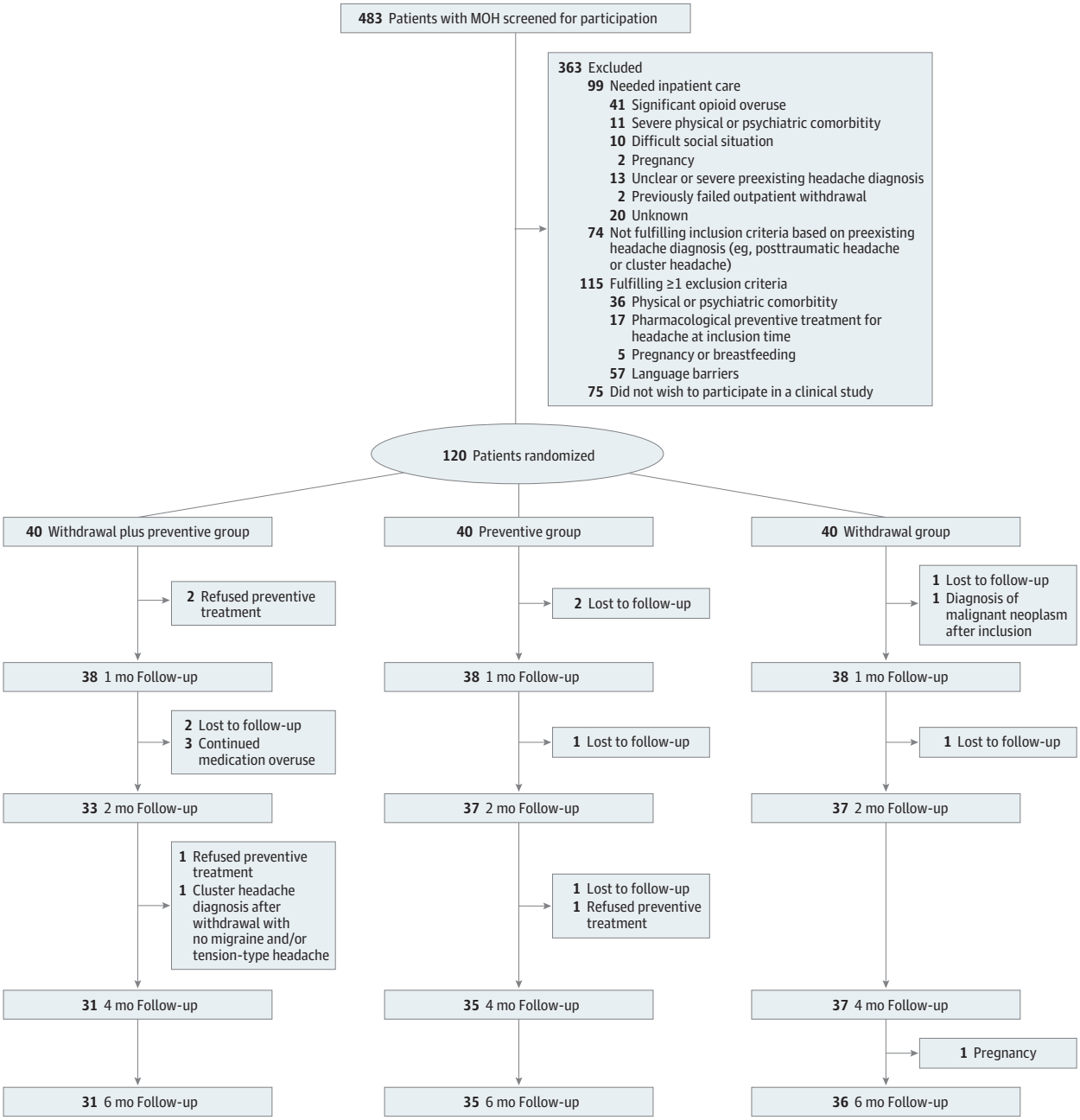
Study Population

From October 25, 2016, to November 19, 2018, 483 patients with MOH were referred to DHC. Of these patients, 195 met the inclusion criteria; 75 refused participation, and 120 were included consecutively in the study (**Figure 1**). Forty patients were randomized to each treatment, and 102 completed the 6-month follow-up (mean [SD] age, 43.9 [11.8] years; 81 women [79.4%] and 21 men [20.6%]), corresponding to a 15% total dropout rate (9 of 40 [22.5%] in the withdrawal plus preventive group; 5 of 40 [12.5%] in the preventive group; and 4 of 40 [10.0%] in the withdrawal group). Baseline characteristics were similar in the 3 groups (**Table 1**). More than 75% of the study population had a single type of medication overuse (29 of 102 [28.4%]), triptans (18 of 102 [17.6%]), or combination analgesics (34 of 102 [33.3%]). Baseline characteristics for noncompleters are documented in eTable 2 in Supplement 2. Six-month follow-up visits were completed on June 28, 2019.

Course of Treatment

Complete discontinuation of short-term analgesics was achieved by 18 of 31 patients (58.1%) in the withdrawal plus preventive group and by 20 of 36 (55.6%) in the withdrawal group (**Table 2**). The remaining patients in the withdrawal and withdrawal plus preventive treatment groups had a minor use of short-term medication (1-9 d/mo), but all stopped overusing. Most patients in the withdrawal plus preventive group (16 of 31 [51.6%]) and the preventive group (19 of 35 [54.3%]) started candesartan preventive treatment (Table 2). After 6 months,

Figure 1. CONSORT Flow Diagram



Patient flow from inclusion at baseline to 6-month follow-up, including all contacts (visits at baseline and 2- and 6-month follow-up and telephone calls at 1 and 4 months). Treatment groups are described in the Introduction section. MOH indicates medication overuse headache.

29 of 31 patients (93.5%) in the withdrawal plus preventive group, 30 of 35 (85.7%) in the preventive group, and 22 of 36 (61.1%) in the withdrawal group received preventive treatments. No unexpected or severe adverse effects were observed (eTable 3 in Supplement 2).

