Chapter 2

A proactive approach to migraine in primary care: a pragmatic randomized controlled trial

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ABSTRACT

Background

Migraine is a common, disabling headache disorder that leads to lost quality of life and productivity. We investigated whether a proactive approach to patients with migraine, including an educational intervention for general practitioners, led to a decrease in headache and associated costs.

Methods

We conducted a pragmatic randomized controlled trial. Participants were randomized to one of two groups: practices receiving the intervention and control practices. Participants were prescribed two or more doses of triptan per month. General practitioners in the intervention group received training on treating migraine and invited participating patients for a consultation and evaluation of the therapy they were receiving. Physicians in the control group continued with usual care. Our primary outcome was patients' scores on the Headache Impact Test (HIT-6) at six months. We considered a reduction in score of 2.3 points to be clinically relevant. We used the Kessler Psychological Distress Scale (K10) questionnaire to determine if such distress was a possible effect modifier. We also examined the interventions' cost-effectiveness.

Results

We enrolled 490 patients in the trial (233 to the intervention group and 257 to the control group). Of the 233 patients in the intervention group, 192 (82.4%) attended the consultation to evaluate the treatment of their migraines. Of these patients, 43 (22.3%) started prophylaxis. The difference in change in score on the HIT-6 between the intervention and control groups was 0.81 (p=0.07, calculated from modelling using generalized estimating equations). For patients with low levels of psychological distress (baseline score on the K10 $\leq$ 20) this change was –1.51 (p=0.008), compared with a change of 0.16 (p=0.494) for patients with greater psychological distress. For patients who were not using prophylaxis at baseline and had two or more migraines per month, the mean HIT-6 score improved by 1.37 points compared with controls (p=0.04). We did not find the intervention to be cost-effective.

Interpretation

An educational intervention for general practitioners and a proactive approach to patients with migraine did not result in a clinically relevant improvement of symptoms. Psychological distress was an important confounder of success. (Current Controlled Trials registration no. ISRCTN72421511.)

INTRODUCTION

Migraine is a common, disabling headache disorder that results in lost quality of life and productivity, both during and between attacks.[1–9] Many patients with migraine suffer unnecessarily because they are not using their medications appropriately, or they are unaware of the possibility of prophylactic treatment. In the Netherlands, 10.3% of patients who take triptans consume 10 or more doses of the drug each month. These patients account for almost half of the costs associated with triptan use.[10] In addition, although more than 25% of patients with migraine have two or more attacks each month, making them eligible for preventive treatment, only 8%–12% of patients use prophylaxis.[2,3,11–13] More than half of the patients with migraine in Dutch primary care who have an indication for prophylaxis have not discussed that option with their general practitioner.[13]

We investigated whether a proactive approach to identifying patients with migraine who are receiving suboptimal treatment (i.e., inviting them to a consultation to evaluate their current treatment regimen and advising them about the options available for treating their migraine) could increase the use of preventive treatment and reduce the overuse of triptans, thereby reducing headache recurrence and associated costs. Our intervention involved educational sessions for general practitioners. Earlier studies aimed at reducing the overuse of other medications in primary care, such as benzodiazepines and anti-depressive drugs, showed that a proactive intervention led to a reduction in the use of medications.[14,15]

Because most patients with migraine in the Netherlands are treated by their general practitioner, we evaluated the costs and effects of a proactive approach to migraine in primary care. We included patients who had two or more attacks per month, because improvement could be reasonably expected in this group.

METHODS

This study involved 64 general practices in a semi-urban area in the Netherlands, between 2007 and 2009. We used a cluster randomized design with general practice as the unit of randomization to prevent contamination.[16]

The study was approved by the Ethical Committee of the Leiden University Medical Center.

Participants

General practitioners were asked to participate in a trial aimed at improving the treatment of migraine in primary care. We provided the physicians with as little information

as possible about the intervention to avoid changes in the behaviour of participants in the control group.

Patients aged 18 years or older were selected from the electronic patient record by the researchers in consultation with the general practitioners. Patients were selected using their prescription data. Patients were eligible for the study if they had received prescriptions for 24 or more doses of triptan in the previous 12 months, or 12 or more doses in the previous 6 months. Exclusion criteria were cluster headaches, cognitive impairment, a severe psychiatric disorder, terminal illness or insufficient understanding of the Dutch language.

