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Prevention of medication overuse in patients with migraine

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ABSTRACT

This multi-center study compared the therapeutic effect of a cognitive-behavioral minimal contact program (MCT) to the effect of a brochure (bibliotherapy) for the prevention of medication overuse headache (MOH) in migraine patients. Seven German headache centers recruited 182 migraine patients with high triptan or analgesic intake frequency. Patients were randomly allocated to either the MCT-group, receiving both an MCT program and an educational brochure or to the biblio-group receiving only the brochure. All participants continued usual medical treatment. Course of headaches, intake of analgesics or triptans after training, 3 months post-training as well as 1–2 years (mean 15.7 months) later and psychological variables were defined as outcome variables. A significant decline was observed in the number of headache days (11.0–8.8), migraine days (7.3–5.7) and medication intake days (7.4–6.1) from pre to post in the MCT-group ($p < 0.001$ each) and in the biblio-group ($p < 0.001$ each). The pre-to-post-improvements were maintained from pre- to short- and from pre- to long-term follow-up ($p < 0.001$ each) in both groups. Both groups improved significantly from pre to post in psychological variables, e.g. pain acceptance: $p < 0.001$; pain catastrophizing: $p < 0.001$; functional pain coping: $p < 0.001$; and pain related internal control beliefs: $p < 0.01$. Psychological improvements remained stable in both groups at short- and long-term follow-up. During the study, none of the patients developed an MOH. MCT- and bibliotherapy are useful in migraine patients to prevent medication overuse headache or the transition of episodic to chronic headache.

1. Introduction

Medication overuse headache (MOH) is the most common continuous headache and the only chronic daily headache (CDH) which is associated with frequent intake of pain medication [19]. In migraine patients, the overuse of analgesics or triptans is the strongest predictor of MOH [43]. A significant predictor of CDH is a high initial headache frequency [20]. Most CDH patients suffer from MOH (up to 67% in [26]). This suggests a causal relationship between medication overuse and the transition from episodic to chronic headache.

The American Headache Consortium [8] recommended that patients with episodic or high-frequency migraine (three and more attacks/month) should undergo psychological therapy as an alternative or supplement to pharmacological treatment. The psychological procedures applied in migraine therapy use the same therapeutic strategies as the behavioral therapy of chronic pain. Their effectiveness is proven [4,18]. The main objectives are "... to increase the patient's control of their headaches, reduce the frequency and severity of headaches, reduce related disability and affective distress" [18].

The significant comorbidity of anxiety and depression in CDH patients suggests that migraine patients with high medication intake frequency would benefit substantially from psychologically-oriented interventions. Anxiety and depression are known to influence intake behavior [32,37] and partly explain the effectiveness of amitriptyline [33] and fluoxetine in the treatment of CDH [36]. Cognitive-behavioral therapy (CBT) alone [4,18] or combined with pharmacological treatment has been shown to be effective in the treatment of CDH patients with and without MOH [3,7,25]. Some trials demonstrated an effect of psychological treatment only in follow-up [16]. Our preliminary investigation [15] showed that intake behavior is determined not only by pain intensity and frequency, but also by an overwhelming fear of loss of social functionality. This suggests that intake behavior can be influenced by psychological interventions.

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A behavioral minimal contact training (MCT) for migraine patients consisting of eight sessions with psychoeducational contents and teaching of pain-coping strategies proved effective in numerous studies and meta-analyses [e.g. 4], with an average effect size (ES) of $d = 0.54–0.77$.

Another common treatment method is bibliotherapy, a therapy by guided reading of material containing information about the physiological and psychological aspects of migraine. Bibliotherapy has a broad application in different medical and psychological contexts and is accepted by both professionals and patients. Meta-analyses [e.g. 24] show the effectiveness of bibliotherapy in different application areas with average effect sizes ranging between $d = 0.57$ and 0.76.

To date, the effects of MCT have not been compared to the effects of bibliotherapy in migraine patients. The present study aimed at comparing the effect of the two treatment methods for prevention of MOH in patients with frequent migraine attacks. We hypothesized that both treatment regimes – MCT- and bibliotherapy – would reduce the medication intake frequency and consequently the risk of MOH, but that patients treated with MCT would have a significantly greater reduction of medication intake days than those treated by bibliotherapy.

2. Methods

The study was approved by the Ethics Committee of the University of Duisburg-Essen, Germany. All participants were provided with written information and gave written consent prior to inclusion.

2.1. Inclusion/exclusion criteria

Migraine patients without MOH according to ICHD-II criteria [19] were included in the study. Inclusion criteria were:

- Patients suffering from migraine with and without aura
- Patients with combined headache (migraine and tension-type headache (TTH), if migraine was the main headache (as reported by the patient)
- Age: 18–65 years
- One of the following conditions:
  - Intake of triptans on >4 and <10 days per month or
  - Intake of analgesics on >7 and <14 days per month during the past three months or
  - Combined intake of triptans and analgesics not exceeding 15 intake days, including a maximum of 9 triptan intake days
- Agreement to participate in one of two study arms by randomization

Exclusion criteria were:

- Significant psychiatric disorder.
- Additional secondary headache.
- Additional chronic pain diseases with pharmacological treatment.
- Insufficient knowledge of the German language.
- Pregnancy.

The inclusion and exclusion criteria were verified by examining the patient's medical files in the recruiting institutions or at the first contact with the patient. Participants missing more than one session during MCT were allowed to continue the MCT, but their data were excluded from statistical analysis.

2.2. Trial design

Migraine patients were randomized into two treatment arms. Half of the participants received MCT to learn the appropriate use of medicines (MCT-group). They also received two educational brochures. The first brochure contained most of the topics covered by the MCT, and the second brochure was a supplementary brochure containing educational material about medication for acute therapy and for prophylaxis of migraine. The other half of the participants received only the information brochures (biblio-group), without any additional face-to-face contact. During the course of the study, all patients continued the medical treatment prescribed by their headache specialist. The MCT- and biblio-interventions were conducted in seven German headache centers located all over Germany.

The treatment effect in both treatment arms was analyzed at the end of the MCT (T1), 3 months after the MCT (T2; short-term follow-up) and 1 – 2.5 years (mean 15.7, range 12–30 months) after the end of the MCT (T3; long-term follow-up). Patients kept a 4-week headache diary and completed psychometric instruments at all three evaluation times. Effectiveness was analyzed by comparing the primary and secondary outcome variables within and between the two groups.