Change in Monthly Headache Days

Headache days per month were reduced by 12.3 (95% CI, 9.3-15.3) in the withdrawal plus preventive group, by 9.9 (95% CI, 7.2-12.6) in the preventive group, and by 8.5 (95% CI, 5.6-11.5) in the withdrawal group. There was no difference among the 3 groups after 6 months (P = .20) or at any other time (**Figure 2**A).

Change in Monthly Migraine Days, Days With Short-Term Medication Use, and Headache Pain Intensity

Figure 2B to D illustrates mean reduction in days with migraine, days with use of short-term medication, and headache pain intensity from baseline to 1, 2, 4, and 6 months. An ex-

Table 1. Baseline Characteristics

Characteristic	Treatment group[a]			
	Withdrawal plus preventive (n = 31)	Preventive (n = 35)	Withdrawal (n = 36)	All (n = 102)
Age, mean (SD), y	43.0 (13.0)	44.6 (11.0)	44.1 (11.7)	43.9 (11.8)
Women	25 (80.6)	28 (80.0)	28 (77.8)	81 (79.4)
Preexisting headache diagnoses				
Chronic migraine	14 (45.2)	20 (57.1)	19 (52.8)	53 (52.0)
Episodic migraine and TTH	11 (35.5)	10 (28.6)	12 (33.3)	33 (32.4)
Chronic TTH	6 (19.4)	5 (14.3)	5 (13.9)	16 (15.7)
Headache, median (range), d/mo	25.0 (15.0-30.0)	23.0 (15.0-30.0)	30.0 (15.0-30.0)	27.0 (15.0-30.0)
Migraine, median (range), d/mo	7.0 (0-30.0)	10.0 (0-30.0)	8.0 (0-30.0)	8.0 (0-30.0)
Total monthly intensity score, mean (SD)[b]	50.2 (14.6)	49.1 (15.2)	51.5 (16.7)	50.3 (15.4)
Previously treated with preventive medication	16 (51.6)	21 (60.0)	14 (38.9)	51 (50.0)
1-2 Failed treatments	15 (48.4)	19 (54.3)	10 (27.8)	44 (43.1)
≥3 Failed treatments	1 (3.2)	2 (5.7)	5 (13.9)	8 (7.8)
Short-term medication use, median (range), d/mo	20.0 (10.0-30.0)	20.0 (12.0-30.0)	25.0 (12.0-30.0)	20.0 (10.0-30.0)
Duration of medication overuse, median (range), y	2.0 (0.33-10.00)	2.00 (0.25-30.00)	3.25 (0.33-60.00)	2.00 (0.25-60.00)
Medication overused				
Simple analgesics	8 (25.8)	8 (22.9)	13 (36.1)	29 (28.4)
Triptans	4 (12.9)	7 (20.0)	7 (19.4)	18 (17.6)
Combination analgesics	11 (35.5)	14 (40.0)	9 (25.0)	34 (33.3)
Combination of medication[c]	8 (25.8)	6 (17.1)	7 (19.4)	21 (20.6)