General practitioners sent eligible patients an invitation letter, together with an information booklet, an informed consent form and a baseline questionnaire. Patients were informed that the aim of the study was to improve the treatment of migraine in primary care and that they might be invited for an evaluation and consultation with their general practitioner. Participants returned the consent form and baseline questionnaire to the researchers.

Randomization

We randomized the practices using a computer generated list after eligible patients had been selected. The randomization was done by a statistician who was unaware of the characteristics of the practices. We stratified practices based on the median percentage of the population of all practices who used two or more doses of triptans per month (i.e., practices where ≥5.9% of the population used ≥2 doses of triptan per month, and practices where <5.9% of the population used ≥2 doses of triptan per month).

Intervention

Physicians in the intervention group received two training sessions, each three hours in length, from two general practitioners with experience in the management of migraine (Jeanet Blom and Frans Dekker). The protocol was based on the headache guideline of the Dutch College of General Practitioners.[17] The training included diagnostic criteria for headache (migraine, tension-type headache, and medication-overuse headache), acute and prophylactic treatment, and treatment of medication-overuse headache (see Appendix 1).

General practitioners were asked to invite patients who had agreed to meet to an evaluation-consultation. During this meeting, the physicians followed a step-wise approach. First, they reconsidered the diagnosis of migraine. If the diagnosis was confirmed, they advised the patient on the appropriate use of medication. Patients who had two or more migraines per month were offered prophylactic treatment. On agreement between the patient and physician, a beta-blocker was started at a low

dose and gradually increased to the dose with the greatest effect and acceptable adverse effects. If this treatment was not effective, patients were prescribed sodium valproate.[18,19] In cases of medication-overuse headache, patients were advised to stop all pain medication for three months, after which their headaches were re-evaluated.[9] Notwithstanding these guidelines, physicians were free to conduct the intervention in their own way because of the pragmatic character of our trial.

Usual care

Physicians in the control group were asked to continue to provide their usual care.[16] These physicians received no additional information on the diagnosis and treatment of headache, and they were not informed as to which patients had agreed to participate in the study. Control patients were not told to which group they had been allocated.

Outcome measures

The primary outcome for the effectiveness of the intervention was patients' scores on the Dutch version of the Headache Impact Test (HIT-6), a six-item questionnaire measuring the severity and impact of headache on a patient's life.[20,21] The minimal clinically important difference on the HIT-6 is a reduction of 2.3 points on a scale ranging from 36 to 78, with a higher score representing more complaints of headache.

We planned two subgroup analyses because we expected to see the largest effect among patients not using prophylactic medication at baseline, and among patients having two or more attacks each month.

One of our secondary outcomes was change in patients' scores on the EuroQol questionnaire. This questionnaire measures quality of life in five domains (mobility, self-care, main activity, social relationships and pain), with the total score ranging from –0.33 (poor quality of life) to 1.0 (good quality of life).[23,24]

In addition to completing the questionnaire, patients were asked to keep a headache diary in which they recorded their medication use, the frequency, severity and duration of migraine attacks, and absences from work due to migraine during a four-week period.

We used the Kessler Psychological Distress Scale (the K10 questionnaire) to determine whether such distress was a possible modifier of effect. Scores on this scale range from 10 (no distress) to 50 (severe distress).[25]

To assess study-induced changes in migraine treatment by the physicians in the control group, data from the electronic patient record on prescriptions and consultation parameters were compared with those from 12 months earlier (baseline).

Follow-up

Questionnaires were sent to all selected patients at baseline. Participants received follow-up questionnaires 3, 6 and 12 months after their evaluation-consultation. Questionnaires could be completed on paper or on a website. Non-responders received a postal reminder after five weeks and a telephone reminder after six weeks. At baseline and at 12 months, prescription data and data on consultation frequency were collected from the electronic patient record.

Sample size calculation

We assumed that 50% of the selected patients would participate and that loss to follow-up would be 10%.[26] To detect a change in score of 2.3 points on the HIT-6 with 80% power at a 5% significance level and an intracluster coefficient of 0.01–0.02, we needed to recruit 60 primary care practices with 900 potential patients.[27]

Statistical analysis

Statistical analysis was done using the intention-to-treat principle, and results are reported at the level of the individual patient. We used generalized estimating equations, correcting for age, sex, baseline scores and clustering of patients per primary care practice.[28] We used independent sample t tests to analyse the non-participants (people who did not give informed consent) and non-responders (people who did not complete the questionnaire after having given informed consent), and to compare attendees (patients who attended follow-up) and non-attendees (patients who did not attend follow-up). In the case of skewed data, we used the nonparametric independent samples test.

