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REVIEW ARTICLE

Medication overuse headache: a critical review of end points in recent follow-up studies

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Abstract No guidelines for performing and presenting the results of studies on patients with medication overuse headache (MOH) exist. The aim of this study was to review long-term outcome measures in follow-up studies published in 2006 or later. We included MOH studies with >6 months duration presenting a minimum of one predefined end point. In total, nine studies were identified. The 1,589 MOH patients (22% men) had an overall mean frequency of 25.3 headache days/month at baseline. Headache days/month at the end of follow-up was reported in six studies (mean 13.8 days/month). The decrease was more pronounced for studies including patients with migraine only (−14.6 days/month) compared to studies with the original diagnoses of migraine and tension-type headache (−9.2 days/month). Six studies reported relapse rate (mean of 26%) and/or responder rate (mean of 28%). Medication days/month and change in headache index at the end of follow-up were reported in only one and two of nine studies, respectively. The present review demonstrated a lack of uniform end points used in recently published follow-up studies. Guidelines for presenting follow-up data on MOH are needed and we propose end points such as headache days/month, medication days/month, relapse rate and responder rate defined as ≥50% reduction of headache frequency and/or headache index from baseline.

Keywords Medication overuse headache · Follow-up · Outcome parameters · Relapse rate · Responders

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Introduction

Worldwide, approximately 1–2% of the adult general population suffers from chronic headache (≥15 days/month) combined with medication overuse [1–6]. The optimal method of treating the many patients with medication overuse headache (MOH) is still controversial, mainly due to lack of placebo-controlled, double-blind, randomized clinical trials [7]. No established consensus for treatment strategies exists for patient with MOH. As a consequence, the therapeutic strategies for the acute phase of detoxification and the use of preventive treatment differ widely between studies [8].

Most previous follow-up studies of patients with MOH are case series and non-randomized studies, which are difficult to interpret. The lack of high-quality studies makes it difficult to draw firm conclusions regarding the management of MOH [8]. During the last two decades, several guidelines for controlled treatment trials for patients with migraine and tension-type headache have been published [9–11], also emphasizing the need of uniform end points. However, no guidelines on performing and presenting the result of studies on MOH patients exist. Due to the lack of

guidelines, it may be of relevance to review the type of end points published in recent follow-up studies of MOH patients.

The aim of this study was to analyze and summarize the long-term outcome measures of MOH patients included in follow-up studies published in 2006 or later.

Methods

Follow-up studies of patients with MOH published in English were identified through PubMed by searching for relevant publications between January 2006 and December 2009. We used the search terms "medication overuse headache" combined with "follow-up." References listed in relevant publications were also examined. All studies were first screened for various aspects of methodology and design, and type of content, to select studies of interest for our purpose. Studies on MOH patients who underwent one type of intervention were labeled case series, whereas studies including at least two types of interventions were labeled controlled studies. We included studies fulfilling the following four minimum criteria:

(1) published in 2006 or later. Recently published studies were preferred because the majority of these studies included patients fulfilling the Headache Classification Committee of the International Headache Society from 2004 (ICDH-2) or later modified versions [12–14];
(2) >6 months' duration of follow-up;
(3) at least two of the following characteristics mentioned explicitly at baseline: primary headache type, headache days/month and/or medication days/month;
(4) at least one of the following end points mentioned explicitly at follow-up: headache days/month, reduction of headache frequency from baseline, medication days/month, reduction of medication days from baseline, responder rate defined as the proportion of individuals with ≥50% reduction of headache frequency from baseline [10], or relapse rate defined as the proportion of individuals with the diagnosis of MOH at the end of follow-up among subjects with "successful withdrawal." In this context patients with successful withdrawal were defined as those not overusing medication after the withdrawal period, regardless of whether they experienced reduction of headache frequency or not.

Statistics

Mean values of the total group of participants were presented if available. If mean values of, for e.g., three subgroups were presented, mean values for the total group were calculated by the following formula: (days/month × number of participants in group A + days/month × number of participants in group B + days/month × number of participants in group C) divided by total number of participants in group A, B and C. Mean reduction of headache days/month (as percentage) from baseline was also calculated.

Results

Initially, 33 studies were identified by the PubMed search. This was reduced to 28 unique studies after removing multiple publications based on the same patients [15–19]. Overall, nine follow-up studies, all clinic-based, fulfilled the four criteria of the present review. To optimize comparisons between studies, 12 months follow-up data were preferred in one study, although 3- and 5-year follow-up data were also available [19]. Five studies included only MOH patients who had had migraine before developing MOH, whereas the remaining four studies also included patient who had had TTH (Table 1) [15, 20–27]. Four follow-up studies were case series without controls [20–22, 26]: one retrospective [20] and three prospective studies [21, 22, 26]. The remaining five studies were categorized as controlled studies with ($n = 3$) [23–25] or without confirmed randomization ($n = 2$) [15, 27] (Table 1).