Abbreviation: TTH, tension-type headache.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.

[b] Values were missing for 5 patients. Measured as a monthly score ranging from 0 to 90 (30 times a daily score of 0, indicating no pain; 1, mild pain; 2, moderate pain; or 3, severe pain).

[c] Includes polyoveruse (n = 1), simple analgesics and triptans (n = 3), simple and combination analgesics (n = 6), triptans and combination analgesics (n = 8), triptans and simple and combination analgesics (n = 1), simple analgesics, triptans, and opioids (n = 1), and triptans, combination analgesics, and opioids (n = 1).

pected difference in reduction of days with use of short-term medication after 1 and 2 months was observed. After 1 month, days per month with short-term medication use were reduced by 21.9 (95% CI, 19.5-24.3) in the withdrawal plus preventive group, by 8.6 (95% CI, 6.6-10.6) in the preventive group, and by 22.0 (95% CI, 19.6-24.4) in the withdrawal group ($P < .001$); after 2 months the reduction was 20.8 (95% CI, 18.2-13.4) in the withdrawal plus preventive group, 10.5 (95% CI, 8.1-12.9) in the preventive group, and 21.7 (95% CI, 19.7-23.7) in the withdrawal group ($P < .001$). After 6 months, there was a tendency toward a higher reduction of the 3 outcomes for the withdrawal plus preventive group that did not reach any statistical difference. Migraine days per month were reduced by 5.0 (95% CI, 1.4-8.6) in the withdrawal plus preventive group, 4.1 (95% CI, 1.1-7.1) in the preventive group, and 3.3 (95% CI, 0.9-5.7) in the withdrawal group ($P = .74$). Days per month with short-term medication were decreased by 14.8 (95% CI, 12.2-17.4) in the withdrawal plus preventive group, 11.3 (95% CI, 8.5-14.1) in the preventive group, and 14.0 (95% CI, 11.2-16.8) in the withdrawal group ($P = .17$). Pain intensity scores were reduced by 28.1 (95% CI, 21.1-35.1) in the withdrawal plus preventive group, 23.7 (95% CI, 17.1-30.2) in the preventive group, and 20.8 (95% CI, 12.2-29.4) in the withdrawal group ($P = .42$).

Response, Remission to Episodic Headache, and Cured MOH

Numbers of patients with treatment response, episodic headache, no medication overuse, and cured MOH are presented in **Table 3**. A difference was found in the distribution of patients with episodic headache at 6 months, when 23 of 31 (74.2%) in the withdrawal plus preventive group reverted to episodic headache compared with 21 of 35 (60.0%) in the preventive group and 15 of 36 (41.7%) in the withdrawal group ($P = .03$). The RR was 1.8 (95% CI, 1.1-2.8; $P = .03$) for reverting to episodic headache, corresponding to an 80% higher chance for reverting to episodic headache in the withdrawal plus preventive group compared with the withdrawal group.

At 6 months, 30 of 31 patients (96.8%) in the withdrawal plus preventive group were cured of MOH, compared with 26 of 35 (74.3%) in the preventive group and 32 of 36 (88.9%) in the withdrawal group ($P = .03$). This corresponds to a 30% (RR, 1.3; 95% CI, 1.1-1.6) better chance of being cured of MOH in the withdrawal plus preventive group than in the preventive group ($P = .03$).

Discussion

We conducted an RCT comparing 3 treatment strategies for MOH, which have been debated for years. Previously, efforts to define the most effective treatment for MOH have included the COMOESTAS multicenter study,[12] which introduced a consensus withdrawal protocol, and a study by Hagen et al,[25] who compared withdrawal and preventive medication. Nevertheless, our study is, to our knowledge, the first attempt to directly compare the 3 debated treatment strategies, addressing the clinically relevant question about how we should treat patients with MOH.