2.3. Study assessment

Patients were recruited through newspaper advertisements (70%) or cooperating medical practices (30%). In each of the participating headache centers, all interested patients were invited to an information session held prior to the beginning of the study. During this session, patients' suitability for the study was determined through a diagnostic screening instrument [14]. This was followed by a short interview in which the underlying disease and inclusion/exclusion criteria were checked. Furthermore, the course of the study (Fig. 1) and all psychometric instruments were presented and headache diaries and prepaid envelopes for postal return were handed out to suitable candidates. After the psychometric instruments were returned and the diaries had been filled out for four weeks (T0), inclusion/exclusion criteria were checked once more. Following this, patients were centrally randomized to one of the two treatment arms using the BiAS program [2] and letters informing the patients to which group they were assigned were sent out. Participants in the MCT-group received a written invitation to the

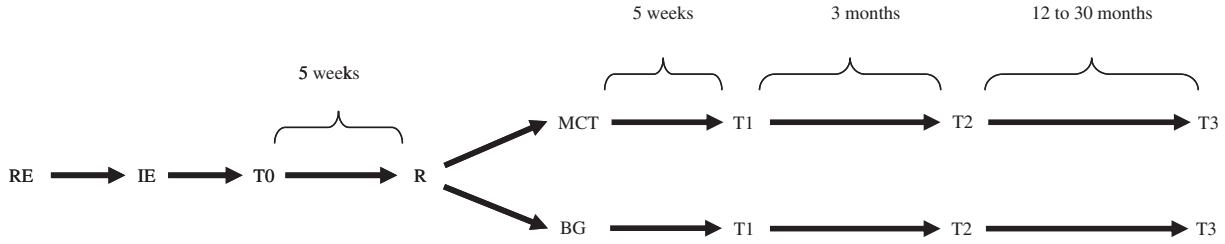

Fig. 1. Study assessment and treatment schedule. RE, recruitment; IE, information evening; T0, measurement at baseline; R, randomization, MCT, minimal contact therapy; BG, biblio-group; T1, measurement immediately after intervention; T2, short-term follow-up-measurement; T3, long-term follow-up-measurement.

first and following treatment session, while participants of the biblio-group received two brochures (information about migraine and medication; description see above). Participants in the biblio-group were instructed to read through the brochures in the following five weeks and answer the questions after each chapter in written form. Additionally, participants in the biblio-group had the opportunity to obtain advice by telephone if they had any questions regarding the brochure. The assessment at the end of the intervention (T1) and the two follow-up-measurements (T2–T3) were conducted again by postal queries.

2.4. Trial interventions

2.4.1. MCT-group

The treatment concept was designed for two general goals: First, it was expected to increase patient's illness-related self-efficacy and accordingly their belief to control the attacks. Second, the treatment should break through the avoidance mechanism which is wide-spread among migraine patients of reducing the fear of a forthcoming attack by early medication (in the sense of avoiding negative reinforcement). The treatment should enable the patients to face rather than avoid the forthcoming situation, including pain and anxiety (in the sense of stimulus confrontation), and to decide in each situation whether non-pharmacological management is possible and appropriate.

To reach these goals, the strategies were (1) to educate and inform patients about concept of MOH, (2) to give them clear guidelines for using medications, (3) to evaluate and address behavioral factors influencing medication consumption, and (4) to teach skills for managing anticipatory fear of migraine attack. To this end, a psychoeducational minimal contact intervention was developed consisting of five sessions with six participants and lasting 2 h (2×50 min plus a 20-min break) each. The MCT was called: "Migraine and medication – which problems can arise and what to do".

The first unit (session) was called "Introduction and syndrome education". Its main components included information about symptoms, pathophysiology and pathopsychology of migraine as well as instructions for progressive muscle relaxation (PMR). During this session, the patients were trained for the first time in PMR. The second unit was called "Medication rules and the risk of Medication Overuse Headache" including information about acute and prophylactic migraine medication and MOH-symptoms and pathomechanisms. A further goal of this second session was to establish a clear behavioral intake algorithm in migraine attack situations, i.e. to develop knowledge about which medication to use in which headache form and when. The third unit was called "Medication intake behavior" aimed at raising awareness for 'external' (e.g. availability of drugs, stock-keeping, iatrogenic risk factors like doctor shopping) and 'internal' (e.g. fear of attack and losing social functioning, stress level in private and professional life) influences on patient's medication intake behavior. The fourth unit was called "general and personal risk factors for drug intake" and established a general risk profile of medication overuse for each patient. The fifth unit was called "everyday transfer" with the aim of establishing individual goals for future drug intake and learning how to make use of social support to control intake behavior. Daily exercise of PMR as well as keeping a daily headache diary had to be performed during the time between all five sessions and after each session, patients were given topic-related homework. At the end of the fifth session, participants of the MCT-group received the brochures given to the biblio-group.

2.4.2. Biblio group

The psychological goals and strategies in the biblio-group were the same as in the MCT-group. The biblio-group was designed as a non-specific treatment group. The participants received two brochures: a detailed brochure as a patient guide with information about physiological and psychological aspects of migraine, MOH and migraine medication. It summarized the topics which were covered by the MCT (see above), written in the style of a self-help manual containing instructions for exercises to minimize drug consumption and instructions for PMR. Each chapter of the brochure ended with questions about the content of the chapter which the patients were to answer. The brochure was called "Migraine and medication – Which problems can arise and what to do".

The second brochure (extended information about migraine medication) contained information material without any exercise instructions. Part one of the brochure described the indication, the pharmacological mechanisms of action and the side-effects of different acute migraine medications, and part two discussed prophylactic medication. Recommendations regarding medication were based on the current 'Medication Guidelines' of the European Federation of Neurological Societies [11].

2.5. Trial sites

The MCT was conducted in seven different and independent headache centers. These centers were outpatient departments of neurology or anesthesiology departments and received standardized written instructions for all MCT-sessions as well as identical sets of treatment material. Each participating center conducted two MCT-groups (2×6 participants) and two biblio-groups (2×6 participants).

2.6. Trainers

The trainers in all seven centers were psychological psychotherapists with special professional education in pain therapy and long-standing experience in the treatment and research of headache syndromes, especially of drug-induced-headache. All trainers participated in a detailed schooling workshop at the coordinating study center in Essen prior to the start of the study.

