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The effectiveness of treatments for patients with medication overuse headache; a systematic review and meta-analysis

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Highlights

- We found low to very low level of evidence of no benefit of prednisone, prophylaxis and various withdrawal interventions.
- We found benefit of 10 days less use of acute medication (low level of evidence) of inpatient treatment compared to outpatient treatment.
- Since no effective treatment with medication is present, the withdrawal strategy will remain the best available advice.

Disclosures

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Abstract

Worldwide, about 1–2% of the adult population suffer from chronic headache due to overuse of pain medication. Guidelines recommend acute withdrawal of medication, but the optimal treatment remains unknown. We aim to evaluate the benefit of treatments for patients with medication overuse headache (MOH).

We performed a sensitive search until November 2015. We selected randomized controlled trials evaluating interventions for adults with MOH. Two independent review authors assessed the eligible trials on risk of bias and extracted data. We calculated effect estimates and for the pooled analysis we used the random effects model. Our primary outcome measures were ‘headache days’ and ‘days with medication’. Outcome data were categorised as short term (up to 12 weeks) or long term (12 weeks or over) outcomes.

This review consists of 16 trials including 1105 patients. Four trials evaluated the use of prednisone with placebo or celecoxib after medication withdrawal; seven trials evaluated various methods of withdrawal versus other methods of withdrawal and five trials evaluated prophylactic medication compared with placebo or ibuprofen. We found no significant differences in headache days between prednisone versus placebo or between outpatient versus inpatient treatment, but we found a significant difference in days with medication. Overall we found no benefit of prophylactic medication versus placebo.

We found low to very low quality of evidence of no benefit of prednisone, prophylaxis and various withdrawal interventions. Since the burden of medication overuse headache for patients is enormous, larger and high quality intervention trials are needed.

Perspective.

This article presents the evidence base of treatments to patients with medication overuse headaches. It seems that the withdrawal strategy will remain the best available advice, although no clear evidence on any treatment of these patients is present.

Introduction

Chronic daily headache is a frequent disorder with a prevalence of 2-5% in the general population [34]. Chronic headache is frequent reason for consultation both in general practice and neurology clinics [34,32,13]. To alleviate headaches medications such as NSAIDs (non-steroidal anti-inflammatory drugs, including aspirin), paracetamol, codeine or dihydrocodeine are frequently taken [36]. Overuse of these medications can have a paradoxical effect and may lead to medication overuse headache (MOH) [15]. Headache secondary to the overuse of medication was first described by Peters and Horton in 1951 and it became more apparent in the last decade in patients e.g. overusing triptans prescribed for migraine [32,23,19]. However chronic overuse of common analgesics, especially the combination of analgesics containing barbiturates, caffeine, and codeine, are the most important drugs that can induce MOH [1]. Also, simple analgesics such as aspirin and paracetamol seem to contribute to MOH [32]. The prevalence of MOH in the general population is estimated to be about 1-2% [16].

The diagnosis of MOH is based on the criteria of the International Classification of Headache Disorders (ICHD) [15]. They defined MOH as a chronic headache disorder (headache on more than 15 days/month for more than three months) in combination with drug overuse (intake on > 10 or 15 days/month for > 3 months) in patients with a pre-existing headache disorder.

In most clinical guidelines, including primary care guidelines, the advised treatment for MOH is education about the condition in combination with complete discontinuation (withdrawal) of the headache medication [16]. However, the advice to discontinue the medication is based on consensus, not on solid evidence [15]. Therefore it is debatable if abrupt withdrawal should be the therapy of choice, as many patients do not succeed in complete withdrawal because of increased headaches [8]. Several interventions have been suggested to reduce the burden of medication withdrawal during the first days. These included analgesics, triptans, sedatives, amitriptyline, valproate, cortisone, relaxation therapies and other preventive medications.

Because of the lack of evidence we aim to summarize the available evidence of common treatments in patients with medication overuse headache presenting in primary care concerning reducing the intensity, duration, and frequency of headache.

Methods

Design

A systematic review with meta-analysis. The protocol is registered in PROSPERO at July 28, 2015 (registration number: CRD42015024913).

Selection criteria

Design. We included randomized controlled trials (RCTs), including crossover trials and cluster-randomized trials.

Patients. The trials had to include adults (16 years or older) with medication overuse headache (MOH) according to the International headache society (IHS) criteria or the ICHD-II criteria (International Classification of Headache Disorders).

Interventions. The included trials had to evaluate all kinds of interventions compared to placebo, no treatment or other active interventions.

Outcomes. The trials had to report the effect of the intervention on at least one patient-reported outcome measure (PROM) such as pain intensity, duration of pain, headache frequency, use of analgesics or depressive complaints. Outcome data were categorised as short term (post treatment up to 12 weeks) or long term (12 weeks or over).

No language restrictions were used.

Search strategy

We searched Medline, Pubmed, and Cochrane from inception to November 1st, 2015 and the Cochrane Controlled Trials Register, Cochrane Library (November 2015). Search terms were: 'medication overuse headache' and 'clinical trials'. Additional strategies for identifying trials included searching the reference lists of review articles and included trials to identify additional trials.

Two review authors (MG,AK) independently screened all titles and abstracts identified by the search for eligibility. Of the selected references we obtained the full text papers and these were again screened for eligibility according to the above-mentioned selection criteria. Disagreements were resolved by discussion.

Risk of bias assessment

Two review authors (MG, AK) independently performed the risk of bias assessment of the included trials. We used the form of the Cochrane Back Review Group including 6 domains (12 items). Items could score 'low risk' when the criteria were met; 'high risk' when it was clear from the publication that the criteria were not met; and 'unclear' when the documentation or description was insufficient to answer low or high risk. Disagreements were resolved by discussion and in case of persistent disagreement, a third review author made the final decision (AV). All trials scoring low risk on the items 'randomization', 'blinding' (only placebo controlled trials) and 'intention to treat analysis' were regarded as of low risk of bias.