All 3 treatment strategies were effective for MOH with no difference in reduction of monthly headache days, rejecting our main hypothesis. Moreover, we hypothesized that there would

Table 2. Treatment Courses

Course	Treatment group, No. (%)			
	Withdrawal plus preventive (n = 31)	Preventive (n = 35)	Withdrawal (n = 36)	All (n = 102)
Course of withdrawal				
Complete	18 (58.1)	NA	20 (55.6)	38 (37.3)
Reduced intake[a]	13 (41.9)	NA	16 (44.4)	29 (28.4)
Rescue medication				
Levomepromazine	12 (38.7)	NA	18 (50.0)	30 (29.4)
Promethazine	19 (61.3)	NA	21 (58.3)	40 (39.2)
Preventive treatment started at baseline				
Metoprolol	5 (16.1)	5 (14.3)	NA	10 (9.8)
Lisinopril	1 (3.2)	2 (5.7)	NA	3 (2.9)
Candesartan	16 (51.6)	19 (54.3)	NA	35 (34.3)
Topiramate	1 (3.2)	1 (2.9)	NA	2 (2.0)
Amitriptyline	8 (25.8)	7 (20.0)	NA	15 (14.7)
Mirtazapine	0	1 (2.9)	NA	1 (1.0)
Preventive treatment until 2 mo				
Plan for preventive medication followed	20 (64.5)	30 (85.7)	NA	50 (49.0)
Few days without preventive medication	4 (12.9)	3 (8.6)	NA	7 (6.9)
Preventive medication started later than planned	4 (12.9)	1 (2.9)	NA	5 (4.9)
Preventive medication stopped	3 (9.7)	1 (2.9)	NA	4 (3.9)
Preventive treatment at 2 mo				
None	3 (9.7)	1 (2.9)	NA	40 (39.2)
Metoprolol	4 (12.9)	5 (14.3)	NA	9 (8.8)
Candesartan	16 (51.6)	18 (51.4)	NA	34 (33.3)
Amitriptyline	6 (19.4)	7 (20.0)	NA	13 (12.7)
Other[b]	2 (6.5)	4 (11.4)	NA	6 (5.9)
Preventive treatment at 4 mo				
None	1 (3.2)	5 (14.3)	13 (36.1)	19 (18.6)
Metoprolol	4 (12.9)	3 (8.6)	2 (5.6)	9 (8.8)
Candesartan	16 (51.6)	17 (48.6)	12 (33.3)	45 (44.1)
OnabotulinumtoxinA (PREEMPT protocol)	1 (3.2)	1 (2.9)	0	2 (2.0)
Amitriptyline	6 (19.4)	6 (17.1)	5 (13.9)	17 (16.7)
Other[c]	3 (9.7)	3 (8.6)	4 (11.1)	10 (9.8)
Preventive treatment at 6 mo				
None	2 (6.5)	5 (14.3)	14 (38.9)	21 (20.6)
Metoprolol	3 (9.7)	4 (11.4)	3 (8.3)	10 (9.8)
Candesartan	17 (54.8)	14 (40.0)	14 (38.9)	45 (44.1)
OnabotulinumtoxinA (PREEMPT protocol)	0	1 (2.9)	0	1 (1.0)
Amitriptyline	5 (16.1)	5 (14.3)	3 (8.3)	13 (12.7)
Other[d]	4 (12.9)	6 (17.1)	2 (5.6)	12 (11.8)

Abbreviations: NA, not applicable; PREEMPT, PHASE 3 Research Evaluating Migraine Prophylaxis Therapy.

[a] Defined as continued use of short-term migraine medication or analgesics during the withdrawal period but not at the level considered as overuse.

[b] Includes topiramate (n = 1) and magnesium (n = 1) in the withdrawal plus preventive group and lisinopril (n = 2), topiramate (n = 1), and mirtazapine (n = 1) in the preventive group.

