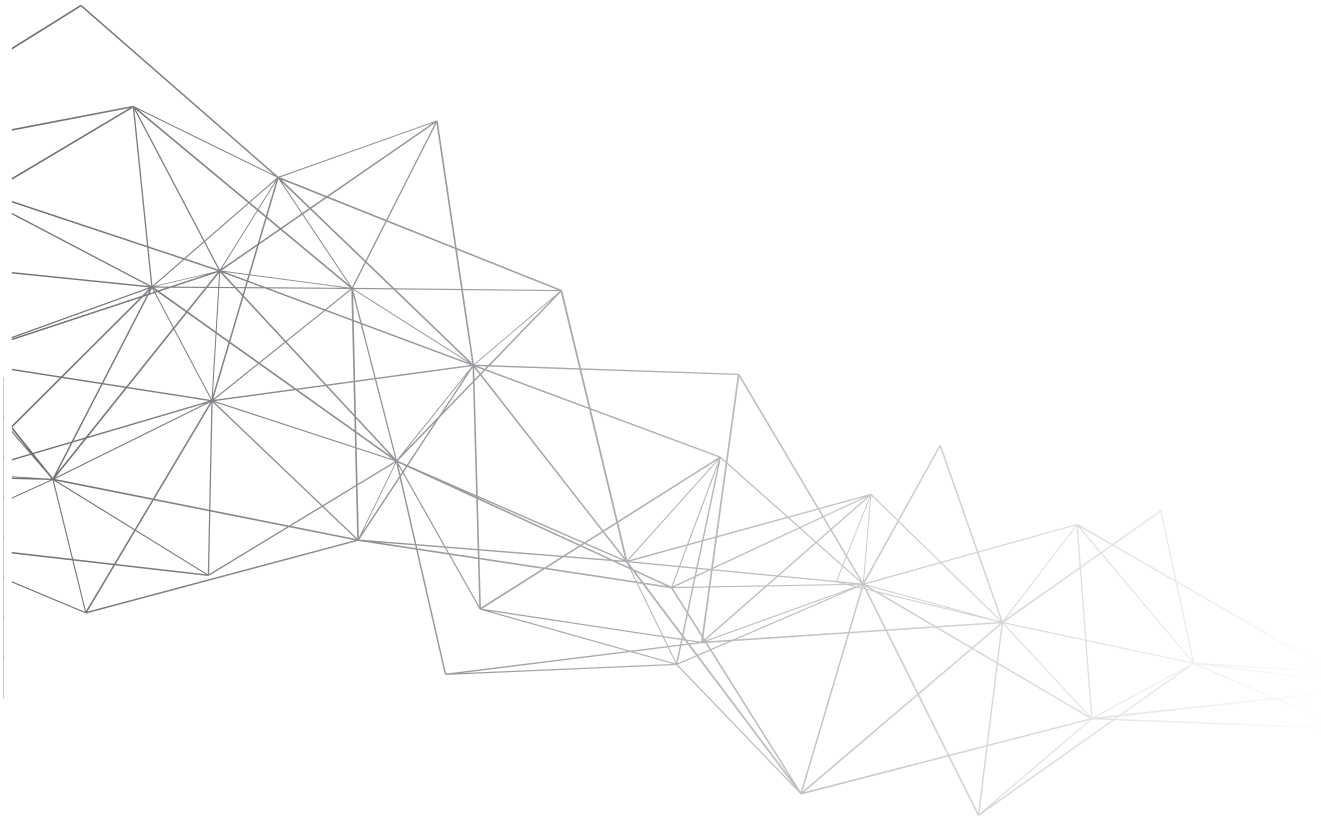
6 CHAPTER

Detoxification in medication-overuse headache, a retrospective controlled follow-up study: Does care by a headache nurse lead to cure?



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Abstract

Aim
To determine whether support of a headache nurse in the treatment of Medication Overuse Headache (MOH) increases successful withdrawal, and to study determinants of response to withdrawal therapy.

Methods
A retrospective controlled follow-up study was performed with 416 MOH patients. All patients were treated with outpatient withdrawal therapy, with two treatment arms: with or without the support of a specialized headache nurse. The outcome measures were: i) successful withdrawal, defined as discontinuation of all headache medication according to the study protocol; and ii) the responder rate, defined as the percentage of patients with ≥ 50% reduction in headache days after successful withdrawal and iii) relative reduction in headache days after successful withdrawal.

Results
Successful withdrawal percentages were significantly higher in the group supported by the headache nurse than in the group without support (73.1% vs. 60.7%; p=0.008), which was confirmed in multivariate analysis (OR 1.73, 95% CI 1.11-2.71, p=0.016). Support by a headache nurse was not associated with response. The underlying headache primary headache diagnosis, determined after withdrawal, was significantly correlated with response.

Conclusion
The support by a headache nurse results in an increased adherence to detoxification.