2.7. Outcome measures

The selection of outcome measures was based on the recommendations of core domains [38] in clinical trials of treatment for chronic pain by the initiative on methods, measurements and pain assessment in clinical trials (IMMPACT I). The selection of psychometric instruments was based on recommendations of the task force in pain diagnosis [9] by the German Chapter of the International Association for the Study of Pain (IASP).

2.7.1. Diary

The primary endpoint of this study was the number of headache medication intake days per month. Secondary endpoints were the number of headache days per month and the pain disability experienced. These variables were assessed using real-time headache diaries. Participants were asked to keep a diary on a daily basis and to record once every evening the presence or absence of headache, their consumption of headache medication and their overall disability due to headache. The daily diary covered the following items: headache (yes/no), migraine (yes/no), tension-type headache (yes/no), mean headache intensity (11-point numerical rating scale (NRS), 0 = no pain and 10 = worst possible pain), mean headache disability (11-point numerical rating scale (NRS), 0 = no disability and 10 = worst possible disability), intake of headache medication (yes/no), type and amount of medication. Diary specifications were to be made for a 4-week period at four measurements (see study design: prior to intervention as well as immediately after that, three months later and 1–2 years later; T0–T3).

2.7.2. Psychometric instruments

Several moderator variables for drug intake behavior were recorded by psychometric instruments prior to as well as immediately after intervention, at short-term follow-up and at long-term follow-up (T0–T3).

2.8. Anxiety and depression

These two core domains in the field of 'emotional functioning' in chronic pain patients (sensu IMMPACT) were assessed using the 'Hospital Anxiety and Depression Scale (HADS)' – German Version [17]. The German HADS is based essentially on the original HADS [42]. It is a self-report rating scale of 14 items (seven items for each subscale) on a 4-point Likert scale (range 0–3). For each subscale, the overall score is generated by the sum of the respective seven item scores (ranging from 0 to 21). The two clinical cut-off scores are 8–10 (= doubtful values) and 11 or higher (= abnormal values). A review of 747 papers [6] revealed that the HADS performs well in assessing the symptom severity of anxiety disorders and depression in both somatic, psychiatric and primary care patients and in the general population.

2.9. Pain acceptance

Acceptance of pain has lately been shown to be an important factor in determining a patient's ability to maintain functioning in the presence of chronic pain. Treatments based on cognitive behavior therapy are beginning to incorporate acceptance strategies. Assessment of acceptance has been facilitated by the development of the Chronic Pain Acceptance Questionnaire (CPAQ). The German adaption of the CPAQ used in this study [31] is based on a revised version of the original English-language instrument CPAQ by McCracken [27,28]. Validation was performed in close cooperation with the original author (translation and re-translation). The German CPAQ is a self-report rating scale of 20 items on a 7-point Likert scale (ranging from 0 = never to 6 = always) containing two subscales. The subscale 'Activity Engagement' (AE; 11 items) refers to the patient's continuation of daily duties and recreation despite persisting pain. The subscale 'Pain Willingness' (PW; nine items) covers the patient's tendency to avoid or control pain. For each subscale, the overall score is generated by the sum of the item scores (11 items resp. 9 items); subscale PW is coded inversely. The maximum score is 66 for the AE-scale and 54 for the PW-scale. The German CPAQ scale is a useful German-language instrument for the measurement of acceptance and shows good psychometric properties. The internal consistency of the total and subscales is 0.84–0.87 (Cronbach's alpha) and the scales are closely related to indicators of psychosocial functioning. Associations with the affective dimension of pain are moderate; association with the sensory dimension is weak.

2.10. Illness-specific locus of control

In the sixties, Rotter [35] defined locus of control as a generalized expectancy concerning the extent to which reinforcements are under internal or external control. People with an external locus of control believe that reinforcements are largely determined by other people, social structures, fate and luck, whereas those with an internal locus of control put more emphasis on personal initiative, ability and effort as the major source of reinforcements. In our study, patients were taught to take account of restrictive rules of drug use. We expected that the medication intake behavior, especially the deliberate restriction of pain medication in doubtful intake situations, would be influenced by the patients' personal initiative and effort, i.e. the internal locus of control. Thus, we used the "Questionnaire for assessment of control beliefs about illness and health" (KKG; German version) as an instrument measuring the illness-specific locus of control [21,22]. Form and content of the KKG are based on the 'Multidimensional Health Locus of Control Scale' (MHLC, [41]) and Rotter's social learning theory. The KKG contains three different subscales: the external (health is controllable by other persons) (EXT), the internal (health is controllable by one's self) (INT) and the fatalistic locus of control (health is not controllable, but dependent on chance or fate) (FATA). Each of the three dimensions is assessed with seven items to be answered on a 6-point Likert scale (range 1 = totally not correct to 6 = totally correct). For each subscale, the overall score is generated by the sum of the respective seven item scores. The statistical values 'objectivity' and 'validity' of the KKG are excellent; retest-reliabilities are between 0.66 and 0.78 and internal consistency between 0.64 and 0.77.

2.11. Pain-related self instructions

It is generally agreed that cognitions are important mediators between pain-evoking situations and emotional or behavioral reactions [e.g. 40]. A number of studies demonstrated that the form of cognitive coping determines responsiveness to treatment and experienced disability of headache patients [e.g. 30]. The assessment of cognitions as an endpoint is a critically important issue in the design, analysis and interpretation of clinical trials in the field of chronic pain [39]. Self-statements are specific cognitive responses to an environmental event (e.g. pain experience), which is guided by underlying cognitive schemata. Their impact on pain behavior is well known [29]. Therefore, Flor et al. [12,13] developed a psychological questionnaire to assess both situation-specific cognitive coping with pain (self-instructions) and the general cognitive schemata. Based on this differentiation, two scales were developed: The pain-related control scale (PRCS) assessing cognitive schemata of pain patients and the pain-related self-statements scale (PRSS) assessing situation-specific cognitive coping with pain. We included the PRSS scale in our study, hypothesizing that the self-statements would correspond to patients' headache experience.

