Chapter 8

Withdrawal therapy in medication overuse headache in General Practice

Submitted

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Abstract

We evaluated the effect of a proactive approach by General Practitioners (GP) of patients with medication overuse headache (MOH) to advise withdrawal. Patients received either 1) an invitation from their GP to visit the practice where withdrawal was advised, or 2) a letter with a discontinuation advice. We compared both interventions to a usual care control group and to outpatients of a university headache centre. Primary outcome measures were success of withdrawal after 3 months and reduction of headache frequency to ≤ 8 days per month after 6 months. Randomisation was done on practice level. In the direct contact group 27 of 79 (34%) patients responded to the invitation, and 21 (27%) consented in withdrawal. Only four of 21 (19%) participants actually discontinued their medication. In the letter group, five of 47 (11%) patients who received the letter actively reported discontinuation. After 6 months, improvement of headache was reported by two of 21 (10%) participants in the direct contact group, 13 of 47 (28%) in the letter withdrawal group, and six of 68 (9%) in the usual care group. Of the 25 referred patients, 22 (88%) reported successful withdrawal after 3 months and seven (28%) improvement after 6 months. We conclude that a direct contact approach by the GP of patients with MOH to advise withdrawal is not effective. A letter with a discontinuation advice seems to be more effective. The perceived need for treatment and compliance is low in non-consulting patients with MOH in the general population.
**Introduction**

Clinical observation suggests that overuse of analgesics and triptans increases headache frequency in susceptible patients, leading to chronic frequent headache (CFH). Chronic frequent headache is a collective term for primary headaches occurring on more than 14 days per month for at least 3 months, often referred to as Chronic Daily Headache. The prevalence is around 4% worldwide. Overuse of acute headache medication is considered the most important risk factor of CFH. The revised International Classification of Headache Disorders (ICHD-II) now includes clinical criteria for Medication Overuse Headache (MOH). A causal relationship between overuse and chronification of headache is assumed because discontinuation of overused medication results in improvement of headache in the majority of patients. There are however no placebo-controlled trials demonstrating efficacy of drug withdrawal, and spontaneous decrease of headache frequency has also been observed in general population surveys. Most information on the effect of withdrawal comes from headache clinics with selected and motivated patients, while the majority of MOH patients are to be found in the general population.

The aim of this study was to evaluate the effect of a proactive approach by GPs of patients with MOH to advice withdrawal. Because patients mostly overuse over-the-counter analgesics and do not consult their GP regularly for headaches, GPs are usually unaware of medication overuse in their patients. Hence, eligible patients had to be identified by a general health survey. We compared two types of active approach by the GP: 1) an invitation to the practice where the intervention (abrupt outpatient withdrawal without replacement therapy) was explained, and 2) a letter from the GP advising patients to abruptly discontinue overuse, without further consultation or replacement therapy. Abrupt outpatient withdrawal has been shown to be effective in analgesic abusing migraineurs seen at specialized headache clinics. The discontinuation letter approach has been applied successfully in long-term benzodiazepine users in family practice. Both interventions were compared to a usual care control group and to abrupt withdrawal in outpatients consulting a university headache centre.
Chapter 8

Methods

General practice

We identified subjects with CFH from a general health survey conducted in 16 general practices in The Netherlands in 2003. CFH was defined as headache on > 14 days per month during three months. We sent a short questionnaire (Q1) to all registered persons aged 25 – 55 years to screen for headache frequency. This sample represents the general population because in The Netherlands almost all persons are registered at a single general practice.

Subjects with CFH received a second detailed questionnaire (Q2) on headache characteristics and medication use. The study design and methodology have been described in detail elsewhere. Of the 246 subjects with CFH, 200 (81%) overused acute headache medication and/or caffeine products. This study was conducted before the publication of the revised IHS criteria for MOH in 2005. We defined overuse as: use of analgesics on ≥ 3 days/week, triptans on ≥ 2 days/week, ergots on ≥ 1 day/week, narcotics on ≥ 10 days/month, and/or use of > 5 cups of caffeine containing beverages a day. Compared to the new IHS criteria, more patients are classified as overusers with our criteria, mainly because of the caffeine overuse subgroup. Caffeine overuse is still an experimental category in the revised ICHD-II.