Introduction

Medication Overuse Headache (MOH) is a highly disabling headache disorder, with a population based prevalence of 0.7 - 1.7% and a preponderance in women. (1-3) The prevalence in headache clinics ranges from 30% in Europe to more than 50% in the USA. (1, 2) MOH is defined in the ICHD-III-beta criteria as headache occurring on half or more days per month as a consequence of regular overuse of acute headache medication (on ≥10 or ≥15 days per month, depending on the type of medication) for more than 3 months. (4) Although consensus about the optimal treatment for MOH is not yet reached, withdrawal of the overused medication is strongly suggested as an essential component in the management of MOH, to reduce headache frequency and improve responsiveness to both acute and prophylactic therapy. (1, 2, 5, 6) Several studies have compared different treatment strategies and some suggested that a simple withdrawal advice is effective. (2, 7-9) In compliance with those studies, acute withdrawal without any concomitant therapy is advised in the national headache guidelines of the Netherlands, and common practice. However, a well-defined selection of patients prone to benefit from simple withdrawal advice has not been established. Withdrawal programmes are increasingly multidisciplinary coordinated, with implementation of patient education and motivational or cognitive behavioural therapy, often realized by a headache nurse. (10-14) Despite of this, the effectiveness of a headache nurse in withdrawal therapy has never been studied in a controlled follow up study. Therefore, the objectives of this study are (i) to determine whether support of a headache nurse in the treatment of MOH increases successful withdrawal, and (ii) to investigate intrinsic patient factors associated with response to withdrawal therapy.

Methods

Study design and population

The current study used a retrospective controlled follow-up approach. Participants were recruited during a period of four years (1 April 2006 - 31 March 2010) among all new patients at the specialized outpatient headache clinic of the Leiden University Medical Centre (LUMC), functioning both as a primary and secondary referral centre with referrals from general practitioners and from colleague neurologists. Inclusion criteria for participants were: (i) age ≥ 18 years; (ii) diagnosis of MOH, defined by the ICHD-II criteria, which are similar to the ICHD-III-b criteria on MOH (supervised by an experienced headache neurologist (MDF, GMT)); and (iii) receiving an advice to withdraw all acute headache medication (triptans, analgesics, combination of both, other medication comprising opioids, ergots or combinations of those medications with analgesics or triptans), prophylactic

medication and caffeine (-containing liquids) during two or three months. (4, 15) Follow up occurred after withdrawal, to determine the final underlying primary headache diagnosis and start further treatment. At the first visit patients were instructed that because of lack of therapeutic options whilst overusing medication, no follow-up visit was offered if they did not succeed to withdraw. Therefore, patients who were lost to follow-up were considered as 'not successfully withdrawn'. Patients were excluded when the final diagnosis was not migraine, tension-type headache or a combination of both. The treatment protocol for patients included between 1 April 2006 and 31 March 2008 (group A) comprised a withdrawal advice by a resident-in-neurology/neurologist. All physicians involved during the total inclusion period, gave the same instructions and maintained the same conditions of withdrawal, according to the standardised protocol at the LUMC. This encompassed an outpatient detoxification with the advice to instantly stop acute headache medication. The duration of the withdrawal period was two months in case of triptan overuse, three months for other types of medication or combinations of medication, and/or caffeine use of ≥ 5 units/day. If patients were on preventive treatment this was tapered off, since the present medication was not effective, and preventive medication regains effectiveness after withdrawal. (6) New preventive treatment was postponed until successful withdrawal was accomplished. Use of escape medication or caffeine (-containing liquids) was not permitted. During the withdrawal period no facility was provided for additional contacts or support. Due to the employment of specialized headache nurse ever since 1 April 2008, patients included between 1 April 2008 and 31 March 2010 (group B), were advised exactly the same withdrawal protocol, but additionally received support during the withdrawal period by a specialized headache nurse. The headache nurse was trained and experienced in headache care, and received additional training on cognitive behavioural therapy. The support by the headache nurse started immediately during the first visit with a 15-30 minutes consultation consisting of a reprise of the withdrawal advice and elaboration on questions of the patient. The consequences for daily professional and social life were discussed and a plan of approach was assembled. Furthermore, strategies for pain management (other than medication treatment) were discussed. Subsequently, the headache nurse contacted all patients two weeks after initiation of the withdrawal period. Depending on the need for support of patients, the headache nurse had additional interaction during the withdrawal period, varying from one to six contacts (median three contacts) by telephone.