PRSS consists of the 9-item subscales 'Catastrophizing' (CATA) and 'Functional Coping' (FUNC); the maximum score for each scale is 45. The items were introduced as 'typical thoughts of persons in pain'. Patients were to rate the items on a 6-point scale, according to how often a statement entered their mind during severe pain (0 = almost never, 5 = almost always). The 'catastrophizing scale' explained 45% of the total variance and the 'coping scale' explained 30% of the total variance. The subscales correlated −0.37 with each other. Cronbach's alpha as a measure of internal consistency was excellent: 0.92 resp. 0.88. PRSS-Catastrophizing explained a significant amount of depression and pain severity variance. The data demonstrate that the PRSS is a reliable and valid instrument for the assessment of cognitive coping with pain including a very good sensitivity to therapeutic change. The PRSS was also used successfully to examine headache patients and their therapy benefit in a huge German multi-center study [5].

A comparable Anglo–American questionnaire does not exist. Most comparable to the PRSS seems to be the "Coping Strategies Questionnaire" (CSQ) [34], because it contains two subscales, which are similar to the subscales of the PRSS: 'catastrophizing' and 'functional pain behavior'.

2.12. Treatment satisfaction

The patient's satisfaction with the intervention was assessed in a telephone interview three months after the intervention. Patients were to rate their satisfaction with the general treatment, the migraine brochure and the medication brochure using the customary

German school grades ranging from 1 = very good to 6 = very bad. Using the same evaluation range (1–6), patients rated the extent of helpfulness of the treatment in reducing medication intake and whether and to what extent they would recommend the treatment to a friend.

2.13. Sample size calculation

The effect size of the difference in efficacy between the two groups (MCT- and biblio-group) could not be exactly estimated because of missing data. With an α-error at 5% and β-risk at 20% (test power = 80%), the sample size was calculated at $n = 78$ per cell to detect a difference between the groups with a standardized difference of $d = 0.40$ (one-tailed test).

2.14. Statistics

Analysis was conducted by 2×4-factorial analysis of variances with repeated measurements on the factor time (T0–T3) and treatment groups as an independent factor.

The primary outcome 'intake days of headache medication' was analyzed by confirmatory testing. No α-adjustment was necessary because only one test was carried out for confirmatory testing. All other statistical tests (effects of treatment or time or interactions of the two measured by diary or psychometric instruments) were considered as exploratory data analyses and conducted using univariate analysis of variance with repeated measurements.

Several calculations were carried out for drop-out analysis. All individuals who dropped out during the investigation were compared in key control variables with the total group of patients participating further. The control variables were age, sex, diagnosis, disease duration, medication, headache days and medication days per month. This comparison was carried out for the drop-out sample at the measurement times T1, T2 and T3. In addition, these evaluations were performed again separately for the two treatment groups (MCT- and biblio-group).

All analyses were conducted using SPSS software for windows (SPSS 13.0, SPSS Inc., Chicago, IL, USA). The following data are presented as mean ± standard deviation and categorical data are presented as counts. P values $\leqslant 0.05$ were considered to be statistically significant. Statistical analyses of the secondary endpoints were performed without alpha adjustment, and therefore these results are considered mainly exploratory [1].

3. Results

The seven centers included a similar number of patients for the MCT-group and the biblio-group. Participating patients did not change their medical treatment significantly during the study period (T0–T3) (e.g. start of new or change in ongoing prophylactic medication).

3.1. Drop-out analysis

As shown in Fig. S1, 182 patients were recruited. After applying the inclusion and exclusion criteria, 169 patients completed the four-week-headache diary and the psychometric instruments. After repeated verification of the inclusion and exclusion criteria, the remaining 158 patients were randomized to the MCT or biblio-treatment.

MCT-GROUP: 75 of 79 patients finished the complete MCT (five sessions) and the assessment immediately after measurement (T1). Two participants dropped out during the MCT because of illness and further two participants quitted because they missed more than one session. Complete data sets for the short-term follow-up (T2) were available for 71 patients. Four patients did not return the psychometric instruments. The long-term follow-up (T3) was completed by 61 patients; four patients' addresses were unknown and six patients did not fill out the instruments.

BIBLIO-GROUP: 71 of 79 patients underwent bibliotherapy. Eight patients did not accept randomization and withdrew from participation in the study. Two of the 71 patients did not return the instruments after the intervention (T1). Complete data sets were available for the short-term follow-up (T2) from all of the remaining 69 patients. The long-term follow-up (T3) was completed by 59 patients; one patient address was unknown and nine patients did not feel up to filling out the instruments.

Demographic and clinical data of the MCT-group and the biblio-group at baseline (T0) are shown in Table 1 ($n = 150$). Of these 150 patients, 30 patients dropped out between baseline and T3 for different reasons (see Fig. S1). Thus, 120 patients delivered complete data sets from baseline to long-term follow-up. Independent sample t-tests and χ^2-tests compared study drop-outs ($n = 30$) and study completers ($n = 120$). Drop-outs and completers did not differ ($p > 0.05$) in age (mean = 45.6 vs. 48.7 years), gender (90% vs. 83% women), duration of migraine illness (mean = 23.6 vs. 25.7 years), medication (90% vs. 86% using triptans), diagnosis (74% vs. 72% migraine without aura), headache days per month at baseline (mean = 11.6 vs. 10.9 days) and intake days per month at baseline (mean = 7.3 vs. 7.4 days).

Furthermore, we divided the completers of any study phase (T1–T3) in MCT-participants or biblio-participants and compared them to the study drop-outs at any measurement. Independent sample t-tests and χ^2 did not reveal any differences between groups at any time in any observed moderator variable.

3.2. Primary endpoint

As can be seen in Fig. 2, there was no difference in the two intervention groups regarding the number of intake days of headache medication at any of the measurement points. Both the MCT-group and the biblio-group improved significantly ($p < 0.001$) from the time prior to intervention (mean $M = 7.2$; SD = 2.5 and $M = 7.6$; SD = 3.1 days before intervention, respectively) to the short-term follow-up ($M = 5.9$; SD = 3.2 and $M = 6.5$; SD = 3.2 days three months later, respectively) (Table 2). None of the patients exceeded the MOH-limit of 15 analgesic or 10 triptan intake days per month.

Table 1
Demography and clinical features of the MCT and the biblio group at T0 (baseline).