For missing data, we used multiple imputation by chained equations, with five iterations for the switching regression model.[29] Results from the imputed data were compared with analyses of the measured data for a sensitivity analysis exploring selective loss to follow-up.[30]

We analysed the cost-effectiveness of the intervention from a societal perspective during the one-year follow-up (see Appendix 2).

RESULTS

Participants

We approached 205 primary care practices, 64 of which (31.2%) agreed to participate. Concern about the workload involved was the main barrier to participation.

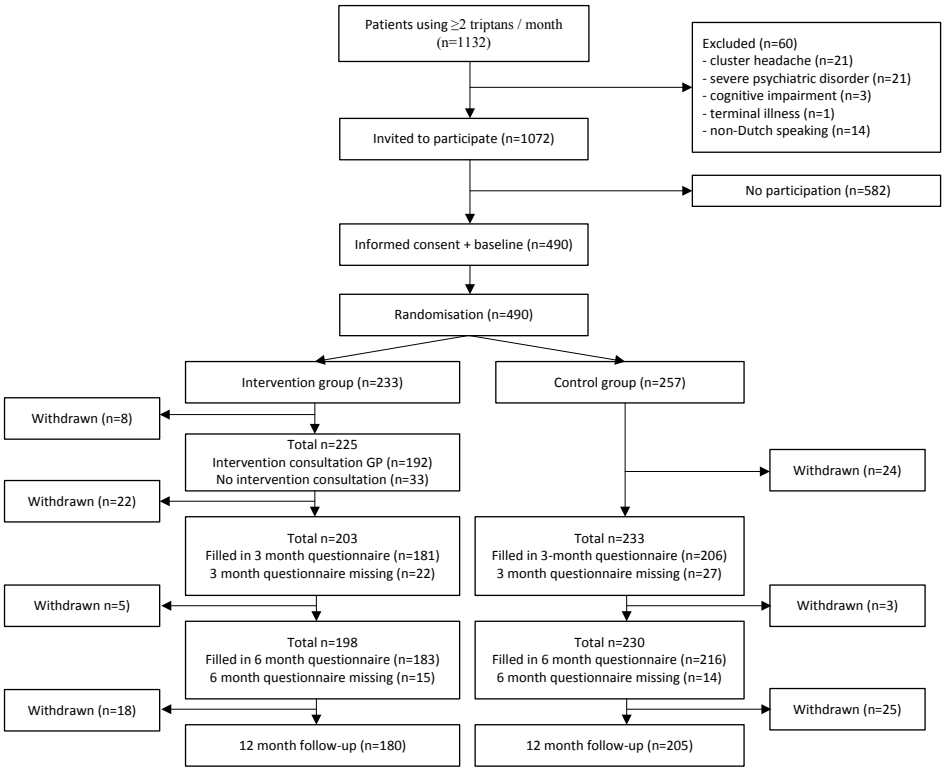

Figure 1. The flow of patients through the trial

Of the 1072 patients eligible for our study, 490 (45.7%) participated. Figure 1 shows the flow of patients through the study. The baseline characteristics of the participants in the control group and intervention group were similar (Table 1).

Non-participants and non-responders

Participants did not differ from non-participants in terms of age, sex, triptan use at baseline, triptans prescribed during the study period, consultations for headache in the previous year, HIT-6 score, EuroQol score and use of prophylactic medication at baseline or at 12 months (data not shown).

Compared with responders, non-responders were slightly younger (44.7 versus 47.8 years at 6-months follow-up [p=0.009], and 44.5 versus 47.9 years at 12-months follow-up [p=0.003]).

Nonresponders at the six-month follow-up had a slightly higher score on the baseline K10 questionnaire than responders (20.8 versus 18.6, p=0.007), suggesting a higher level of psychological distress.

No differences were found between non-responders and responders in terms of sex, number of triptans prescribed at baseline, HIT-6 or EuroQol scores at baseline, use of

Table 1. Baseline characteristics of the 490 participants in the trial. Values are means (SD) unless stated otherwise.