Measurement

Two trained examiners obtained medical information from the outpatient clinic administration, patient letters and medical files, using the same methods and criteria to select patients and classify data. The outcome measures were: i) successful withdrawal, defined as a completed medication- and caffeine- free

period; ii) response, defined as ≥ 50% reduction in headache days after successful withdrawal; and iii) relative reduction in headache days after successful withdrawal, since a reduction <50% may be considered clinically relevant as well. (16) The number of headache days at baseline and at follow up were collected to calculate outcomes measures. In case of missing data on response (n=24 patients), patients reporting 'strong improvement', 'nearly no headache' or 'no headache' at follow-up were considered as a ≥ 50% reduction in headache days(responder), and patients reporting 'aggravation', 'no improvement' or 'some to moderate improvement' at follow-up were considered as a < 50% reduction in headache days (non-responder). This subjective classification and the classification based on absolute change in headache days were highly correlated (n=75, r = 0.80, p<0.001). To be able to find associations between potential intrinsic determinants and our outcome measures, we collected data on gender, age, pre-existing headache type, final primary headache after successful withdrawal, number of headache days at baseline, number of medication days at baseline, type of overused medication, and caffeine units per day. Pre-existing headache and final primary headache at follow-up were classified according to ICHD-II/ICHD-III-b criteria as: i) migraine; ii) tension-type headache; and iii) combination of both migraine and tension-type headache. (4, 15) Because of the typical blurred presentation of primary headache at baseline, which is often the case during a period of medication overuse, the pre-existing headache was in some cases impossible to determine (n=85). Therefore, final primary headache diagnosis was used in the analysis. In any case, pre-existing and final headache diagnoses were fairly correlated (n=182, r=0.62, p<0.001). Type of acute medication was classified as: i) triptans, ii) analgesics (paracetamol/acetaminophen and/or NSAIDs), iii) combination of triptans and analgesics, and iv) other medication, comprising opioids, ergots or combinations of those medications with analgesics or triptans. No approval of the local ethics committee was necessary as the study was a retrospective follow-up study and all data were analysed anonymously.

Data analysis and statistics

Baseline characteristics were reported as mean ± SD or absolute numbers with percentages. The number of headache days and medication days at baseline were grouped into daily (30.4 days/month) and non-daily (<30.4 days/month), because of the non-parametric distribution of the data. Differences in means between groups were tested with independent samples *t*-tests and one-way ANOVAs. Differences in proportions were tested using x^2 tests. Patients were stratified into 'successfully withdrawn' and 'not successfully withdrawn', the latter including patient who were lost to follow-up. All patients were included in the analysis of the first outcome (successful withdrawal). Successfully withdrawn patients were included in the analysis of the second and third outcomes (response respectively relative reduction). Univariate logistic regression models were used to test crude

associations. Analyses were rerun as a multivariate model, adjusting for the potential confounding effects of all variables that were tested in the univariate model. For all analyses, two-tailed *p*-values < 0.05 were considered as statistically significant. All statistical analyses were performed using SPSS 17.0 (SPSS inc., IBM, USA).

Results

Participants and descriptives

The total study flow is shown in Figure 1. Of 2086 new outpatients, 416 patients were diagnosed with MOH and advised to withdraw medication, 163 without (group A) and 253 with support of a headache nurse (group B). Both groups differed significantly in gender, age, type of medication and daily use of medication (Table 1). Although the absolute number of new headache patients visiting the outpatient headache clinic raised in the last two years of the inclusion period, the proportion of patients who met inclusion criteria remained the same (19.0% in group A and 20.6% in group B). To detect shifts in population composition due to exclusion of patients, lost to follow-up or missing data, differences between the total included population (n=416) and the population that had successfully withdrawn (n=267) were explored. No major differences in composition occurred.

Effectiveness of support by a headache nurse in successful withdrawal in MOH

As shown in Table 2, the percentage of patients with successful withdrawal was significantly higher in the group with support of the headache nurse than the group without support (73.1% vs. 60.7%, p = 0.008, Absolute risk reduction = 12.4%, Number Needed to Treat = 8). As a consequence of the instructions at the first visit (not to come for a second visit if withdrawal was not successful) a larger proportion of patients of group A did not visit for a second time, and were lost to follow up (27.0% vs. 12.3%). However, the results were similar when lost to follow-up patients were analysed as a separate group. The support by a headache nurse was significantly associated with the odds for successful withdrawal in multivariate regression (Odds Ratio [OR] 1.73; 95% CI, 1.11 – 2.71; p=0.016)(Table 3), indicating that the support by a headache nurse enhances successful withdrawal, independent of age, the number of headache days, medication days and type of medication overuse at baseline. Daily use of headache medication and a higher ager were associated with lower odds for successful withdrawal (OR 0.50; 95% CI 0.30 – 0.83; p=0.008 resp. OR 0.98; 95% CI 0.96 – 0.99; p=0.017).