Treatment	MCT	BG
Demography		
n	79	71
Age (years)	47.7 ± 8.9	48.4 ± 10.1
Range	26–68	26–71
Gender		
Men (%)	5 (6)	9 (13)
Women (%)	74 (94)	62 (87)
Clinical features		
Medication		
Mono analgesics (%)	8 (10.1)	8 (11.3)
Combination analgesics (%)	3 (3.8)	3 (4.2)
Triptans (%)	68 (86.1)	60 (84.5)
Diagnosis		
Migraine without aura	54 (68.4)	51 (71.8)
Migraine with aura	3 (3.8)	0 (0)
Migraine with and without aura	22 (27.8)	20 (28.2)
Duration of migraine (years)	26.1 ± 12.9	24.3 ± 11.6
Range	2–50	3–55

MCT, minimal contact therapy.
BG, biblio group.

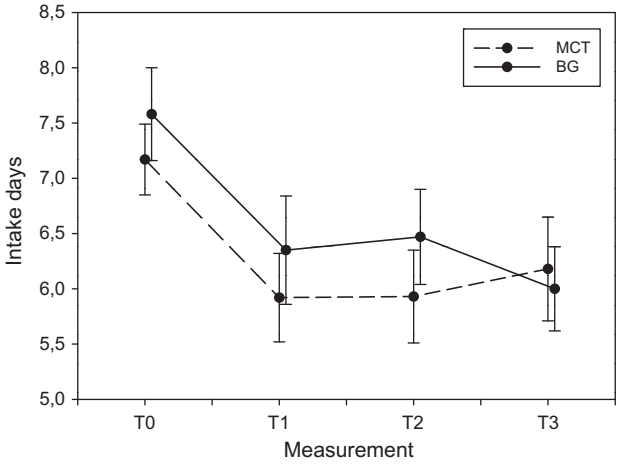

Fig. 2. Medication intake days (mean ± standard error of mean) per month in the minimal contact therapy (MCT) and the biblio-group (BG) before (T0) and directly after (T1) intervention and at 3-months follow-up (T2) and 1–2 years-follow-up (T3).

3.3. Diaries

Intervention groups did not differ significantly on any diary variable at any follow-up time. Both groups improved from the time prior to intervention to the assessment immediately after intervention and achieved unremitting success at short-term and long-term follow-up (Table 2). Headache days, migraine days, medication intake on headache days and intake on migraine days decreased significantly ($p < 0.001$) in both groups. Headache disability did not differ between the groups and did not improve within the groups at any assessment time.

3.4. Psychometric instruments

Psychological variables did not show group differences (Table 3): the psychometric instruments exhibited the same general trend as the diary data. Both groups improved equally and considerably after the treatment on the following psychological variables: better ability to continue everyday duties and activities despite pain (CPAQ-AE; $p < 0.001$), less catastrophizing pain cognitions (FSS-CATA; $p < 0.001$), more functional pain cognitions (FSS-FUNC; $p < 0.001$) and higher belief of internal control over disease and health (KKG-INT; $p < 0.01$) were found. The following variables did not show improvement: avoidance and control of pain (CPAQ-PW), anxiety (HADS-A) and depression (HADS-D), external control belief (KKG-EXT) and fatalistic control belief (KKG-FATA).

3.5. Diaries – post hoc-analyses dividing sample into participants with high and low initial headache frequency

Because of the high degree of standard deviation in the diary variables (see Table 2), we subsequently divided the study sample according to two different criteria: the number of headache days and the number of medication intake days. In both cases, division followed the 50%-distribution of the sample.

First we divided the sample into a group with initially high headache frequency (10–31 days per month) and a group with low headache frequency (3–9 days per month). We carried out an analysis of variance with repeated measurement to analyze headache and intake days for both groups.

Fig. 3 shows the development of headache days for both treatment groups and subgroups over time. It is obvious that patients with high headache frequency improved to a greater extent after treatment in monthly headache days (MCT-group from 14.8 days prior to intervention to 10.8 days at long-term follow-up = 27.0% improvement; biblio-group from 13.7 days prior to intervention to 10.5 days at long-term follow-up = 23.4% improvement; $F = 17.23$, $p < 0.001$) than patients with low headache frequency (MCT-group from 7.0 days prior to intervention to 5.9 days at long-term follow-up = 15.7% improvement; biblio-group from 7.0 days prior to intervention to 6.0 days at long-term follow-up = 14.3% improvement; $F = 3.89$ $p = 0.016$).

The same tendency could be seen in the frequency of medication on headache days: Patients with high headache frequency

Table 2
Results of 2 × 4 analysis of variance with the factors 'treatment' (MCT/BG) and 'repeated measurement' (T0–T3) for the diary variables.

Variable (n = MCT vs. BG)	Measure	MCT M (SD)	BG M(SD)	Analysis of variance			
				F-value	Time effect	Group effect	Group × time
Headache days (n = 60 vs. 55)	T0	11.40 (5.92)	10.51 (4.98)	$F = 20,03$	$p < 0.001^{***}$	n.s.	n.s.
	T1	9.17 (5.45)	8.47 (5.54)				
	T2	8.55 (5.51)	8.11 (4.82)				
	T3	8.68 (5.29)	8.33 (5.15)				
Migraine days (n = 60 vs. 55)	T0	7.23 (3.70)	7.27 (3.82)	$F = 10,10$	$p < 0.001^{***}$	n.s.	n.s.
	T1	5.60 (3.79)	5.78 (4.01)				
	T2	6.15 (3.97)	5.45 (3.16)				
	T3	6.15 (4.02)	5.84 (3.76)				
Headache disability (n = 59 vs. 55)	T0	4.46 (1.80)	4.16 (1.56)	$F = 0,24$	n.s.	n.s.	n.s.
	T1	4.49 (2.01)	4.13 (1.97)				
	T2	4.61 (1.97)	4.25 (1.88)				
	T3	4.39 (2.16)	4.40 (1.73)				
Intake at headache days (n = 60 vs. 55)	T0	7.17 (2.48)	7.58 (3.11)	$F = 7,74$	$p < 0.001^{***}$	n.s.	n.s.
	T1	5.92 (3.10)	6.35 (3.66)				
	T2	5.93 (3.23)	6.47 (3.20)				
	T3	6.18 (3.65)	6.00 (2.82)				
Intake at migraine days (n = 60 vs. 55)	T0	5.27 (2.25)	6.25 (2.98)	$F = 6,54$	$p < 0.001^{***}$	n.s.	n.s
	T1	4.30 (2.76)	5.04 (3.11)				
	T2	4.83 (3.00)	4.75 (2.82)				
	T3	5.03 (3.52)	5.02 (2.78)				

Treatments: MCT, minimal contact therapy; BG, biblio group.
Measurements: T0, before treatment; T1, directly after treatment.
T2, follow-up 3 months after treatment; T3, follow-up 1–2 years after treatment.
M, mean; SD, standard deviation; *F*-value, value of analysis of variance.