Data extraction

Two review authors (MG,AK) performed the data extraction from the original reports and a third review author (AV) checked this. The extracted data included description of patients, numbers of participants, dropout rates, description of the interventions and control interventions (dose, study duration), duration of follow-up and data of outcomes (means, standard deviations, confidence intervals and numbers of patients recovered).

Data analysis

If sufficient data was available (i.e. means and standard deviation or number recovered), we calculated effect estimates: a (standardised) mean difference ((S)MD) for continuous outcomes, or relative risk (RR) for dichotomous outcomes. Each of these estimates was reported with a 95% confidence interval (95%CI).

In case of clinical homogeneity concerning the patient population, the type of intervention and control interventions we performed statistical pooling (using random effects model). Statistical heterogeneity was determined using I^2 tests, which was interpreted as follows: 0% to 40% no heterogeneity; 40% to 70% moderate heterogeneity; and 70% to 100% considerable heterogeneity.

We assessed the quality of the evidence using the GRADE approach. The quality of the evidence starts at high when at least two trials provide results for a particular outcome. The quality is reduced (downgraded) by one level for each of the following domains not met: a) limitations of the study design (> 25% of the participants come from studies with a high risk of bias); b) inconsistency (statistical heterogeneity ($I^2 > 40\%$) or inconsistent findings among studies (< 75% of the participants reported findings in the same direction)); c) indirectness (generalizability of the findings); d) imprecision of results (total number of participants < 300 for a dichotomous outcome and < 400 for continuous outcome); and e) 'other', such as publication bias, a flawed design or massive

dropout. Single randomised trials ($n < 400$) were considered inconsistent and imprecise and provided low-quality evidence, which could be further downgraded to very low-quality evidence.

Results

Search results

Initially, 186 references were identified by the search and two other references were selected from reviews on MOH. After screening for title and abstract we performed full text screening of 21 publications of which 18 were regarded eligible presenting 16 trials (see figure 1). Three publications were excluded because of no RCT [10], including only children [33] and not including MOH patients [31].

Figure 1: flow chart

Description of trials

The number of participants in each study-arm ranged from 7 [7] to 49 [2] with a total of 1105 patients included in this review. The dropout rate ranged from 4.9 to 30% (mean 15.8%). The age from the participants ranged from 16 to 72 years of age. The mean percentage of females in the trials was 80.2% (range: 66.6 to 91%) (see table 1).

Table 1 Characteristics of included studies

Interventions

Four trials evaluated prednisone of which three compared it with placebo and one with celecoxib. Dosages of prednisolone varied between 60 – 100mg/day. All trials reduced the dosages during the treatment period, which varied between 5 – 6 days. Seven trials compared a method of withdrawal (advice only, acute withdrawal, outpatient or inpatient program, follow-up by neurologist or general practitioner, biofeedback, preventive medicine) and five trials evaluated prophylactic medication of which four compared it with placebo and one with ibuprofen. All trials included a baseline period (or qualification) of about four weeks prior to the randomization. The mean (\pm SD) total treatment period was 22.1 (\pm 36.1) days.

Outcome measures

Different outcome measures were used, but all reported some measure of headache (e.g. number of headache days per month, number of days without headache, headache intensity, headache improvement or analgesic use). All trials used diaries to assess the outcomes. Some trials used improvement scores or calculated a mean headache pain intensity or a headache index. The timing of the outcome measurement varies between 15 days to 36 months. Ten trials only reported short-term results, most frequently at 8 to 12 weeks; while five trials also included a long-term outcome measure varying between 6 – 36 months after randomization (see table 1).

Risk of bias assessment

The risk of bias assessment showed a mean number of items per study that scored low risk of bias of 5.9 (out of maximum of 12), with a range from 2 to 10 items (see table 2). Most of the trials scored positive on random sequence generation, group similarity at baseline and timing of outcome assessments. However selective outcome reporting, co-interventions, incomplete outcome data (selective loss to follow-up, or loss to follow-up > 15%) and compliance were unclear in many trials. Six trials were considered as of low risk of bias [12,17/18,22,24,29,35].

Table 2 risk of bias assessment

Efficacy of interventions

Prednisone trials

Three trials compared a prednisone with placebo group during the period of withdrawal [2,22,25], of which one trial is of low risk of bias [22]. Two trials presented data for calculation of the effect estimate, but due to heterogeneity in the outcomes no statistical pooling was possible. Another trial of low risk of bias evaluated the effectiveness of celecoxib compared with prednisone [35].

We found no differences between the prednisone or placebo groups in the use of rescue medication (RR=0.3 (95%CI: 0.09; 1.3); 1 study; 20 participants) [22]. We also found no differences between the groups in days with severe or moderate headache or days without headache [2]. Furthermore we found no statistical significant differences between prednisone and celecoxib at 8 days in headache days (MD=0.3 (95%CI: -0.2; 0.7)), headache frequency (MD=1.3 (95%CI: -7.1; 9.7)) and the use of rescue medication (RR=1.7 (95%CI: 0.9; 3)) in one trial (of low risk of bias) with 97 participants [35].

Overall we conclude that there is low to very low quality of evidence for no difference between prednisone and placebo or celecoxib on various headache outcome measures (single studies downgraded by design).