Variables associated with response and relative reduction to withdrawal therapy

The support by a headache nurse was not associated with response (OR: 1.42; 95% CI, 0.78–2.60; p=0.25) (Table 4). The responder rate, defined as the percentage of patients with ≥50% reduction in headache days, was not significantly different in both groups (no support 35.5%, with support 46.0%, p=0.098, Figure 2). The relative reduction in headache frequency, also showed no significant association with support by a headache nurse (B: 1.92; 95% CI, -7.75–11.60; p=0.70) This indicates that there is no effect of the support by the headache nurse on reduction of headache days when successfully withdrawn. The underlying primary headache disorder, that remained after the withdrawal, was significantly associated with relative reduction and response, with a three times increased odds for response in case of migraine when compared to tension type headache (OR 0.31, 95% CI 0.16-0.63; p<0.001), and a nine times increased odds in case of migraine when compared to migraine with tension type headache (OR 0.11; 95% CI 0.05-0.24; p<0.01)(Table 4). This gives a clear indication that the reduction in headache frequency was highest in the migraine group and lowest in the migraine with tension type headache group (Table 4, also depicted in Figure 2). The relative reduction in headache days, was 34.2% ± 38.9 for the total group and was significantly different between persons with migraine, tension type headache, and combined migraine and tension type headache (resp. 56.1% ± 32.1, 26.0% ± 39.6 and 16.0% ± 31.9) (Figure 3). As shown in Table 4, gender and age were not associated with response, nor was the number of headache days or number of medication days at baseline. Furthermore, neither the type of medication that was overused (simple analgesics, triptans, combination of both, or other medication) nor caffeine use was associated with response. These covariates were not associated with relative reduction as well.

Discussion

Being the first controlled follow-up study, this study shows that support of a headache nurse during simple withdrawal therapy increases the chance that a patient with Medication Overuse Headache (MOH) successfully withdraws from overused medication. In this manner, the high drop-out percentage seen in outpatient withdrawal therapy can be reduced. (7) As expected, the reduction in headache days during withdrawal therapy is independent of the support of a headache nurse, as this is more likely to be influenced by intrinsic, patient related factors. The current study shows that patients with migraine as the solely underlying headache disorder have a higher chance at response to withdrawal therapy.

The strengths of this study include the controlled design in a large, representative study population of MOH patients. Although randomisation was not achievable,

the retrospective design is particularly suited to determine the effect of the headache nurse, since we studied the insulated effect of the nurse and there were no ethical issues or risk of blinding failure. We changed our treatment protocol of patients with MOH during our inclusion period by the employment of a headache nurse in April 2008, but no other changes regarding to treatment protocol or referral strategies were introduced. In a prospective controlled study, the recruitment procedure would lead to a highly motivated population, and it would be extremely difficult to blind patients for receiving or not receiving support by a nurse, since patients must be informed about the nature of a study. One group of patients would thus be instructed not to contact the outpatient clinic at any moment, whilst they know about the availability of support to the other group. This will definitely introduce disappointment and other expectations and will bias the results in favour of the intervention. The results of our retrospective study are not influenced by this kind of bias.

There are also some limitations of our study design. Firstly and most importantly, there was no ability to collect data of patients who did not return for a second visit and were, therefore, stated as lost to follow-up. Since patients were explicitly instructed that they were not allowed to revisit in case of unsuccessful withdrawal, and they were informed that no additional treatment would be supplied, we consider the majority of the lost to follow up patients as unsuccessfully withdrawn. We reckon the possibility that lost to follow-up is caused by economic reasons negligible due to the health care system in our country, and the visit could be changed to a 15-30 minute telephonic appointment in case patients definitely could not miss work. Analysis considering lost to follow-up as unsuccessfully withdrawn shows similar result as analysis with lost to follow-up patients as a separate group. Secondly, for the reason of uncertainty about diagnoses before withdrawal, we diagnosed the primary headache disorder only after successful withdrawal, and used this diagnosis. Still, the pre-existing primary headache diagnosis was fairly correlated with final diagnosis. Thirdly, long-term effects of withdrawal were not investigated in this study. Considering the high recidivism rate, it would be interesting in future research to study the long term effect of a headache nurse in patients with MOH after withdrawal. However, the long term effect of a headache nurse on medication overuse was beyond the scope of this study as we specifically wanted to investigate the response to the initial withdrawal period. In many countries patients with MOH are usually unwilling to endure acute withdrawal therapy. Patients in these countries refuse to discontinue their medication on the grounds that the withdrawal symptoms will be too serious or they are afraid to lose their jobs if they will be ill for a longer period because of the withdrawal symptoms. There is usually a drug treatment started with prophylactics although it is recognized that it often fails if the patient continues to overuse acute headache medication. Therefore, it was of our main interest to show the high success rate of acute withdrawal with the support of a headache nurse.

In literature, several withdrawal therapies, sometimes with the support by a headache nurse for MOH patients have been described, but no other study investigated the insulated effect of a headache nurse and uniform endpoints are lacking, hampering direct comparison between studies. (11-14, 16)

Possible explanations and implications

The headache nurse has an unmistakable effect on succeeding withdrawal therapy. Previous studies suggest that patients with (chronic) headache or high headache related disability, are more prone to use unsuitable coping mechanisms (17), score low on pain acceptance (18) and high on catastrophizing scales, and experience a low internal pain control. (19) In patients with migraine, pain control and self-management can be improved by behavioural therapy. (20) We hypothesize that contact with a headache nurse influences the above mentioned factors and thus will help patients to endure the withdrawal period. Patients with tension-type headache and the combination of migraine and tension-type headache seem to benefit less from withdrawal therapy than patients with migraine alone, which may suggest that the pathophysiological mechanism of medication overuse differs between different underlying primary headache syndromes.