Table 3
Results of 2 × 4 analysis of variance with the factors 'treatment' (MCT/BG) and 'repeated measurement' (T0–T3) for the psychometric variables.

Variable (n = MCT vs. BG)	Measure	MCT M (SD)	BG M (SD)	Analysis of variance			
				F-value	Time effect	Group effect	Group × time
CPAQ-AE (n = 59 vs. 57)	T0	31,30 (10,44)	30,22 (8,47)	F = 18.684	p < 0.001***	n.s.	n.s.
	T1	34,76 (10,59)	33,51 (9,52)				
	T2	34,56 (10,85)	34,88 (9,39)				
	T3	35,50 (10,76)	34,38 (9,41)				
CPAQ-PW (n = 59 vs. 57)	T0	25,90 (10,05)	26,72 (8,78)	F = 2,45	p = 0.091	n.s.	n.s.
	T1	24,54 (17,04)	25,80 (11,07)				
	T2	22,52 (8,85)	23,41 (7,96)				
	T3	26,76 (9,59)	25,21 (7,62)				
FSS-CATA (n = 60 vs. 58)	T0	28,18 (7,95)	27,24 (6,40)	F = 19.31	p < 0.001***	n.s.	n.s.
	T1	24,81 (7,21)	26,34 (13,74)				
	T2	24,20 (7,30)	25,53 (7,29)				
	T3	21,42 (10,34)	22,10 (8,52)				
FSS-FUNC (n = 60 vs. 58)	T0	27,96 (6,30)	27,92 (5,84)	F = 9.787	p < 0.001***	n.s.	n.s.
	T1	31,27 (6,01)	29,74 (5,51)				
	T2	34,15 (14,66)	29,83 (6,14)				
	T3	29,51 (7,29)	29,18 (6,27)				
HADS-A (n = 60 vs. 57)	T0	5,90 (1,91)	5,84 (2,49)	F = 1.350	p = 0.257	n.s.	n.s.
	T1	6,70 (2,53)	6,51 (2,22)				
	T2	6,18 (2,31)	6,35 (2,24)				
	T3	5,87 (3,75)	6,19 (4,09)				
HADS-D (n = 60 vs. 57)	T0	4,40 (1,55)	4,56 (1,07)	F = 0.646	p = 0.462	n.s.	n.s.
	T1	4,65 (1,16)	4,54 (1,18)				
	T2	4,78 (1,17)	4,75 (1,30)				
	T3	4,77 (4,18)	4,91 (3,99)				
KKG-INT (n = 60 vs. 58)	T0	24,71 (5,79)	24,36 (4,55)	F = 4,105	p = 0.009**	n.s.	n.s.
	T1	26,23 (4,51)	24,50 (4,73)				
	T2	26,18 (5,31)	25,11 (4,37)				
	T3	26,30 (4,30)	25,20 (4,90)				
KKG-EXT (n = 60 vs. 58)	T0	20,78 (4,88)	21,48 (4,54)	F = 0,277	p = 0.822	n.s.	n.s.
	T1	20,98 (5,35)	20,90 (5,22)				
	T2	21,02 (5,74)	21,19 (5,10)				
	T3	20,98 (5,47)	20,72 (6,80)				
KKG-FATA (n = 60 vs. 58)	T0	17,67 (6,69)	19,29 (6,23)	F = 0,344	p = 0.783	n.s.	n.s.
	T1	17,97 (6,31)	19,29 (7,20)				
	T2	16,80 (6,32)	19,52 (6,09)				
	T3	18,45 (6,73)	18.35 (6,54)				

Treatments: MCT, minimal contact therapy; BG, biblio group.
Measurements: T0, before treatment; T1, directly after treatment.
T2, follow-up 3 months after treatment; T3, follow-up 1–2 years after treatment.
M, mean; SD, standard deviation; *F*-value, value of analysis of variance.
CPAQ-AE, subscale 'activity engagement' of the "Chronic Pain Acceptance Questionnaire" (CPAQ).
CPAQ-PW, subscale 'pain willingness' of the "Chronic Pain Acceptance Questionnaire" (CPAQ).
FSS-CATA, subscale 'catastrophising cognitions' of the "Pain-related self instructions" (FSS).
FSS-FUNC, subscale 'functional cognitions' of the "Pain-related self instructions" (FSS).
HADS-A, subscale 'anxiety' of the "Hospital anxiety and depression scale" (HADS).
HADS-D, subscale 'depression' of the "Hospital anxiety and depression scale" (HADS).
KKG-INT, subscale 'internal control' of the "Illness-specific locus of control" (KKG).
KKG-EXT, subscale 'external control' of the "Illness-specific locus of control" (KKG).
KKG-FATA, subscale 'fatalistic control' of the "Illness-specific locus of control" (KKG).

reduced their intake of headache medication much more than patients with low initial headache frequency (MCT-group from pre = 8.1 to long-term follow-up = 6.8; biblio-group from pre = 9.6 to long-term follow-up = 6.9; F = 7.36, p < 0.001) than patients with low headache frequency (MCT-group from pre = 5.9 to long-term follow-up = 5.4; biblio-group from pre = 5.4 to long-term follow-up = 5.0; F = 2.46 p = 0.074).

3.6. Diaries – post hoc-analyses dividing the sample into high and low medication intake frequency

Secondly, we divided the sample into a group with initially high intake frequency of medication (7–15 days per month) and a group with low intake frequency (3–6 days per month). Fig. 4 shows the development of intake days for both treatment groups and subgroups over time. Again it is obvious that patients with high intake frequency improved to a greater extent after treatment regarding monthly intake days (MCT-group from 9.1 days prior to intervention to 7.0 days at long-term follow-up = 23.1% improvement; biblio-group from 9.7 days prior to intervention to 6.7 days at long-term follow-up = 30.9% improvement; F = 12.61, p < 0.001). Patients with low intake frequency did not improve (MCT-group from 5.1 days prior to intervention to 5.3 days at long-term follow-up = 3.9% impairment; biblio-group from 4.7 days prior to intervention to 5.0 days at long-term follow-up = 6.4% impairment; F = 0.31, n.s.).