CFH subjects with medication and/or caffeine overuse were allocated into three trial arms: 1) direct contact, 2) discontinuation letter, and 3) usual care. We randomized on general practice level by drawing practice numbers from a box. Subjects in the direct contact group were invited to participate in a study on treatment of chronic headaches. Interested subjects could make an appointment with their GP. Because abrupt withdrawal of medication needs careful explanation and motivation, the exact treatment plan was not revealed until the first visit: three months of abrupt withdrawal, followed by re-evaluation of headache type. If necessary, prophylactic therapy would be started according to the treatment guidelines of the Dutch General Practitioners' Association. The letter group received a letter from their GP stating that chronic headaches could be caused by overuse of analgesics and caffeine. Subjects were advised to abruptly discontinue analgesic and caffeine use for three months. It was explained that withdrawal usually leads to withdrawal symptoms with an increase of headache, but is then followed by an improvement of headache. They received an invitation for an appointment with their GP after three months to evaluate their headaches. The usual care group was not contacted. In the letter withdrawal group and the usual care group all subjects
received a third questionnaire (Q3) after six months to measure outcome. In the direct contact group only subjects who attended visit 1 and had started withdrawal received Q3.

**Outpatient neurology clinic**

To provide evidence that abrupt withdrawal can be effective in an outpatient setting, we compared the results of withdrawal in the GP setting to those at the headache centre of the outpatient neurology clinic of Leiden University Medical Centre (LUMC). Consecutive patients with CFH and medication and/or caffeine overuse who were referred to our clinic were invited to participate in the study. The need for abrupt withdrawal was carefully explained and patients were motivated in the same way as in the direct contact group in general practice. Patients returned for visit 2 after three months, in which headache was evaluated and prophylaxis started if necessary. During the three month withdrawal period they received no supportive medication or help. Participating patients completed Q2 at baseline and Q3 after 6 months to measure outcome.

**Outcome measures**

Primary outcome measures were success of withdrawal and improvement of headache. Withdrawal was considered successful if subjects reported use of acute headache medication and caffeine on less than 3 days in total during the withdrawal period of 3 months. Improvement of headache was defined as a headache frequency of \( \leq 8 \) days per month after 6 months. Secondary outcome measure was reduction of headache related disability.

We assessed the impact of headache on daily life and disability by the Headache Impact Test (HIT-6). This is a validated questionnaire consisting of six items that cover various content areas of health-related quality of life: pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress. Answers are given on a five-point scale ranging from "never" to "always", each answer counts for 6, 8, 10, 11, or 13 points respectively. All items are summed to a total HIT-6 score that ranges from 36 to 78. Higher scores indicate a greater impact, with scores of 49 or lower reflecting "little or no impact" and above 60 "severe impact".
Statistical analysis

Statistical analysis was performed with SPSS, version 12.01. Differences between groups are presented with 95% confidence intervals (95% CI). One-way ANOVA was used to compare continuous variables between groups, and chi-square test for categorical variables. Paired samples t-test was used to compare continuous variables between baseline and after treatment. We analysed according to the intention-to-treat principle. We used last-observation-carried forward method to fill in missing values.

The Medical Ethics Committee of the Leiden University Medical Center approved the study.

Results

General practice

Six practices were randomised into the direct contact arm (number of CFH patients = 79), five into letter withdrawal (n = 47), and five into usual care (n = 68). Demographic characteristics of subjects in the three treatment arms are presented in Table 1. There were no relevant differences in demographic variables between treatment arms. Only 53 (28%) of all CFH subjects had consulted their GP for headaches in the past six months. Medication overuse consisted mainly of over-the-counter analgesics. Only five patients overused triptans.