Nowadays the view on treatment of MOH shifts from the traditional 'withdrawal therapy first' towards an approach in which prophylactic therapies are started before patients are withdrawn from the overused medication. Randomised trials in chronic migraineurs with topiramate and onabotulinum toxin A, contributed significantly to the debate whether, and when, detoxification is necessary in the treatment of MOH. (21-24) From these trials the question remains, however, whether the effect is clinically relevant. Moreover, the studies lack adequate reporting of plausible blinding failure, and most importantly, in these trials withdrawal was not advocated. To illustrate, the responder rate of migraineurs in our study is comparable to the responder rate in the pooled results of the onabotulinum toxin A trials. We realize that in our population not many patients overuse barbiturates or opiates, which enables acute medication withdrawal, in accordance with our national guidelines. Nevertheless, our study shows that with the support of a headache nurse, comprising only one face-to-face contact and a median of three contacts by telephone, 75% of MOH patients succeed to undergo a highly cost-effective outpatient withdrawal therapy, which is easily implemented in general neurology practice.

Figures and tables

Table 1: Baseline characteristics of patients with medication overuse headache, included for primary analysis, without (group A) and with (group B) support by a headache nurse (n = 416).

	A. No headache nurse (n=163)	B. Headache nurse (n=253)	*p*
Gender, % female	102 (63%)	196 (78%)	**0.001***
Age at time of diagnosis	47.5 ± 10.7	44.4 ± 14.6	**0.014****
Headache days			
% daily	93 (57%)	151 (60%)	0.60*
median (interquartile)	30.4 (17.4-30.4)	30.4 (19.1-30.4)	0.41***
Medication			**0.040***
Analgesics only	83 (51%)	126 (50%)	
Triptans only	20 (12%)	13 (5%)	
Analgesics + triptans	51 (31%)	93 (37%)	
Other medication	9 (6%)	21 (8%)	
Caffeine units/day	5.7 ± 4.2	5.3 ± 3.6	0.55**
Medication days			
% daily	73 (45%)	95 (38%)	0.14*
median (interquartile)	21.7 (15.0-30.4)	20 (14.3-30.4)	0.37***

Values are the absolute numbers with corresponding % or means ± SD. Significant p values are depicted in bold.

* x^2 test
** two-tailed independent samples *t*-test
*** Independent Samples Mann-Whitney U test

Table 2: Successful medication withdrawal, defined as a 2-3 months medication- and caffeine-free period, in patients with MOH following withdrawal therapy without (group A) and with (group B) support by a headache nurse (n = 416).

	A. No headache nurse (n=163)		B. Headache nurse (n=253)		*p*
Medication withdrawal					
Successful	99	(60.7%)	185	(73.1%)	**0.008****
Not successful *	64	(39.3%)	68	(26.9%)	

MOH = Medication Overuse Headache. Values are the absolute numbers with corresponding %.

* Including patients who are lost to follow-up and therefore considered not successfully withdrawn 44 (27.0%) resp. 31 (12.3%).
** x^2 test

Table 3: Odds Ratios (1. univariate; 2. multivariate, adjusted for all mentioned covariates) for successful withdrawal, defined as a 2-3 months medication- and caffeine-free period (n = 416).

Variable	1. Univariate OR [95% CI]	*p*	2. Multivariate OR [95% CI]*	*p*
Gender				
Male	1.00	.	1.00	.
Female	1.09 [0.69 – 1.72]	0.72	0.88 [0.53 – 1.44]	0.60
Age	**0.98 [0.96 – 0.99]**	**0.002**	**0.98 [0.96 – 0.99]**	**0.017**
Headache nurse				
No support	**1.00**	**.**	**1.00**	**.**
Support	**1.76 [1.16 – 2.68]**	**0.008**	**1.73 [1.11 – 2.71]**	**0.016**
Headache days (baseline)				
Non-daily	1.00	.	1.00	.
Daily	0.97 [0.64 – 1.48]	0.90	1.36 [0.82 – 2.25]	0.24
Medication				
Analgesics	1.00	.	1.00	.
Triptans	0.97 [0.44 – 2.16]	0.94	1.22 [0.52 – 2.25]	0.65
Analgesics/triptans	0.87 [0.55 – 1.38]	0.55	0.80 [0.50 – 1.30]	0.37
Other	0.55 [0.25 – 1.20]	0.14	0.68 [0.29 – 1.61]	0.38
Caffeine use *	0.99 [0.94 – 1.05]	0.84	1.00 [0.94 – 1.06]	0.93
Medication days (baseline)				
Non-daily	**1.00**	**.**	**1.00**	**.**
Daily	**0.54 [0.35 – 0.81]**	***0.003***	**0.50 [0.30 – 0.83]**	**0.008**