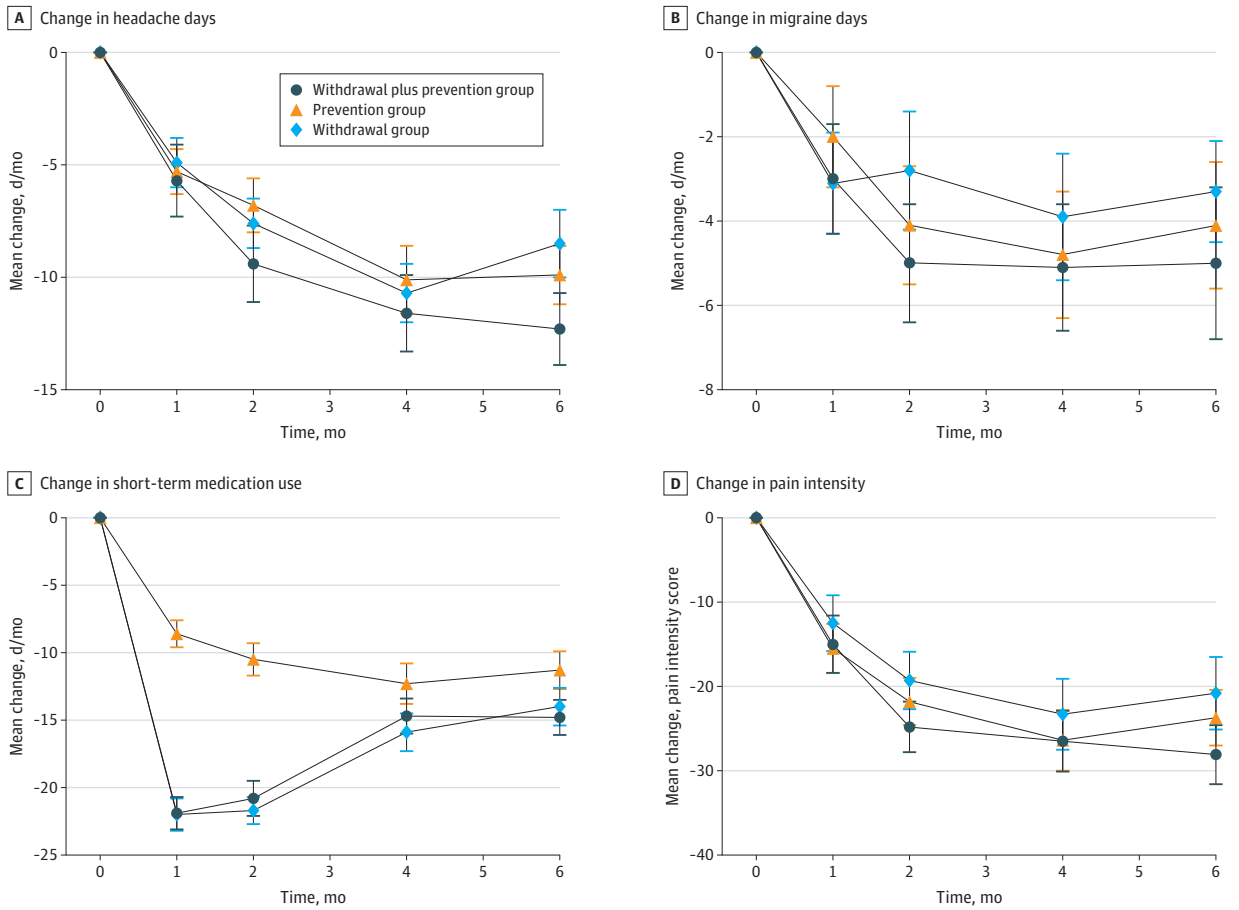
[c] Includes magnesium (n = 1), lamotrigine (n = 1), and candesartan and gabapentin (n = 1) in the withdrawal plus preventive group; topiramate (n = 2) and mirtazapine (n = 1) in the preventive group; and lisinopril (n = 3) and flunarizine (n = 1) in the withdrawal group.