Method of withdrawal

Three trials compared inpatient treatment with outpatient treatment [26,27,5]; all of high risk of bias. The treatment regimen in 2 trials consisted of 8 days of prednisone (60 mg/day for 2 days; 40 mg/ day for 2 days; 20 mg/day for 4 days), and personalized preventive treatment either done at home or during visits at the headache center [26, 27]. In the third trial patients received amitriptylin 20-40mg and metoclopramide for 8 days either at home or at the headache center [5]. We were able to pool the data of these trials concerning number of responders, reduction in headache days and days with medication use (see figure 2, 3 and 4). Overall we found no statistical significant differences between the inpatient or outpatient treatment on number of responders (RR=1.2 (95%CI: 0.5; 2.8); 3 trials short term, 231 participants; $I^2=73\%$) and headache days (MD=8.9 (95%CI: -9.5; 27.3); 3 trials, 219 participants; $I^2=83\%$). We found a statistical significant reduction of 10.5 (95%CI: 2.6; 18.5; 2 trials, 148 participants, $I^2=0\%$) days with medication use in favor of the inpatient treatment. Furthermore we found no statistical significant difference between a brief intervention by the GP versus usual care [18], abrupt withdrawal versus preventive treatment [14], follow-up by the neurologist versus follow-up by the GP [3], in- or outpatient treatment versus no treatment [26], or between biofeedback assisted relaxation therapy versus no treatment [11].

Therefore we conclude that there is very low quality of evidence for no difference between inpatient or outpatient treatment on the number of responders or headache days (downgraded by design, inconsistency and imprecision). Furthermore there is low quality of evidence for benefit of inpatient treatment

compared to outpatient treatment in days with acute medication (downgraded by design and imprecision). For all other treatments there is low (single studies) to very low quality (single studies, downgraded by design) of evidence for no benefit.

Figure 2: effect of outpatient versus inpatient treatment on number of responders

Figure 3: effect of outpatient versus inpatient treatment on reduction in headache days

Figure 4: effect of outpatient versus inpatient treatment on reduction in days with medication use

Prophylactic medication

In five trials the effect of prophylactic medication was compared with placebo or ibuprofen in reducing headache and analgesic use [7,20,24,28,29]. Two trials are of low risk of bias [24,29]. The evaluated medications were: valproate [29], nabilone (versus ibuprofen) [24], botilium toxin type A [28], topiramate [20] and amitriptyline [7]. We decided to pool only the results of valproate and topiramate as both are anti-epileptica (see figure 5 and 6). Overall we found no statistical significant difference between valproate or topiramate in the reduction of headache days (MD=7.9 (95%CI: -0.7; 16.4); 2 trials, 123 participants; $I^2=95%$) or days with medication use (MD=8 (95%CI: -0.3; 16.4); 2 trials, 123 participants; $I^2=94%$). The trial on valproate was of low risk of bias. Furthermore we found no differences on our outcome measures between botiliumtoxin type A versus placebo and nabilone versus ibuprofen both in single studies [24,28]. On the other hand we found a slight statistical significant difference between amitriptyline and placebo [7].

Therefore we conclude that there is very low quality of evidence for no benefit of anti-epileptics compared with placebo concerning the reduction of headache days and days with medication (downgraded by design, inconsistency and imprecision). Furthermore we conclude that there is low to very low quality of evidence for no benefit of prophylactic medication compared with placebo concerning headache days and medication use (single studies, downgraded by design).

Figure 5: effect of prophylaxis on reduction of headache days

Figure 6: effect of prophylaxis on days with medication use

Discussion

Main findings

Overall we found no benefit of prednisone, prophylactic medication or different withdrawal strategies (low to very low quality of evidence) in the treatment of patients with medication overuse headache. We only found benefit of 10 days less use of acute medication (low quality of evidence) of inpatient treatment compared with outpatient treatment. Overall we found low to very low quality of evidence. Out of the 16 trials found, six were considered as of low risk of bias, and all were of low power (less than 50 patients per treatment group).

Comparison with other literature

Several other (systematic) reviews have been published evaluating the effectiveness of treatments for patients with MOH [4,13,16,21]. All reviews included studies with varying designs, including patient series and cohort studies. They performed no separate analysis on (randomized) controlled trials; therefore their conclusions were more positive compared to ours.

Strengths and limitations

This is the first systematic review including randomized controlled trials only about the treatment of patients with MOH. Because of our broad search strategy we were able to include a large number of trials for treatment of MOH, larger than in other reviews. Nevertheless, most included trials were small, lacked sufficient power and the majority was considered of high risk of bias (low quality).

Second, we did not search for grey literature as this is very time consuming and it is uncertain whether it would influence our current results. Grey literature concern studies that have not been published for various reasons (publication bias). One of the reasons not to publish is a negative outcome. Due to the low number of studies per intervention we have not been able to evaluate publication bias, but we do not think publication bias is a problem in our review, as more negative studies would not have changed our conclusions. Third, selective outcome reporting could not be assessed, as we found no registry of protocols. Fourth, a broad variety of outcome measures were used to observe the effect of treatment of MOH. Although most of the trials used a headache diary to measure the decrease in headache duration and headache intensity and the decrease in acute headache medication as relevant outcome measures, there was a variety on how these outcome measures were measured. This clinical heterogeneity made it difficult to draw firm conclusions. Fifth, we dichotomized the timing of outcome measurement between short-term and long-term outcome. Due to the fact that just a few studies reported sufficient

data we were unable to look more closely at different endpoints. Long-term outcomes are preferred to evaluate whether the interventions maintain their effect, but we were unable to draw conclusions on long term effect such as responders to treatment and relapses. Lastly, the definition of MOH might have differed between various trials also due to changes in the IHS criteria for MOH over time and thus the severity of MOH patients in the trial might vary, as in some trials this was not defined or explicitly mentioned.