Table 1 Demographic characteristics by treatment arm

<table>
<thead>
<tr>
<th></th>
<th>General Practice</th>
<th>LUMC</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Direct contact N = 79</td>
<td>Letter N = 47</td>
</tr>
<tr>
<td>Age, y (SD)</td>
<td>44 (9)</td>
<td>41 (9)</td>
</tr>
<tr>
<td>Female</td>
<td>58 (77)</td>
<td>30 (64)</td>
</tr>
<tr>
<td>Low education</td>
<td>32 (41)</td>
<td>14 (30)</td>
</tr>
<tr>
<td>Medication overuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analgesics</td>
<td>58 (73)</td>
<td>36 (77)</td>
</tr>
<tr>
<td>Triptans</td>
<td>1 (5)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Caffeine overuse</td>
<td>50 (63)</td>
<td>32 (68)</td>
</tr>
</tbody>
</table>

Values are n (%) unless stated otherwise. LUMC: outpatient neurology clinic at Leiden University Medical Centre.
Flow of patients in the trial is shown in Figure 1. In both the direct contact and the letter withdrawal group only one third responded to an invitation for treatment of chronic headaches. In the direct contact group 21 subjects started withdrawal. Mean number of headache days per month was 21 (SD 8). The number of drop-outs in the direct contact group was high: only five patients returned for visit 2 after three months, four reported successful withdrawal. In the letter withdrawal group five of fourteen patients who showed up for visit 1 reported successful withdrawal at t = 3 months. Six patients attempted, but did not succeed in withdrawal. Three did not even try because they did not believe it would help them.

At t = 6 months, Q3 was completed by 11/21 patients (52%) in the direct contact group, 27/47 patients (57%) in the letter withdrawal group and by 44/68 (65%) in the usual care group. Assuming that non-respondents had no improvement of headache, improvement to ≤ 8 headache days per month was reported by two of 21 (10%) patients in the direct contact group, and by six of 68 (9%) patients in the usual care group (difference 1%, 95% CI -11 to 20), and thirteen of 47 (28%) in the letter withdrawal group, a difference of 19% (95% CI 5 to 34) with usual care.

HIT scores at baseline and at t = 6 months are presented in Table 2. Using last observation carried forward, HIT scores decreased 0.6 (SD 3.8) in the direct contact group and increased 0.9 (SD 4.0) in the usual care group, mean difference in change 1.5 (95% CI -2.8 to -0.2). In the letter withdrawal HIT scores decreased 0.9 (SD 3.2), difference in change with usual care -1.8 (95% CI -3.2 to -0.4).

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Direct withdrawal</th>
<th>Letter withdrawal</th>
<th>Usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>n = 78</td>
<td>n = 47</td>
<td>n = 67</td>
</tr>
<tr>
<td></td>
<td>62 (6)</td>
<td>62 (6)</td>
<td>59 (7)</td>
</tr>
<tr>
<td>At 6 months</td>
<td>n = 11</td>
<td>n = 27</td>
<td>n = 44</td>
</tr>
<tr>
<td></td>
<td>61 (10)</td>
<td>61 (7)</td>
<td>60 (5)</td>
</tr>
</tbody>
</table>

Table 2 HIT scores in General Practice

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Direct withdrawal</th>
<th>Letter withdrawal</th>
<th>Usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Direct-Usual (95% CI)</td>
<td>Letter-Usual (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.8 (0.6 to 5.0)</td>
<td>2.7 (0.2 to 5.1)</td>
<td></td>
</tr>
<tr>
<td>At 6 months</td>
<td>0.6 (-3.7 to 5.0)</td>
<td>0.4 (-2.5 to 3.4)</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean (SD) unless stated otherwise.
Outpatient neurology clinic

Of 36 eligible patients, 25 participated in the study and completed Q2. Characteristics are presented in table 1. Mean number of monthly headache days was 24 (SD 6). Main differences with the GP patients were the higher educational level in LUMC patients and the overused medication. Nine patients (36%) overused triptans only, 12 (48%) analgesics only, and four (16%) both. Seven subjects (28%) also overused caffeine. Flow of patients is shown in Figure 1. Of the 25 participants, 22 returned for visit 2; 21 succeeded and one did not succeed in withdrawal. Of the three patients who did not return, two did not succeed in withdrawal and one did. Thus, of the 25 patients who started withdrawal, 22 (88%) indeed succeeded in withdrawal. Eighteen patients completed Q3 at t = 6 months, of whom seven (39%) reported improvement to ≤ 8 headache days per month, which is 28% of all participants.