* n=409, due to missing data

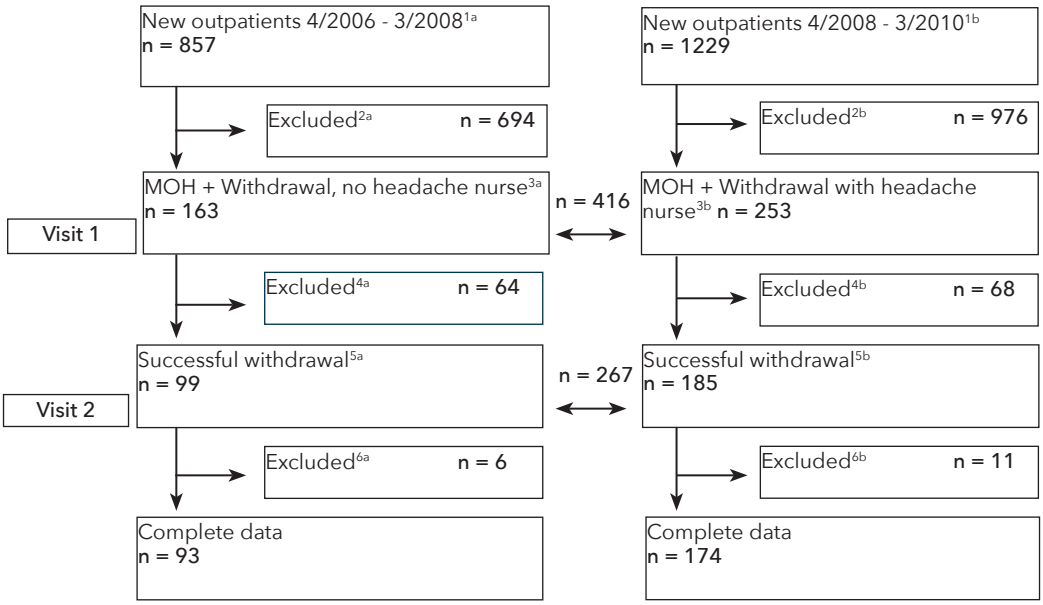
Table 4: Odds Ratios (1. univariate; 2. multivariate, adjusted for all mentioned covariates) for response, defined as a ≥ 50% reduction in headache days, following medication withdrawal (n = 267).

Variable	1. Univariate OR [95% CI]	*p*	2. Multivariate OR [95% CI]	*p*
Gender				
Male	1.00	.	1.00	.
Female	1.43 [0.82 – 2.49]	0.21	1.14 [0.59 – 2.18]	0.70
Age	1.00 [0.98 – 1.02]	0.87	1.00 [0.98 – 1.02]	0.78
Headache nurse				
No support	1.00	.	1.00	.
Support	1.55 [0.92 – 2.60]	0.10	1.42 [0.78 – 2.60]	0.25
Diagnosis				
Migraine	**1.00**	**.**	**1.00**	**.**
TTH	**0.26 [0.14 – 0.46]**	**< 0.001**	**0.31 [0.16 – 0.63]**	**< 0.001**
TTH and migraine	**0.10 [0.05 – 0.22]**	**< 0.001**	**0.11 [0.05 – 0.24]**	**< 0.001**
Headache days (baseline)				
Non-daily	**1.00**	**.**	1.00	.
Daily	**0.47 [0.28 – 0.77]**	**0.003**	0.84 [0.45 – 1.57]	0.58
Medication				
Analgesics	1.00	.	1.00	.
Triptans	1.00 [0.41 – 2.47]	1.00	0.54 [0.18 – 1.61]	0.27
Analgesics / triptans	1.63 [0.95 – 2.78]	0.08	1.24 [0.64 – 2.41]	0.52
Other	0.52 [0.16 – 1.69]	0.28	0.38 [0.11 – 1.33]	0.13
Caffeine use	1.01 [0.94 – 1.08]	0.79	1.02 [0.94 – 1.11]	0.61
Medication days (baseline)				
Non-daily	**1.00**	**.**	1.00	.
Daily	**0.45 [0.27 – 0.77]**	**0.003**	0.63 [0.33 – 1.22]	0.17