[d] Includes magnesium (n = 1), pizotifen (n = 1), candesartan and gabapentin (n = 1), and candesartan and onabotulinumtoxinA (PREEMPT protocol) (n = 1) in the withdrawal plus preventive group; lisinopril (n = 1), topiramate (n = 2), and mirtazapine (n = 3) in the preventive group; and lisinopril (n = 1) and flunarizine (n = 1) in the withdrawal group.

be no significant difference between the withdrawal plus prevention and withdrawal strategies in reducing monthly headache days, and no significant difference was found. Nevertheless, the numerically largest reductions in headache days, migraine days, days with short-term medication use, and headache pain intensity were seen in the withdrawal plus preventive group. Also, patients in the withdrawal plus preventive group had a significantly better chance of being cured of MOH than patients in the preventive group. Finally, significantly more patients in the withdrawal plus preventive group reverted to episodic headache compared with the withdrawal group.

For decades, the optimal treatment strategy for patients with MOH has been discussed. Several studies have estimated the effect of withdrawal therapy, and the combination of withdrawal and preventive therapy for MOH was tested in a multinational, multicenter study (COMOESTAS).[12,26] In the COMOESTAS study, headache days per month were reduced by a mean of 14, 68% of participants stopped medication overuse and reverted to episodic headache, and 91% were cured of MOH. Our withdrawal plus preventive strategy was similar to the withdrawal protocol in the COMOESTAS study, and the results were comparable. A previous open-label RCT[13] (n = 53)

Figure 2. Change in Primary and Secondary Outcomes



Data are shown as mean values with standard error of mean (error bars). Headache days per month (A) counted all days with and without migrainelike features per month, without any lower limit for duration or intensity. Migraine days per month (B) counted days with migrainelike features and/or headache responding to triptans. Change in short-term medication use (C) counted days with short-term medication use. Change in pain intensity (D) was measured as a monthly score ranging from 0 to 90 (30 times a daily score of 0, indicating no pain; 1, mild pain; 2, moderate pain; or 3, severe pain). Groups are described in the Introduction.

Table 3. Response, Episodic Headache, and Cured MOH at Follow-up

Outcome at follow-up	Treatment group, No. (%)			*P* value[a]
	Withdrawal plus preventive (n = 31)	Preventive (n = 35)	Withdrawal (n = 36)	
Response (≥50% reduction in headache days per month)				
2 mo	14 (45.2)	10 (28.6)	10 (27.8)	.25
6 mo	17 (54.8)	17 (48.6)	13 (36.1)	.29
Episodic headache				
2 mo	17 (54.8)	19 (54.3)	12 (33.3)	.12
6 mo	23 (74.2)	21 (60.0)	15 (41.7)	.03
No medication overuse				
2 mo	31 (100)	19 (54.3)	36 (100)	<.001
6 mo	27 (87.1)	21 (60)	25 (69.4)	.05
Cured MOH				
6 mo	30 (96.8)	26 (74.3)	32 (88.9)	.03

Abbreviation: MOH, medication overuse headache.

[a] *P* values calculated using the χ^2 test.

compared 2 withdrawal strategies, one with complete stop of all painkiller therapy for 2 months and the other with a reduced intake of painkillers to 2 days per week. In both strategies, preventive treatments were started after 2 months only if needed. The complete cessation of analgesics was the most effective approach in reducing headache days (10 days) and mi-

graine days (7 days), reverting chronic to episodic headache (in 70% of patients), and curing MOH (in 89% of patients). The remission and cured MOH rates were similar to our present findings in the withdrawal plus preventive group.

Diener et al[27] reported significant reduction in migraine days per month (−3.5 vs 0.8 days) in a double-blinded, placebo-controlled RCT with topiramate, in which 78% of the study population had medication overuse at baseline. In the PREEMPT (Phase 3 Research Evaluating Migraine Prophylaxis Therapy) study,[18] a subgroup of 904 patients with chronic migraine and medication overuse were randomized to onabotulinumtoxinA or placebo. The investigators reported that treatment with onabotulinumtoxinA significantly reduced headache frequency by 8 days per month (approximately 40% from 20 d/mo at baseline) compared with 6 days per month in the placebo group. A recent placebo-controlled RCT[28] (n = 179) estimated the add-on effect of onabotulinumtoxinA to 3-month complete withdrawal without any additional effect and found reduction in headache days of 26% vs 20% (corresponding to 5.6 vs 4.4 days) in the placebo group after 12 weeks.