Recommendations

The benefit of most interventions in patients with MOH needs further evaluation in larger trials of low risk of bias. Patients with MOH are a difficult to treat group of patients both in primary and secondary care. Often they have been using medication for a long period and their quality of life is severely influenced by the number of days with a headache. In clinical guidelines, education about the condition and a complete discontinuation of the headache medication is advised [6,9,30,32]. The withdrawal advice is based on consensus. In our review, we hoped to identify effective treatments to support the discontinuation of the headache medication in patients with MOH. Unfortunately, we found no benefit of the various withdrawal interventions in patients with MOH. The scientific search for an effective treatment or advice for patients with MOH is urgently needed. Future studies should in our view focus on evaluating the treatment that is recommended in the guidelines, which is discontinuation of headache medication and education. This intervention should be designed in a way that it has optimal change to be effective, meaning that discontinuation should be accompanied with clear guidance and proper education. Although the evaluation of various withdrawal techniques is not evaluated in such a way that it enables us to draw a clear conclusion on its benefit, it might still be a promising treatment that needs proper evaluation.

Finding a relevant clinical outcome measure (and measure this comparable in future trials) remains a challenge. Patients with MOH often suffer from chronic primary headaches for years. Because of the headaches they use pain medication. Treating the overuse of pain medication does not mean that the original headaches (e.g. tension type headache or migraine they had initially) will also disappear. Therefore measuring headache intensity or headache frequency might not be the appropriate outcome measure in trials with MOH patients as these are also the outcomes relevant to the original headache. In that case, the end point of the trial might be whether the headache intensity or the frequency of their initial headache (tension-type or migraine) is retained and the intervention for MOH was thus effective. In future trials we recommend a follow-up of at least 12 months to be able to capture possible relapses. Future studies should include large groups of patients (preferably at least 60 participants per study group) and evaluate the most frequently prescribed intervention (i.e. discontinuation of headache medication + education), preferably compared to usual care to be able to evaluate additional effectiveness. Extra attention needs to be paid to the choice of outcome measures; e.g. relapse or response to treatment seem to be proper outcome measures these do not interfere with the complaints of the initial or original headache.

In **conclusion**, research on effective treatments in patients with medication overuse headaches is needed. The guidelines consist of recommendations based on consensus as evidence still is lacking. In clinical guidelines, both in primary and secondary care, the advised treatment for MOH is education about the condition and complete discontinuation of the headache medication. Since no effective treatment with medication for patients with MOH is present, this withdrawal strategy will remain the best available advice.

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Legend

Table 1: Study characteristics

Table 2: Risk of bias assessment

Figure 1: Flow chart

Figure 2: Inpatient versus outpatient treatment, responders

Figure 3: Inpatient versus outpatient treatment, headache days

Figure 4: Inpatient versus outpatient treatment, days with medication use

Figure 5 Prophylaxis versus placebo, headache days

Figure 6 Prophylaxis versus placebo, medication days

Table 1: Study characteristics

Study	Patients	Interventions	Outcome measures	Results Mean (SD)	Effect estimates* MD, RR (95%CI)
Taghdiri 2015	MOH + migraine (IHS criteria). Private clinic, Iran; n=97. Women 91%	A: Prednisone 75mg/day, n=45 (n=42) B: Celecoxib , 400mg/day, n=52 (n=38) All patients: rescue medication Treatment: 5 days, than tapering down dosage (20 days total treatment) Follow-up: 8 weeks	HA-d: nr of headache days HA-freq: % reduction of headache days/week Rescue medication (intake frequency)	HA-d 8 wk: A: 1.02 (1.0); B: 1.29 (1.0) HA-freq 8 wk: A: 78.1% (16.2); B: 79.4% (21.6%) Rescue medication: 8 days: A: 29% (11/38) B: 47.6% (20/42)	HA-d 8 wk: MD=0.3 (-0.2; 0.7) HA-freq 8 wk: MD=1.3 (-7.1; 9.7) Rescue medication: 8 days: RR=1.7 (0.9; 3)
Kristoffersen 2012, 2015 Cluster-randomised trial	Self-reported MOH by general practitioners (GP), Norway. N=75; 52 (out of 60) women (87%)	A: Brief intervention by GP , n=30 (n=24) B: Usual care , n=45 (n=36) Follow-up at 3 months	Responders (>50% reduction in HA-d) HA-d: Headache days/ month Med: Medication days/ month	Responders 3 mo A: 8/24 (33%); B: 2/36 (6%) HA-d 3 mo: A: 17.4 (11.4); B: 24.6 (7.5) Med 3 mo: A: 13.4 (11.5); B: 21.7 (7.7)	Responders RR=6 (1.4; 25.9) HA-d: MD: 7.2 (12.4; 2) Med: MD: 8.3 (13.5; 3.1)
Sarchielli 2014	MOH + migraine (IHS), Neurology clinic, Italy; n= 88; 69 women (84%)	A: Valproate up to 800mg/day; 12 weeks maintenance, n=44 (n=37) B: Placebo , n=44 (n=36) Treatment: 12 weeks Follow-up: 24 weeks	Responders: >50% reduction in HA-d HA-d: Number of headache days/ month, change Med: Number of days with acute medication, change	Responders 12 wk: A: 18/44 (40.9%) B: 10/44 (22.7%) HA-d 12 wk: A: -8.1 (6.7); B: -4.6 (6.8) Med 12 wk: A: -8.6 (6.8); B: -4.9 (8.8)	Responders: RR=1.8 (0.9; 3.5) HA-d: MD: 3.5 (0.4; 6.6) Med: MD: 3.7 (7.3; 0.1)
Rossi 2013	Complicated MOH + migraine; n=137; 110 women (80.3%)	A: Advice alone , n=46 (n=35) B: Outpatient program advice + prednisone, n=46 (n=37) C: Inpatient program advice + prednisone, n=45 (n=43) Treatment: 10 days Follow-up: 5, 10 weeks	Responders HA-d: Headache days/ month (% reduction) Med: Medication days/ month (% reduction) HA-freq: Headache frequency (> 50% reduction)	Responders 10 wk: A: 28/35 (80%); B: 28/37 (75.7%); C: 40/43 (93%) HA-d 10 wk: A: 44 (25); B: 49.8 (28); C: 73 (22)	Responders A vs B: RR=1.1 (0.8; 1.5); A vs C: RR=0.7 (0.5; 0.8); B vs C: RR=0.6 (0.5; 0.8) HA-d: A vs B: MD: 5.8 (-6.5; 18.1) A vs C: MD: 29 (18.4; 39.6) B vs C: MD: 23.2 (12; 34.4)