The same tendency was observed with regard to headache frequency: Patients with high intake frequency improved to a greater extent after treatment (MCT-group from pre = 14.1 to long-term follow-up = 10.6; biblio-group from pre = 12.6 to long-term follow-up = 9.4; F = 17.63, p < 0.001) than patients with low intake frequency (MCT-group from pre = 8.5 to long-term follow-up = 6.6;

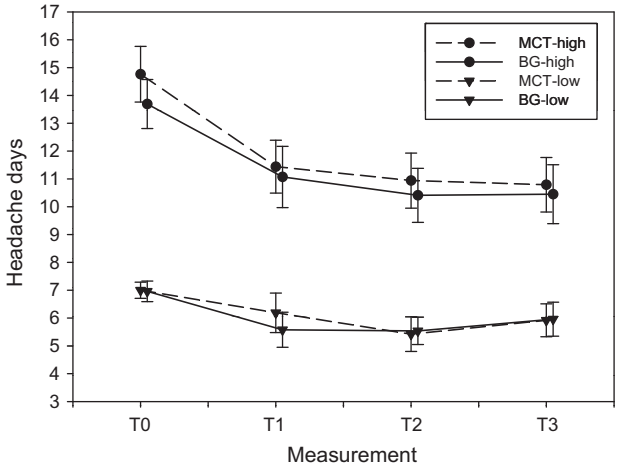

Fig. 3. Headache days (mean ± standard error of mean) per month in the minimal contact therapy (MCT) and the biblio-group (BG) before (T0) and directly after (T1) intervention and at 3-months follow-up (T2) and 1–2 years-follow-up (T3) and differentiated for patients with initially high (10–31 headache days per month) and low headache frequency (3–9 headache days per month). MCT-high = patients in the minimal contact therapy with high headache frequency. BG-high = patients in the biblio-group with high headache frequency. MCT-low = patients in the minimal contact therapy with low headache frequency. BG-low = patients in the biblio-group with low headache frequency.

biblio-group from pre = 7.7 to long-term follow-up = 6.8; $F = 3.44$ $p = 0.020$).

3.7. Treatment satisfaction

Finally, we assessed the patient's satisfaction with the treatments using a separate questionnaire. Only 103 patients provided statements. Table 4 shows the appraisals of both groups: Patients in the MCT-group were generally more satisfied with the treatment ($M = 1.7$; SD = 0.6) than patients in the biblio-group ($M = 2.8$; SD = 1.0) ($p < 0.001$). While the migraine brochure elicited more satisfaction in the MTC-group ($p = 0.001$) than in the biblio-group, the medication brochure ($p = 0.056$) met with equal satisfaction in both groups. Patients in both groups rated the interventions as very helpful for reducing their medication intake frequency, but the MCT-group rated the intervention significantly more helpful than the biblio-group ($p < 0.001$). Similarly, patients in the MCT-group agreed to a greater extent to the question whether they would recommend the treatment to a friend or relative ($p < 0.001$).

Analyzing the relation between general treatment satisfaction and improvement in intake days or in headache days revealed no significant correlation for any treatment condition or for the total sample ($p > 0.05$).

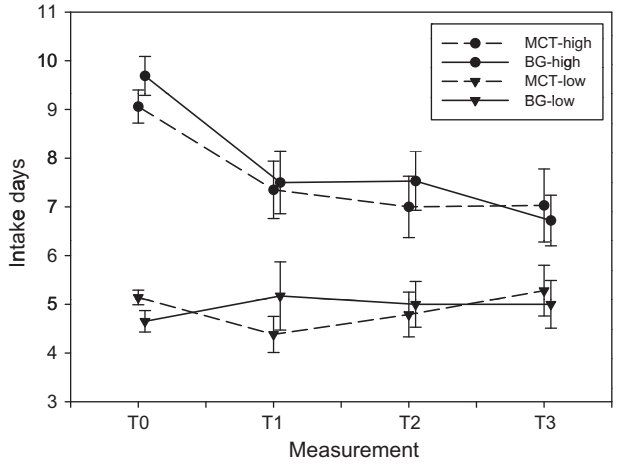

Fig. 4. Medication intake days (mean ± standard error of mean) per month in the minimal contact therapy (MCT) and the biblio-group (BG) before (T0) and directly after (T1) intervention and at 3-months follow-up (T2) and 1–2 years-follow-up (T3) and differentiated for patients with initial high (7–15 intake days per month) and low intake frequency (3–6 intake days per month). MCT-high = patients in the minimal contact therapy with high intake frequency. BG-high = patients in the biblio-group with high intake frequency. MCT-low = patients in the minimal contact therapy with low intake frequency. BG-low = patients in the biblio-group with low intake frequency.

4. Discussion

Our study presents a very effective and cost-saving program that prevents MOH in a high-risk population. During the observation period lasting up to two years, no patient of the study sample, regardless of treatment arm, developed MOH. In contrast, the number of medication days was reduced from one to 10 days less than at baseline in 54% of all patients at short-term follow-up. Furthermore, 18% of all patients suffering from migraine remained stable and only 17% worsened, reporting one to five more days of medication. The mean reduction of drug intake days was 1.5 days.

Our primary hypothesis was confirmed. Due to the relationship between medication overuse and chronicity of headache [e.g. 20,23], we expected not only a reduction of medication intake but also a reduction of headache days: from baseline to short-term follow-up, 72% of all patients improved by one to18 fewer headache days, 9% remained stable and 13% worsened by one to five more headache days per month. The mean headache reduction was 2.5 days per month.

Our study should be discussed in light of the findings in two earlier studies, showing a benefit of combined pharmacological and behavioral treatment after drug withdrawal in patients with MOH. Altieri et al. [3] studied 26 MOH patients with migraine as primary headache over a period of 12 months. Half of the patients underwent psychoanalysis-based psychotherapy combined with medication during detoxification. Patients showed much better results in headache parameters compared to patients receiving pharmacological mono-therapy. However, the study had some methodological limitations, e.g. the small sample size (13 per group) and unrandomized procedures; patients were assigned to one of the treatment conditions based on the psychologist's opinion about patient's compliance with the psychotherapeutic intervention. Grazzi et al. [16] compared the benefit of combined medication and biofeedback to drug treatment alone in 61 MOH patients. Both groups showed similar improvements, lasting up to one year. However, three years after the intervention, the patients in the combined treatment group showed significantly greater improvement than the drug-treated patients. This result was limited by a selection bias due to skewed randomization. Furthermore, the interventions were not standardized and were not administered in a multi-center design.