TTH: Tension-type headache

Figure 1: Study population flow chart

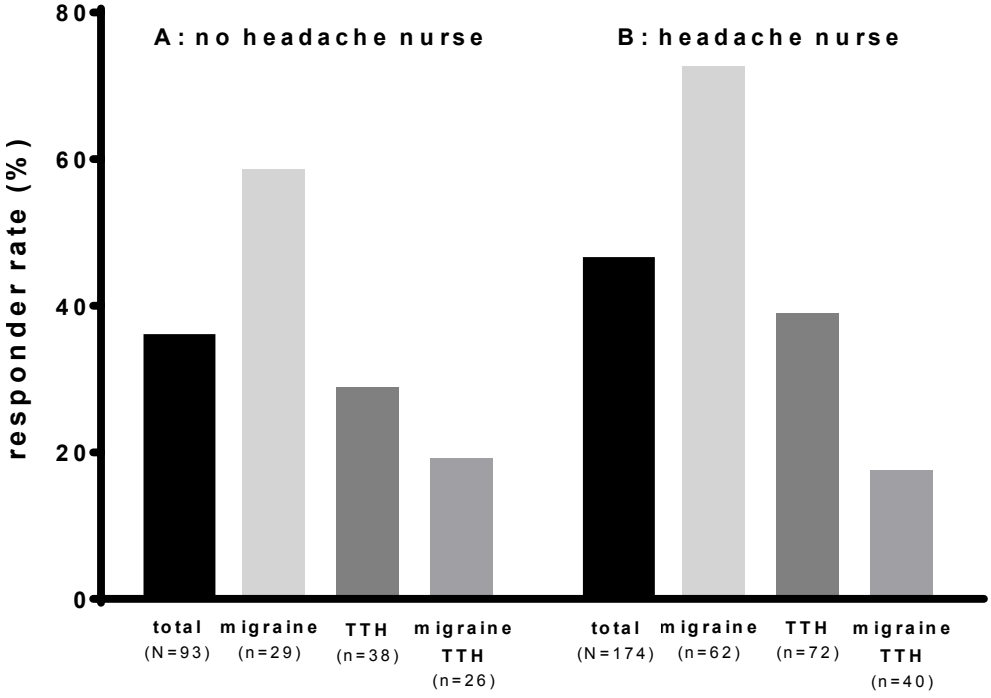
MOH= Medication Overuse Headache
TTH = Tension-Type Headache



[1]*New outpatients:* New patients at the LUMC outpatient headache clinic
[2]*Excluded:* No medication overuse ([2a] n=645 [2b] n=893); Age < 18 years ([2a] n=1 [2b] n=3); No withdrawal therapy ([2a] n=21 [2b] n=35); Withdrawal therapy elsewhere ([2a] n=27 [2b] n=45)
[3]*Diagnosis MOH and advice is to withdraw medication:* [3a] without support by a headache nurse; [3b] with support by a headache nurse
[4]*Excluded:* Patient is not willing to start withdrawal ([4a] n=5 [4b] n=13); Unsuccessful withdrawal ([4a] n=15 [4b] n=24); Lost to follow-up ([4a] n=44 [4b] n=31)
[5]*Successful withdrawal*: 2-3 months medication- and caffeine-free period.
[6]*Excluded:* No migraine, TTH or combination ([6a] n=1 [6b] n=2); Missing data on primary headache, number of headache days or caffeine use ([6a] n=5 [6b] n=9)

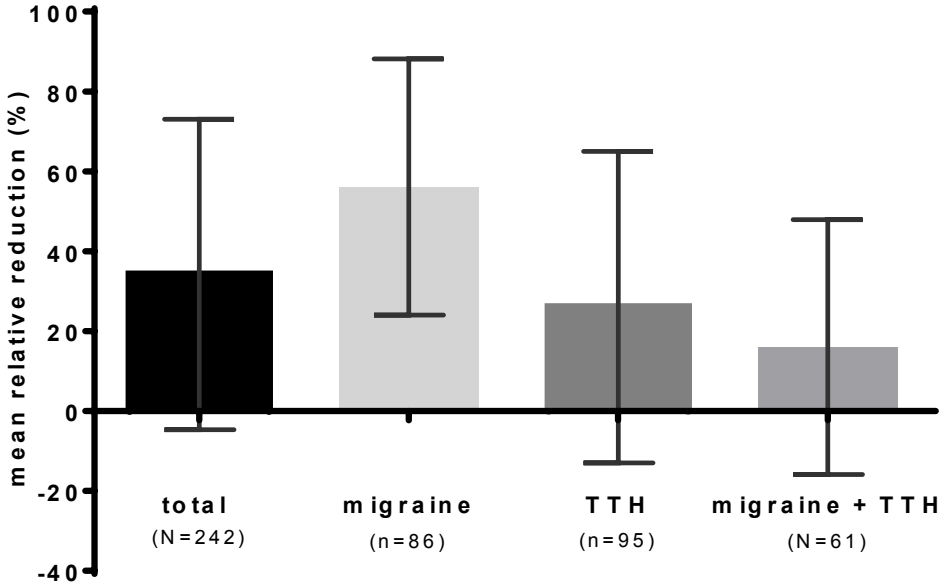
Figure 2: The responder rate, defined as the percentage of patients with a ≥ 50% reduction in headache days, following medication withdrawal with and without support by a headache nurse, subdivided by diagnosis (N = 267).