HIT score at baseline (n = 25) was 66 (SD 5). At t = 6 months, the 18 respondents had a mean HIT score of 64 (SD 4), a mean decrease of 3.3 (95% CI 1.3 to 5.3). Using last observation carried forward, mean decrease of HIT score at t = 6 months was 2.4 (95% CI 0.9 to 3.9) in the total group. HIT scores decreased 5.3 points in patients who improved (n=7) and 2.1 points in those who didn’t (n=11), mean difference in change -3.2 (95% CI -7.1 to 0.7).

Discussion

This study shows that an active approach by GP’s to identify patients with CFH and analgesic overuse and invite them to the practice for a discontinuation advice has no beneficial effects. Two important conclusions can be drawn from this study. First, the perceived need for treatment is low if patients do not consult their GP for headache; even though the impact of headache is high, only one third responded to an invitation for treatment for chronic headaches. Secondly, when patients are informed about medication overuse headache and are advised to discontinue their medication, most of them will not comply. This is in contrast to patients who are referred to the neurology clinic where most patients comply with abrupt outpatient withdrawal. The difference in compliance is probably due to difference in motivation.
Medication overuse headache has characteristics of substance dependence disorders. Drop-outs and relapse are common problems in studies on modification of addictive behaviours. Prochaska and DiClemente have done extensive research on self-initiated and professionally facilitated change of addictive behaviours and constructed a Stages of Change model. The circle of motivation is shown in Figure 2. Individuals modifying addictive behaviour move through a series of stages from precontemplation to maintenance. Precontemplation is the stage at which there is no intention to change behaviour. These people are unaware of their problems and show resistance to recognizing a problem. They only consult therapists under pressure from others. In the contemplation stage, they are aware of their problem, weighing the pros and cons of the problem and are thinking about overcoming it. Preparation is a stage that combines intention and behaviour. They have made some reductions, such as smoking five cigarettes less, but have not yet reached full abstinence. They are intending to take real action in the next month. Action is the stage in which individuals truly modify their behaviour. This stage requires considerable commitment of time and energy. After action comes maintenance. This is the stage in which people work to prevent relapse and consolidate the gains attained during action. Two important implications can be derived from this model. First, relapse is part of modifying addictive behaviours. Individuals typically recycle through the stages several times before achieving long-term maintenance. Secondly, interventions should be tailored according to the stage of readiness to change of the patient. When action-
oriented treatment programs are offered to patients who are not in the action stage, only small numbers will be interested in joining and large numbers will drop out of the program after registering. Several self-help programs have been launched for smoking cessation with great publicity, and have typically recruited only 1-5% of eligible smokers. The vast majority of addicted people are not in the action stage.

If we assume that MOH is a behavioural disorder, we could speculate that non-consulting patients, who are actively approached by their GP to discuss withdrawal, will not comply because they are in the precontemplation stage. General public information about medication overuse headache could move medication overusers into the contemplation stage. Consulting patients in primary care can move from contemplation into preparation stage. Most patients, however, like to be referred to a specialist to make sure that their headaches are not secondary before they are convinced that medication overuse is the key problem and that they are the only ones who can change this. The neurologist will therefore see more patients who are in the preparation stage and are willing to take action. Key feature of treatment will be motivating patients into the action stage and keeping patients in the maintenance stage by installing prophylaxis. Once patients have relapsed, the GP can try to convince patients to try withdrawal again, referring to the patient’s previous success.