Study	Patients	Interventions	Outcome measures	Results Mean (SD)	Effect estimates* MD, RR (95%CI)
		Non adherence to the treatment in group A (23.9%), B (19.5%), C (4.4%)		Med 10 wk: A: 62.5 (23); B: 63.6 (26); C: 75.2 (23) HA-freq 10 wk: A: 25/35 (71.4%); B: 26/37 (70.3%); C: 38/43 (88.4%)	Med: A vs B: MD: 1.1 (-10; 12.4) A vs C: MD: 12.5 (2.4; 22.8) B vs C: MD: 12.6 (1.8; 23.4) HA-freq: A vs B: RR=1 (0.7; 1.4); A vs C: RR=0.6 (0.5; 0.8); B vs C: RR=0.6 (0.5; 0.8)
Rabe 2012	MOH + migraine or episodic tension-type headache (IHS criteria). Neurological department university hospital, Germany; n=96	A: Prednisone 100mg, n=48 (n=37) B: Placebo , n=48 (n=41) All patients: calcium, potassium and ranitidine 300 mg and rescue medication Treatment: 5 days Follow-up: 5 and 14 days	HA-h: hours with moderate to severe headache HI: Headache Index Rescue medication (intake frequency)	HA-h: 5 days: A: 29.6; B: 27.7 14 days: A: 74.9; B: 69.8 HI: 5 days: A: 0.80; B: 0.85 14days: A: 0.91; B: 0.96 Rescue medication: 5 days: A: 1.1 B: 2.3 14 days A: 3.6 B: 6.4	
Pini 2012 Cross-over study	MOH (ICHD-II criteria) University hospital, Italy, n=30, 20 (66.6%) women	A: Nabilone 0,5mg, n=26 B: Ibuprofen 400mg, n=26 Treatment: 8 weeks, wash out 1 week	HI: Headache days/ month HA-int: VAS pain score PFD: Pain free days /month DAI: Daily analgesic intake	HI: A: 0.72 (0.3); B: 0.78 (0.3) HA-int: A: 5.7 (1.9); B: 6.6 (2.2) PFD: A: 8.1 (9.3); B: 6.6 (6.3) DAI: A: 0.89 (0.5); B: 1.34 (0.9)	HI MD: 0.1 (-0.1; 0.2) HA-int: MD: 0.9 (-0.2; 2) PFD: MD: 1.5 (-2.8; 5.8) DAI: MD: 0.5 (0.05; 0.9)
Creac'h 2011	MOH (>15 days / month, 3 months; >15 days analgesic use) referred to a pain center, France; N=82; 56 women (79%)	A: Outpatient treatment , n=41 (n=36) B: Inpatient treatment , n=41 (n=35). All patients: amitriptylin 20-40mg and metoclopramide Treatment: 8 days Follow-up: 2 months and 2 years	Responders HA-d: % reduction in headache days/ month SI: subjective improvement (%)	Responders: 2 mo: A: 21/36 (59%); B: 13/35 (38%) 2 yr: A: 16/36 (45%); B: 14/35 (40%) HA-d: 2 mo: A: 51 (35); B: 41 (30) 2 yr: A: 55 (33); B: 53 (36) SI:	Responders: 2 mo: RR=1.6 (0.9; 2.6) 2 yr: RR=1.1 (0.6; 1.9) HA-d: 2 mo: MD: 10 (-5.2; 25.2) 2 yr: MD: 2 (-14.1; 18.1) SI: 2 mo: MD: 7 (-5.9; 19.9) 2 yr: MD: 5 (-12.2; 22.2)

Study	Patients	Interventions	Outcome measures	Results Mean (SD)	Effect estimates* MD, RR (95%CI)
				2 mo: A: 63 (32); B: 56 (23) 2 yr: A: 46 (39); B: 41 (35)	
Sandrini 2011	MOH + migraine (IHS), Headache centres, Italy; n= 68; 45 women (81%)	A: Onabotulinum toxin type A , 16 injections, n=33 (n=27) B: Placebo , 16 injections, n=35 (n= 29) All patients: IV saline solution, vitamin complex, glutathione 600mg, alizapride 0.25mg and clordemetildiazepam Treatment: 8 ± 2 days Follow-up: 12 weeks	HA-d: Number of headache days/ month Med: mean days with acute pain medication consumption	HA-d: A: 12.0 (9.0); B: 15.9 (9.5) Med: A: 10.7 (10.1); B : 14.3 (9.1)	HA-d: MD: 3.9 (-1; 8.8) Med: MD: 3.6 (-1.5; 8.7)
Hagen 2009, 2011	MOH Outpatient clinic University hospital, Norway, n=61	A: Abrupt withdrawal + preventive treatment after 3 months, n=22 (n=14) B: Preventive treatment from 1 st day, n=19 (n=16) C: Control , no advice to stop, n=20 (n=18) Follow-up: 3, 5 and 12 months	Responders (>50% reduction in HI) HI: Headache index	Responders 12 mo: A: 10/19 (53%); B: 5/20 (25%) HI 3 mo: A: 33 (242); B: -169 (167); C: -36 (186) HI 12 mo: A: -19 (251); B: -201 (288)	Responders: RR=2.1 (0.9; 5.0) HI: A vs B: MD= 202 (-51; 353) A vs C: MD= 69 (-84; 222) B vs C: MD= 133 (14; 252) HI: A vs B: MD= 182 (-11; 375)
Pageler 2007	MOH (ICHD-II criteria) N=20, 17 women (85%)	A: Prednisone 100mg, n=10 (n=9) B: Placebo , n=10 (n=9) Rescue medication: lysine acetylsalicylic acid (1000mg, iv) Treatment: 5 days Follow-up: 120 hours	HA-h: hours with moderate to severe headache Rescue medication (number of patients, mean dosages)	HA-h: 72h: A: 18.1 B: 36.7 120h: A: 27.2; B: 42.7 Rescue medication: A: 2 patients, 11 dosages; B: 6 patients, 21 dosages	Rescue medication: RR=0.3 (0.09; 1.3)
Boe 2009	MOH (IHS criteria). All patients were included in Boe 2007 and entered this study after 4 weeks withdrawal therapy	A: Follow-up by primary care physician , n=46 (n=38, n=30) B: Follow-up by neurologist , n=47 (n=42, n=41) Follow-up: 3, 6, 9 and 12 months	HA-0: Days without headache HA-index: MH Recurrence: Number of patients with recurrent MOH	HA-0 12 mo: A: 132 (75); B: 123 (83) HA-index 12 mo: A: 1.02 (0.5); B: 1.04 (0.6) Recurrence 12 mo: A: 9/38 (24%); B: 7/42 (17%)	HA-0: MD: 9 (-28; 46) HA-index: MD: -0.02 (-0.3; 0.2) Recurrence: RR=1.4 (0.6; 3.4)