Responder rate group A (no headache nurse) = 35.5%, responder rate group B (headache nurse) = 46.0% (x^2 test, p = 0.098)



TTH = tension-type headache

Figure 3: The mean relative reduction in headache days of successfully withdrawn patients and subdivided by diagnosis. (n = 242, due to missing data in 25 patients, one-way ANOVA: $p < 0.001$)



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TTH = Tension-Type Headache

References

1. Diener HC, Limmroth V. Medication-overuse headache: a worldwide problem. Lancet Neurol. 2004;3(8):475-83.
2. Evers S, Marziniak M. Clinical features, pathophysiology, and treatment of medication-overuse headache. Lancet Neurol. 2010;9(4):391-401.
3. Russell MB. Headache: Medication overuse headache--seeking a management consensus. Nature reviews Neurology. 2014;10(6):309-10.
4. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33(9):629-808.
5. Silberstein SD, Olesen J, Bousser MG, Diener HC, Dodick D, First M, et al. The International Classification of Headache Disorders, 2nd Edition (ICHD-II)--revision of criteria for 8.2 Medication-overuse headache. Cephalalgia. 2005;25(6):460-5.
6. Zeeberg P, Olesen J, Jensen R. Discontinuation of medication overuse in headache patients: recovery of therapeutic responsiveness. Cephalalgia. 2006;26(10):1192-8.
7. Tassorelli C, Jensen R, Allena M, De Icco R, Sances G, Katsarava Z, et al. A consensus protocol for the management of medication-overuse headache: Evaluation in a multicentric, multinational study. Cephalalgia. 2014;34(9):645-55.
8. Rossi P, Di Lorenzo C, Faroni J, Cesarino F, Nappi G. 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(9):1097-105.
9. Rossi P, Faroni JV, Nappi G. Short-term effectiveness of simple advice as a withdrawal strategy in simple and complicated medication overuse headache. Eur J Neurol. 2011;18(3):396-401.
10. Andrasik F, Grazzi L, Usai S, Buse DC, Bussone G. Non-pharmacological approaches to treating chronic migraine with medication overuse. Neurol Sci. 2009;30 Suppl 1:S89-93.
11. Bhola R, Goadsby PJ. A trans-cultural comparison of the organisation of care at headache centres world-wide. Cephalalgia. 2011;31(3):316-30.
12. Diener HC, Gaul C, Jensen R, Gobel H, Heinze A, Silberstein SD. Integrated headache care. Cephalalgia. 2011;31(9):1039-47.
13. Gaul C, van Doorn C, Webering N, Dlugaj M, Katsarava Z, Diener HC, et al. Clinical outcome of a headache-specific multidisciplinary treatment program and adherence to treatment recommendations in a tertiary headache center: an observational study. J Headache Pain. 2011;12(4):475-83.
14. Jensen R, Zeeberg P, Dehlendorff C, Olesen J. Predictors of outcome of the treatment programme in a multidisciplinary headache centre. Cephalalgia. 2010;30(10):1214-24.
15. The International Classification of Headache Disorders: 2nd edition. Cephalalgia. 2004;24 Suppl 1:9-160.
16. Hagen K, Jensen R, Boe MG, Stovner LJ. Medication overuse headache: a critical review of end points in recent follow-up studies. J Headache Pain.

2010;11(5):373-7.
17. Wieser T, Walliser U, Womastek I, Kress HG. Dysfunctional coping in headache: avoidance and endurance is not associated with chronic forms of headache. Eur J Pain. 2012;16(2):268-77.
18. Dindo L, Recober A, Marchman J, O'Hara MW, Turvey C. One-day behavioral intervention in depressed migraine patients: effects on headache. Headache. 2014;54(3):528-38.
19. Wiendels N.J. SP, Knuistingh Neven A., Rosendaal F.R., Zitman F.G., Assendelft W.J.J., Ferrari M.D. The role of catastrophizing and locus of control in chronic frequent headache. Chronic frequent headache in the general population. Leiden2008.
20. Merelle SY, Sorbi MJ, van Doornen LJ, Passchier J. Migraine patients as trainers of their fellow patients in non-pharmacological preventive attack management: short-term effects of a randomized controlled trial. Cephalalgia. 2008;28(2):127-38.
21. Diener HC, Bussone G, Van Oene JC, Lahaye M, Schwalen S, Goadsby PJ, et al. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. Cephalalgia. 2007;27(7):814-23.
22. Silberstein S, Lipton R, Dodick D, Freitag F, Mathew N, Brandes J, et al. Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. Headache. 2009;49(8):1153-62.
23. Dodick DW, Turkel CC, DeGryse RE, Aurora SK, Silberstein SD, Lipton RB, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache. 2010;50(6):921-36.
24. Diener HC. Detoxification for medication overuse headache is not necessary. Cephalalgia. 2012;32(5):423-7.