Headache diary was used in five studies during the follow-up [20, 22–25] and most likely used, although not explicitly stated, in two additional studies [15, 27]. In eight studies (Table 1) [15, 21–27], 12-month follow-up data were available. Two Italian studies used the criteria for chronic migraine proposed by Silberstein and Lipton in 2000 [15, 22], whereas the remaining patients fulfilled the Headache Classification Committee of the International Headache Society from 2004 (ICDH-2) [20, 23, 25, 27] or later modified versions [21, 24, 26]. Although the specific treatment protocol differed widely between the nine studies, all studies included abrupt withdrawal as a part of the protocol (Table 2). Prophylactic treatment was initiated during the first week in the majority of studies (range 1–90 days) (Table 2).

The 1,589 MOH patients (22% men) included in the nine different studies had an overall mean of 25.3 headache days per month (range 22.5–27.0) at baseline. Headache days at the end of follow-up were reported in six studies ($n = 582$, mean follow-up duration 11.3 months, mean −13. 8 days/month = 45% decrease from baseline) [15, 20, 22, 24, 25, 27]. The mean decrease was more pronounced for the studies including patients with migraine only ($n = 290$, mean follow-up duration 12 months, −14.6 days/month = 56% decrease from baseline) [15, 22, 27] than among those with migraine and TTH ($n = 29$,

Table 1 Study characteristics at baseline

Study, reference	Country	Number included (% men)	Age group (range)	TTH included	Duration (months)	Design
2006 [20]	Denmark	337 (27)	17–86	Yes	8	Retrospective case series
2007 [21]	Serbia	240 (24)	17–76	Yes	12	Case series
2007 [22]	Italy	106 (18)	19–71	No	12[f]	Case series
2008 [23]	Italy	118 (16)	–	No	12	Randomized controlled[a]
2009 [24]	Norway	61 (39)	18–70	Yes	12	Randomized controlled[b]
2009 [25]	Norway	100 (26)	18–70	Yes	12	Double-blind RCT[c] + randomized controlled[c]
2009 [26]	Italy	215 (19)	–	No	12	Case series
2009 [27]	Italy	93 (–)	–	No	12	Controlled[d]
2009 [15]	Italy	260 (–)	–	No	12	Controlled[e]

[a] Three groups: advice alone versus structured detoxification as in- or outpatient

[b] Three groups: prophylactic treatment from the start without detoxification versus standard outpatient detoxification program without prophylactic treatment from the start versus no specific treatment (controls)

[c] Two groups: placebo-controlled, double-blind randomized controlled trial (RCT) evaluating efficacy of prednisolone on withdrawal headache followed by an controlled design evaluating long-term outcome of patients treated by neurologist versus GP

[d] Two groups; randomization not stated: behavioral plus pharmacological treatment versus pharmacological treatment only

[e] Two groups, randomization not stated: inpatient versus day-hospital withdrawal treatment

[f] Data on 3 and 5 years follow-up also available

Table 2 Initial treatment strategies

Study, reference	Abrupt withdrawal?	In- or outpatient	Days at hospital	Infusion therapy?	Onset of preventive drugs
2006 [20]	Yes	Outpatient	0	No	After 2 months
2007 [21]	Yes	In- or outpatient	8	Yes	During the first weeks?[b]
2007 [22]	Yes	Inpatient	10	Yes	Day 6
2008 [23]	Yes	Inpatient	8	Yes	Day 1
2009 [24]	Yes[a]	Outpatient	0	No	Day 1 or after 3 months
2009 [25]	Yes	Inpatient	3	No	After 1 months
2009 [26]	Yes	Inpatient	10	Yes	Day 4 or 5
2009 [27]	Yes	Day patient	5	Yes	Day 5?[b]
2009 [15]	Yes	In- or day patient	7	Yes	Day 6

[a] Abrupt withdrawal in one out of three groups

[b] Incomplete information

mean follow-up duration 10.7 months, −9.2 days/month = 36% decrease from baseline) [20, 24, 25]. The response rate and relapse rate were reported in only three [20, 24, 25] and four studies [21, 23, 25, 26], respectively, with a mean of 28 and 26% (Table 3). Medication days/month at the end of follow-up was reported in one study only [24], whereas two studies revealed information about change in the headache index at follow-up compared to baseline (data not given) [24, 25].

Discussion

Study design and treatment strategy differ widely between the studies, and direct comparisons should be done with caution. However, in a recent review it was suggested that differences in withdrawal therapy strategy seem to have no major impact on long-term outcome [8]. If true, an overall 45% reduction in headache days and a 28% response rate during 1 year should be expected for the group of MOH patients in an open-labeled setting. However, the tendency of remission or worsening over time must be taken into account since these factors may overestimate the effect of treatment [28]. It should be emphasized that the lack of control group in all studies (except one) increases the risk that these results may be explained, at least in part, by the natural history or regression from the mean. These flaws may be avoided in randomized, double-blind, placebo-controlled studies. In one placebo-controlled study evaluating the efficacy of topiramate without withdrawal, a more