Study	Patients	Interventions	Outcome measures	Results Mean (SD)	Effect estimates* MD, RR (95%CI)
	N=93; 62 women (78%)				
Boe 2007	MOH (IHS criteria) Recruited by general practitioners, Norway. N=102; 74 women (73%)	A: Prednisone: 60-60-40-40-20-20 mg, n=51 (n=49) B: Placebo, n=51 (n=48) All patients: metoclopramide alimemazine or levopromazine in low doses for insomnia Treatment: 6 days Follow-up: 4 weeks	HA-d: Headache days HA-0: Days without headache Impr: Improvement score	HA-d: 6 d: A: 1.6 (0.7); B: 1.5 (0.7) 4 wk: A: 1.4 (0.7); B: 1.4 (0.5) HA-0: 6 d: A: 1.1 (1.6); B: 1.1 (1.9) 4 wk: A: 7.2 (7.7); B: 7.6 (7.8) Impr: 4 wk: A: 11.8%; B: 12.1%	HA-d: 6 d: MD: 0.1 (-0.2; 0.4) 4 wk: MD: 0 (-0.3; 0.3) HA-0: 6 d: MD: 0 (-0.7; 0.7) 4 wk: MD: 0.4 (-3.5; 2.7)
Rossi 2006	MOH + migraine, (ICHD-II criteria) Headache centre, Italy N=118; 99 women (83.8%)	A: Advice only, n= 40 (n=37) B: Outpatient withdrawal, n= 39 (n=34) C: Inpatient withdrawal, n= 39 (n=34) B and C: prednisone 8 days (60 mg/day, 2 days; 40 mg/ day, 2 days; 20 mg/day, 4 days), and personalized preventive treatment Follow-up: 8 weeks	Responders: no headache or an episodic headache character HA-d: % reduction in headache days/ month Med: % reduction in doses of symptomatic medication/ month	Responders: A: 31/40 (77.5%) B: 28/40 (70%) C: 30/40 (75%) HA-d 8 wk: A: 67.6 (25); B: 61.2 (34); C: 73 (19) Med 8 wk: A: 76.6 (22); B: 71.7 (32); C: 81 (13)	Responders: A vs B: RR=1.1 (0.9; 1.4) A vs C: RR=1 (0.8; 1.3) B vs C: RR=0.9 (0.7; 1.2) HA-d: A vs B: MD: 6.4 (-7.6; 20.4) A vs C: MD: -5.4 (-15.7; 4.4) B vs C: MD: -11.8 (-24.9; 1.3) Med: A vs B: MD: 4.9 (-8; 17.8) A vs C: MD: -4.4 (-12.7; 3.9) B vs C: MD: -9.3 (-20.9; 2.3)
Mei 2006	MOH + migraine (IHS criteria) N=50; 24 women (out of 35) (69%)	A: Topiramate 25mg/day increased in 4 weeks to 100mg/day in 2 doses at least 50mg/day; 8 weeks maintenance, n=30 (n=21) B: Placebo, n=20 (n= 14) Treatment: 12 weeks	HA-d: Number of headache days/month Med: Number of days with acute medication	HA-d 12 wk: A: 3.14 (0.91); B: 15.36 (4.38) Med 12 wk: A: 3.19 (1.04); B: 15.43 (4.43)	HA-d: MD: 12.2 (9.9; 14.6) Med: MD: 12.2 (9.9; 14.6)
Grazzi 2002 Quasi randomised	MOH + migraine (IHS criteria) Neurology outpatient clinic, Italy; N=61; 51 women (84%)	A: Biofeedback assisted relaxation therapy, 8 sessions once a week; n=19 B: No treatment, n= 42 All patients: inpatient pharmacological treatment: 10	Responders (>50% reduction in symptoms) HA-d: Headache days/ month Med: Number of analgesics/ month Relapse	Responders 3 yr: A: 11/16 (69%); B: 22/38 (58%) HA-d 3 yr: A: 11.2; B: 18.1 Med 3 yr:	Responders: RR=1.2 (0.8; 1.8) Relapse: 1 yr: RR=0.6 (0.1; 2.4) 3 yr: RR=0.3 (0.1; 1.1)