The discontinuation letter seems to have been more effective than the direct approach. Perhaps the direct approach is perceived as too much interference from the GP. Most MOH patients have had frequent headaches for years and are used to buy analgesics themselves. Our letter with information about MOH and the advice to discontinue analgesics led to improvement of headache in a considerable percentage of patients. The effect was comparable to a discontinuation letter to long-term benzodiazepine users in family practice in the Netherlands. Apparently, the information offered in the letter increases awareness of the paradoxical effect of analgesics and the effect of withdrawal, which may enhance responsibility and move patients into the action stage. Outcome could theoretically be improved by a stage-tailored letter aimed at inducing forward stage transition. A mailing of letters from general practices may be a cost effective minimal intervention but will be limited by the fact that MOH is a hidden epidemic: the GP does not know who has MOH since most patients overuse analgesics, which are OTC products and most patients do not consult their GP for chronic headaches.
Even more patients could improve if they were treated with prophylactic medication. The percentage of referred patients who improved to ≤ 8 days per month after six months was disappointing when compared to success rates in other studies.\textsuperscript{6,15} However, if we view the referred patients as a highly selected, difficult to treat population, improvement to ≤ 8 days/month in 28% of patients could be considered a clinically relevant outcome. The referred patients had a higher HIT score than the GP patients, indicating a higher impact of headaches and more disability. Unfortunately, we did not have a usual care control group of referred patients to compare improvement. Since most patients succeeded in discontinuing their medication, we need to focus on improving headache treatment after withdrawal.

Although HIT scores decreased in both GP withdrawal groups as opposed to an increase in the usual care group, there were no differences in headache disability between three GP treatment arms after six months. In referred patients withdrawal with subsequent improvement of headache led to a slight reduction of disability. We expected the HIT scores to change more than five points, since previously we found that the difference between HIT scores in CFH patients and patients with infrequent headaches was ten points (Chapter 4, Wiendels et al., submitted). After six months, mean HIT score was still above 60, indicating severe impact. The fact that the remaining headaches after withdrawal are as disabling as before withdrawal could reflect suboptimal treatment in these patients. On the other hand, the responsiveness of the HIT could be suboptimal. Recently, it was found that among patients with CFH a decrease of 2.3 points over time reflects a meaningful improvement.\textsuperscript{16} And HIT scores declined three points on average among headache patients reporting improvement in performing daily activities.\textsuperscript{10} Although it has shown to be responsive to self-reported change in headache impact, more studies are needed to better understand the responsiveness of the HIT in clinical trials.

The reason for randomisation on practice level was to accommodate the GP. It would have been very difficult for a GP to motivate some patients into withdrawal and conduct "usual care" in others. A disadvantage of randomisation on practice level is that a doctor's effect on success of withdrawal is difficult to rule out. But the low number of patients with improved headache made it impossible anyhow to analyse determinants of success.
We conclude that an active approach of analgesic overusing patients by the GP to offer them a
treatment program including withdrawal is not effective, while a letter with information on
medication overuse headache and an advice to discontinue may be more effective and
simpler. Whether differences in compliance between non-consulting patients, consulting
patients and referred patients are due to differences in motivational stage of change has to be
studied. Outpatient withdrawal in referred patients is successful. However, treatment after
withdrawal is of equal importance to improve headache and prevent relapse.
References

16. Coeytaux RR, Kaufman JS, Chao R, Mann JD, Devellis RF. Four methods of estimating the minimal important difference score were compared to establish a clinically significant change in Headache Impact Test. J Clin Epidemiol 2006;59:374-380.
Figure 1 Flow of patients.

General Practice Overusers, n = 200

- Invitation n = 79
  - Visit 1 n = 27
    - Withdrawal n = 21
      - Drop-outs: 16
  - t = 3
    - Visit 2 n = 5
      - Q3 completed n = 11

- t = 0
  - Excluded: 6
    - 5 no CFH
    - 1 no overuse

- Letter n = 47
  - t = 6
    - Q3 completed n = 27

- Usual care n = 68
  - Q3 completed n = 44

Tertiary Care Overusers, n = 36

- Visit 1 n = 36
  - Excluded: 11
    - no consent
  - Withdrawal n = 25
    - Drop-outs: 3
  - Visit 2 n = 22
  - Q3 completed n = 18

6 Not eligible:
- 4 severe comorbidity
- 1 moved
- 1 language problems

Withdrawal:
- 5 no CFH
- 1 no overuse

6 Not eligible:
- 4 severe comorbidity
- 1 moved
- 1 language problems