The strength of our study was the high control of potential bias. A possible therapist bias was controlled by the multi-center design and central schooling of all therapists. Also, the therapists were all psychotherapists and had long-standing experience in psychological treatment of headache syndromes. The interventions were highly standardized and identical standardized and validated materials and manuals were used by all centers. A possible patient bias was controlled by the inclusion of patients from primary care settings. Randomization bias was minimized by strict central assignment of patients to the treatment arm. A possible medication bias was controlled by documentation of drug intake during the whole study period.

The present study examined the additional effectiveness of interactive education over exclusive biblio-education. But we

Table 4
Comparison (*t*-tests, unpaired samples) of the patient's satisfaction between the MCT and the biblio group with the treatment satisfaction expressed in six German school grades (1 = very good up to 6 = very bad).

Variable	MCT (n = 51) M (SD)	BG (n = 52) M (SD)	p
General evaluation of treatment	1.71 (0.58)	2.81 (1.03)	<0.001
Satisfaction with the migraine broschure	1.49 (0.54)	1.92 (0.76)	<0.001
Satisfaction with the medication broschure	1.65 (0.54)	1.92 (0.84)	n.s.
Treatment is helpful for reducing medication intake	1.90 (0.61)	2.58 (0.78)	<0.001
Recommendation of treatment to a friend	1.04 (0.20)	1.46 (0.73)	<0.001

Treatments: MCT, minimal contact therapy; BG, biblio group.
M, mean; SD, standard deviation; *p*, *p*-value.

found similar improvements in both treatment groups and in all parameters at each of the measurement times. The following may explain why patients in the biblio-group got so involved in the study and why they benefited:

1) We strengthened the biblio-treatment arm by using highly-elaborated material.
2) We conducted regular written examinations of the educational contents to control the learning success (knowledge check in both treatment groups once a week; five in total).
3) We promised all treated patients personal feedback of their individual treatment success, if wanted.
4) It is possible that five training MCT-session are not sufficient to achieve a superiority over the bibliotherapy.
5) The selected recruitment may have led to the effect that highly-motivated patients felt addressed by this offer. Many interventions have been shown to be very effective in highly-motivated patients, even those approaches that require a high degree of initiative, like the bibliotherapy in our design. Other results may be expected in standard care, which should be clarified in subsequent studies.

However, the outcomes between the MCT-group and the biblio-group were not similar for all variables. The MCT-patients reported a higher rate of satisfaction and perceived the intervention as more helpful than patients in the biblio-group.

The analysis of psychological variables paralleled the results of diary data: Both groups benefited from the treatment regarding pain acceptance (CPAQ), cognitive coping with pain (FSS) and internal control of pain (KKG) and maintained their improvement for months or years (long-term follow-up: 12–30 months). None of the psychological variables correlated significantly with changes in diary variables at any of the measurement times. Therefore, a causal relationship between diary and psychological variables cannot be assumed.

Level of depression or anxiety remained uninfluenced regardless of treatment at each of the follow-ups. This was unexpected because depression and anxiety are regarded as the most important psychosocial factors in episodic migraine becoming chronic [e.g. 10]. Actually, lowering headache days ("de-chronification"), as was achieved in our study, should have improved feelings of 'loss of control' and therefore consequently of depression and anxiety. Presumably this did not happen, because patients in the MCT (5.9 resp. 4.4) as well as in the biblio-group (5.8 resp. 4.6) showed inconspicuous anxiety and depression values in HADS at T0 (critical cut-off for both constructs: >7 = questionable and >9 = conspicuous).

Dividing the participants into two groups showed that the benefit was greater for patients with high headache frequency and for patients with high intake frequency. Regression to the mean may play a role. The more headache or intake days a patient has, the more potential he or she has to improve.

Our evaluations are based on an analysis-per-protocol (APP) and not on an intention-to-treat analysis (ITT). This raises the question whether the approach leads to false results due to different drop-out characteristics in the two groups and could thus mean a violation of randomization. Since the number of drop-outs is nearly equal in the two treatment groups and the analysis of control variables (age, sex, duration of migraine illness, medication, diagnosis, headache and intake days per month at baseline) did not reveal any differences between the two drop-out groups, any such violation should not have affected our main results. Psychotherapy is an incremental process over several weeks. Consequently, the last observation for patients, who quit earlier, will indicate more pain than that of patients, who drop-out just before the end of the study. The ITT method of 'carrying forward the last observation' might result in outcomes which depend extremely on the time at which the patient left the study. Patients who realize after the first week of bibliotherapy that they are members of a non-active-treatment group may leave earlier and therefore will have higher pain scores than patients in the active treatment group.

There are some shortcomings in our study:

(1) We compared two specific active treatments. Further studies should include a third treatment group containing unspecific interventions, e.g. muscle relaxation, to assess the effects of unspecific and specific interventions.
(2) The improvements in both groups did not reach clinical relevance until we analyzed patients with high and low headache burden separately.
(3) The FSS and KKG results suggested the importance of pain coping in the process of headache improvement, but we did not include a comprehensive coping instrument.
(4) We expected that internal control beliefs lead to better medication management and a better result of treatment than external control beliefs and therefore used the KKG. But in hindsight, we would state that an instrument measuring not only control but also competence beliefs, i.e. self-efficacy would be a more appropriate choice for observing patients' pain-coping behavior.

5. Conclusion

In this study, both MCT- and bibliotherapy proved to be beneficial for migraine patients with a high-frequency of attacks. None of the patients developed MOH and the vast majority were able to reduce their medication intake days throughout the study period. In conclusion, the treatment can prevent medication overuse in patients at risk. Furthermore, almost all patients experienced significantly fewer headache days per month then before study participation, suggesting that both treatment forms seem effective in preventing headache chronification. The beneficial effect was greater in patients with a high rather than a low headache frequency. Moreover, those patients who benefit from treatment do so on a long-term basis. The positive impact of the treatment, in terms of less headache and fewer intake days, remained effective

for up to 2 years. This significant clinical improvement could be achieved by written education; however, patients were more satisfied with personal psychological treatment (MCT). Therefore, MCT plus a brochure should be the first choice in preventing and treating MOH in migraine patients.

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Conflict of interest

There are no conflicts of interest associated with this study.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2010.07.032.

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