Study	Patients	Interventions	Outcome measures	Results Mean (SD)	Effect estimates* MD, RR (95%CI)
		days bioarginine iv, indomethacin im (3-4 days), metoclopramide iv, diazepam im, parenteral neuroleptics, prednisone + prophylactic medication Follow-up: 12, 36 months		A: 20.1; B: 4.9 Relapse: 1 yr: A: 2/19 (10%); B: 8/42 (20%) 3 yr: A: 2/16 (12.5%); B: 16/38 (41%)	
Descombes 2001	MOH (IHS criteria), Neurology centre, France N= 20, 14 (out of 17) women (83%)	A: Amitriptyline chlorhydrate iv (25mg to 75mg, one week, amitriptyline tablets 75mg 4 weeks), n=10 B: Glucose solution iv (1 week), capsule with trihexyphenidyl (2mg) for 4 weeks. n=10, (n=7) Treatment duration: 1 week Follow-up: 4 weeks	HA-f: headache frequency Pain: Quality of live subscale (QOL)	HA-f 4 wk: A: -10.6 (1.9); B: -6.8 (3.8) QOL pain 4 wk: A: -33 (8); B: -20 (11)	HA-f: MD: 3.8 (0.8; 6.9) QOL pain: MD: 13 (3.5; 22.5)

* A positive score on MD, or and RR>1 means in favor of first mentioned intervention

IHS: international headache society; ICHD-II criteria: International Classification of Headache Disorders-2nd edition; IV: intravenous; N= number; RR: relative risk; MD: mean difference; mg: milligram; SD: standard deviation; CI: confidence interval; d: days; wk: weeks; mo: months

Mean headache (MH) calculated by the formula: $MH (0-3) = (a + b + c) / \text{number of days recorded}$, where 'a' is the number of days with mild headache x 1, 'b' is the number of days with moderate headache x 2 and 'c' is the number of days with severe headache x 3.

Headache index (HI) per month calculated by the sum of the products of 'headache days/month' combined with 'mean daily hours with headache' and 'mean daily headache severity' on days with headache

Table 2: Risk of bias assessment

	Randomisation		Blinding			Data handling		Selective outcome reporting	Other				Total
	Ade-quate	Con-cealed	Partici-pants	Care-givers	Outcome assessors	Incomplete outcome data	Intention to treat analysis		Baseline similarity	Co-interventions	Com-pliance	Timing	
Taghdiri 2015	L	L	L	L	L	H	H	L	L	?	?	L	8
Kristoffersen 2012 / 2015	L	L	L	L	L	L	L	L	L	?	?	L	10
Sarchielli 2014	L	L	L	L	L	H	L	L	L	?	?	L	9
Rossi 2013	L	L	?	?	?	H	H	?	L	?	H	L	4
Rabe 2012	L	L	L	L	L	H	H	?	L	L	?	L	7
Pini 2012	L	?	L	L	L	L	L	?	L	?	?	L	8
Hagen 2009 / 2011	L	L	?	?	?	H	L	L	L	?	?	L	5
Creach 2011	?	?	?	?	?	H	H	?	L	?	?	L	2
Sandrini 2011	L	L	L	L	L	H	H	?	L	?	?	L	7
Boe 2009	L	L	L	L	L	H	H	?	L	?	L	L	8
Pageler 2008	L	L	L	L	L	L	L	?	L	?	?	L	9
Boe 2007	L	L	L	L	L	L	H	?	L	?	?	L	8
Rossi 2006	L	?	L	?	L	H**	H	?	L	?	L	L	5
Mei 2006	?	?	?	?	?	H	H	?	L	?	?	L	2
Grazzi 2002	H*	?	?	?	?	L	H	?	?	?	?	L	2
Descombes 2001	?	?	?	?	?	H	H	?	L	?	?	L	3

L: low risk of bias; H: high risk of bias; ?: unclear

* Quasi-randomization: all patients at large distance from hospital may decline from intervention