One of the CGRP mAbs, erenumab (in 70- and 140-mg formulations), reduced monthly migraine days by 6.6 (95% CI, 5.3-8.0) compared with a reduction of 3.5 (95% CI, 2.4-4.6) days with placebo after 3 months in a subgroup analysis of a double-blinded RCT of patients with chronic migraine and medication overuse (n = 274).[19] In a comparable study design, fremanezumab reduced headache days with moderate-to-severe pain intensity by 5.2 days when administrated once a month, compared with 2.5 headache days with placebo.[20] Double-blinded placebo-controlled RCTs investigating the add-on effect of monoclonal CGRP mAbs to withdrawal therapy are yet to come.

Only 1 RCT[25] (n = 56) compared withdrawal treatment, preventive treatment, and a control group. No significant differences were found among the groups in terms of headache frequency after 3 and 5 months, but after 1 year, headache days per month were reduced more in the preventive group (10.3; 95% CI, 5.8 to 14.8) compared with the withdrawal group (5.1; 95% CI, −0.9 to 9.3).[25]

We expected that patients in the withdrawal group would have fewer monthly headache days, similar to the complete withdrawal group in the previously published open-label RCT.[13] However, the previous study was conducted in a more intensive multidisciplinary setting. In the present study, headache days per month in the withdrawal group increased from the 4- to the 6-month follow-up. The explanation could be that only 61.1% of patients in the withdrawal group were receiving preventive treatment at 6 months, compared with 93.5% in withdrawal plus preventive group and 85.7% in the preventive group. If patients are treated by the withdrawal approach, more awareness must be given to education and starting proper preventive treatment right after withdrawal. Patients with previous MOH due to frequent headache need effective medication to prevent development of a new chronic headache and relapse of MOH. Arguments for postponing the start of preventive treatment could be uncertain headache diagnosis during medication overuse, prior use of ineffective preventive treatment, and fear of adverse effects of ineffective preventive treatments.

Based on the current results and owing to probable withdrawal symptoms, the withdrawal strategy should not be recommended for treatment of patients with more complex MOH. However, the withdrawal strategy may still be effective when treating less severely affected patients, as previously reported.[13,14] This strategy requires carefully educated and prepared patients.

Of interest, the reduction in monthly headache days in the preventive group was higher than the reductions seen in some RCTs with onabotulinumtoxinA, topiramate, and CGRP mAbs[17-19,28] but comparable to the effect in the study of Hagen et al[25] comparing withdrawal and preventive treatments. It has been reported that even simple advice about medication overuse was effective in preventing and treating simple forms of MOH, and an awareness campaign about MOH was conducted in Denmark in the autumn of 2016.[29-31] The question is whether patients in the preventive group improved owing to an effective preventive treatment, or whether they reduced intake of painkillers inspired by information about withdrawal therapy or via information from the internet, for example, from the national awareness campaign about MOH conducted in the autumn of 2016 favoring a restricted use of analgesics.[31] Nevertheless, patients in the preventive group reduced intake of painkillers by approximately 50% already after 2 months. Potentially, this reduction could have contributed to the treatment outcome.

Strengths and Limitations

Withdrawal therapy is impossible to blind, and the study design was the most feasible and practicable to address this clinical problem. The major strength of our study is the high clinical relevance. The results are easily applicable to most patients with MOH, and all 3 treatment strategies were outpatient programs that may also be feasible in primary and secondary care. More than 75% of the study population had a single type of medication overuse: simple analgesics. Most patients considered ineligible for participation were excluded owing to a more complex form of MOH, for example, comorbidities as described in Figure 1, making the study less applicable for this subgroup of patients. Less than 10% of patients referred to the DHC in the inclusion period (41 of 483) were excluded owing to opioid overuse. In other countries, opioids are still regularly prescribed for migraine treatment; for example, the CaMEO (Chronic Migraine Epidemiology and Outcomes) study recently reported that 36% of 2388 patients with migraine were opioid users.[32]

The dropout rate was as expected and equally distributed among the 3 treatment groups. No specific patterns were seen among dropouts in terms of baseline characteristics or change in headache days. Therefore, the risk of attrition bias owing to incomplete data is considered low, and an intention-to-treat analysis was considered unnecessary and was not performed.

Conclusions

All 3 treatment strategies for MOH were effective. Withdrawal therapy combined with preventive medication therapy from the start of withdrawal was the most effective treatment according to several secondary end points and is recommended as the preferred management of MOH.

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