Table 3 End points used in nine follow-up studies

Study, reference	Number of dropouts (%)	Headache days/ month baseline	Duration of follow-up (months)	Headache days/month Follow-up	Medication days/ month baseline	Medication days/ month follow-up	Response rate[a] Number (%)	Relapse rate Number (%)
2006 [20]	162/337 (48)	27	8	15[e]	–	–	67/337[b] (20)	–
2007 [21]	–	24.6	12	–	–	–	–	95/240 (39.6)
2007 [22]	22/106 (21)	26.1	12	11.5	–	–	–	–
2008 [23]	37/118 (31)	26.8	12	–	–	–	–	17/83 (20.5)
2009 [24]	5/61 (8)	24.1	12[b]	17.1[e]	23.2	8.0	14/41[c] (34)	–
2009 [25]	20/100 (20)	25.4	12	16.7[e]	–	–	27/93[d] (29)	16/80 (20)
2009 [26]	43/215 (20)	22.5	12	–	21.6	–	–	38/172 (22)
2009 [27]	36/93 (39)	26.2	12	12.0	–	–	–	–
2009 [15]	111/260 (43)	25.3	12	10.4	–	–	–	–
Number	8	9	9	6	2	1	3	4
Mean	29	25.3	11.6	13.8	–	–	28	25.5

[a] Calculation of response rate (proportion of individuals with ≥50% reduction in headache frequency from baseline) differ between the three studies with respect to (a) number of participants included in the analysis and (b) time interval before evaluation

[b] Analysis of 337 participants (all included) evaluated after a mean of 8 months

[c] Analysis of 41 individuals evaluated after 12 months (20 controls excluded because of 5 months follow-up duration)

[d] Analysis of 93 individuals evaluated 3 months after withdrawal

[e] TTH patients included

moderate decrease in headache days/month (approximately 25%) was found among MOH patients with chronic migraine [29].

The most important finding in the present review was a lack of uniform end points used in the nine follow-up studies. Headache days/month was the most commonly presented, followed by relapse rate and/or responder rate. Surprisingly, only two studies explicitly reported medication days/month at baseline [24, 26] and only one study did so at the end of follow-up [24], although this was crucial when considering the diagnosis of MOH and relapse rate. Although not clearly stated, one may assume that most studies had collected information about medication days/month at baseline according to MOH diagnosis based on ICDH-2 or later modified versions. Less informative than medication days/month is the total number of medication doses consumed per month that was reported in four studies [15, 22, 23, 27]. The definition of responders varied between studies. In the study by Rossi et al. [23], responders were defined as those who had headache <15 days per month and intake of symptomatic medication <10 days/month 2 month after withdrawal treatment. However, using this definition (although it fulfills the ICDH-2 criteria), patients may be defined as responders even with a minor reduction in headache and intake of medication. In our opinion defining a responder as a patient with ≥50% reduction of headache frequency from baseline is more informative, although other definitions, e.g., ≥25% reduction of headache frequency from baseline, can be clinically meaningful for MOH patients [10]. Furthermore, for MOH patients headache index rather than headache days may more correctly reflect the total suffering [11]. Two studies had included such data based on frequency, duration and intensity [24] or frequency and intensity (named mean headache in the publication) [25] recorded in headache diaries. One may still discuss what the optimal definition of a responder is, but we would favor studies on MOH treatment that aim at ≥50% reduction in headache index from baseline. This was used as a secondary end point in one study [25]. In accordance, headache index as a primary efficacy measure has been proposed in the revised version of the guidelines for controlled trials of prophylactic drugs in chronic tension-type headache [11]. However, for headache frequency one should acknowledge that less ambitious definition of end points, e.g., those with ≥25% reduction of headache index from baseline, can be clinically meaningful [10].

In one out of the four studies reporting relapse rates [21, 23, 25, 26], the calculation was restricted to individuals who had an improvement of headache at follow-up after 2 months [23]. However, in the study by Bøe et al. [25], a much lower relapse rate at 12 months follow-up was found among individuals with ≥50% improvement score at 3 months follow-up than among those without such improvement (4 vs. 28%). Thus, a higher relapse rate may be expected if individuals with no or some improvement of headache frequency after successful withdrawal are included in the analysis.

The review demonstrated a lack of uniform end points in recently published follow-up studies of patient with MOH.

If possible, the evaluation of long-term outcome of patient with MOH should be based on headache diary information preferentially including data on headache days/month, headache intensity and medication days/month. We recommend that at the end of follow-up, minimum headache days/month and medication days/month are included, since these end points are needed to calculate relapse rate. In addition, we recommend that headache intensity and attack duration are included and that the responder rate is defined as $\geq$50% reduction of headache frequency and/or headache index from baseline. However, including end points such as $\geq$25% reduction of headache frequency and/or headache index may add useful information to the final selection of end points that should be preferred in the future. There is a need for increasing awareness of methodological issues in clinical follow-up studies for MOH. Guidelines for MOH studies including use of end points are needed.

Conflict of interest None.

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