** Two patients were excluded because they showed no improvement during study period

Figure 1: Flow chart

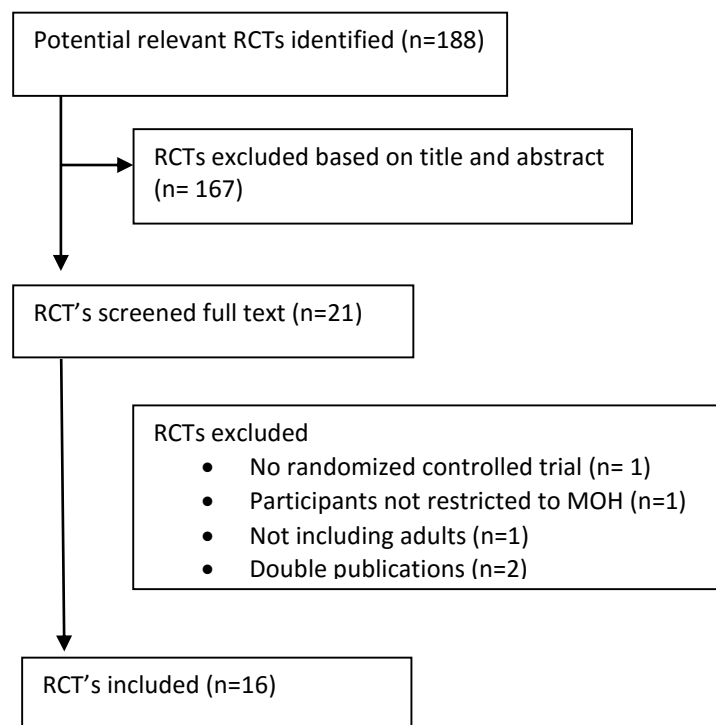


Figure 2: Inpatient versus outpatient treatment, responders

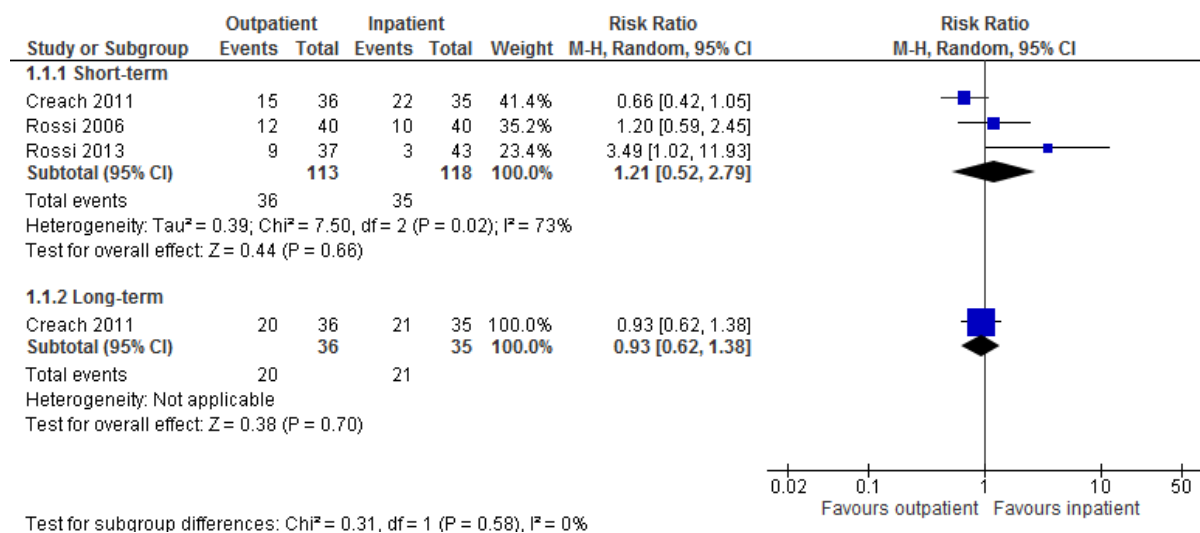


Figure 3: Inpatient versus outpatient treatment, headache days

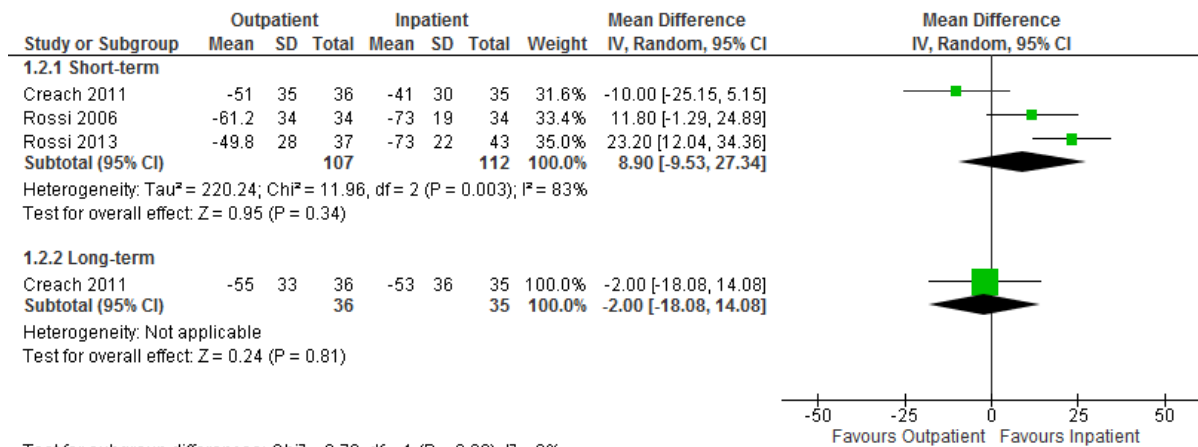


Figure 4: Inpatient versus outpatient treatment, days with medication use

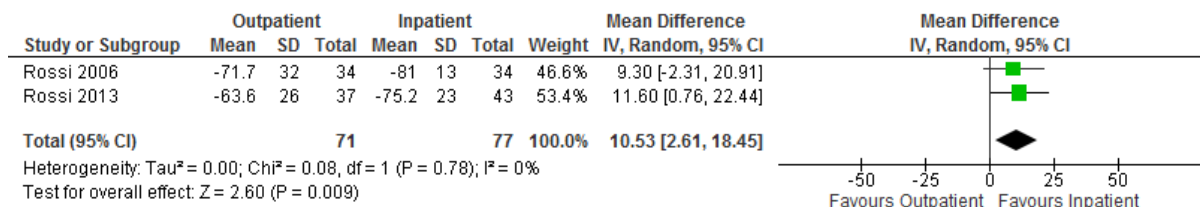


Figure 5 Prophylaxis versus placebo, headache days

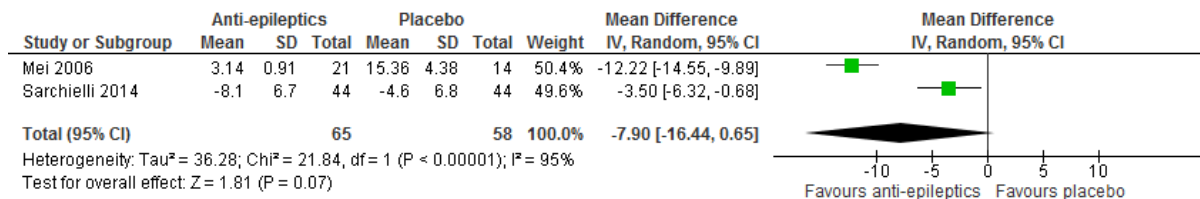


Figure 6 Prophylaxis versus placebo, medication days