	Intervention group n=233	Control group n=257
Age in years	47.5 (10.7)	47.0 (9.4)
Female, %	83.7	86.8
Triptans per month past year	5.2 (4.3)	5.1 (3.8)
Consultations for migraine past year	0.81 (1.2)	0.80 (1.3)
% prophylaxis*	32.2	27.6
% beta blocker	23.6	20.6
% sodium valproate	4.3	1.9
% other prophylaxis	5.2	5.4
Headache	n=229	n=254
HIT-6 score	61.6 (5.5)	61.9 (5.0)
Depressive/anxiety symptoms	n=228	n=250
K10 score	19.6 (6.8)	18.4 (5.7)
Quality of life	n=230	n=254
EQ5D score	0.80 (0.21)	0.83 (0.18)
Migraine attacks last month	n=219	n=235
n <2 attacks/month (%)	81 (34.8)	89 (34.6)
n ≥2 attacks/month (%)	152 (65.2)	168 (65.4)
Absence from work (days/month)	n=205 0.47 (1.12)	n=224 0.59 (1.28)
Absence from work last 3 months	n=220 1.29 (3.13)	n=251 1.48 (2.60)
No. of triptans used last month total	n=198 5.11 (4.37)	n=212 4.88 (3.61)

HIT-6 = Headache Impact Test, K10 = Kessler Psychological Distress Scale, SD = standard deviation
* Data missing for five patients in the intervention group and four patients in the control group

prophylactic medication at 12 months, and number of triptan doses prescribed during the study period (data not shown).

Non-responders at six months in the intervention group had a slightly lower baseline EuroQol score than non-responders in the control group (median score 0.78 versus 0.84, p=0.015). No differences were found on any of the other parameters at 6 and 12 months (data not shown).

Outcomes

The evaluation-consultation was attended by 192 (82.4%) of the patients in the intervention group (Figure 1). There were no differences between the baseline characteristics of attendees and those of non-attendees (data not shown).

In the intervention group, 28.3% (43/152) of patients not using prophylaxis before the trial received a prescription for a prophylactic agent, compared with 14.2%

Table 2. Medications used by participants during the trial

	Intervention group n=226*	Control group n=247*	p-value
Prophylaxis			
Prophylaxis at baseline (%)	74 (32.7)	71 (28.7)	
Stopped prophylaxis during trial period (% of patients using prophylaxis at baseline)	18 (24.3)	15 (21.1)	0.40#
No prophylaxis at baseline (%)	153 (67.7)	176 (71.3)	
Started prophylaxis during trial period (% of patients not using prophylaxis at baseline)	43 (28.1)	25 (14.2)#	0.001#
Triptans			
Doses per month, mean (SE)	4.80 (0.32)	5.30 (0.29)	0.72^

SE = standard error

* Data of 7 intervention patients and 10 control patients not available

Chi-square test

^ T-test

(25/176) of patients not using prophylaxis in the control group (Table 2). However, the number of prescriptions for triptan was comparable between the two groups (Table 2). Medication-overuse headache was diagnosed in seven patients, each of whom was advised to stop all pain medications. Five of these patients lowered their use of pain medications, but none of the patients stopped using them completely (data not shown).

Intracluster coefficient

The intracluster coefficient of our study was –0.048, meaning that there was no clustering of headache complaints by general practice.[27] Post hoc, we calculated a power of 87% for this study.

Primary outcome

At six months, the HIT-6 questionnaire was completed correctly by 80.2% (393/490) of the participants. The change in HIT-6 scores did not differ between the intervention and control groups (Table 3). Subgroup analyses showed some significant, but not clinically relevant, differences.[22]

At 12 months, the HIT-6 questionnaire was completed by 78.2% (383/490) of participants. The intervention group reported a greater decrease in HIT-6 score than the control group (–4.01 versus –2.97). A similar difference was seen in all subgroups (Table 3).

Table 3. Change in score on the headache inventory test at 3, 6 and 12 months for all participants and subgroups corrected for clustering, age, sex and score at baseline

	Intervention group		Control group		Adjusted between-group difference (95% CI)	p-value
	No. of respondents	Mean change (SE)	No. of respondents	Mean change (SE)		
Total group						
3 months	181	-2.64 (0.44)	205	-2.11 (0.39)	-0.72 (-1.80;0.36)	0.191
6 months	181	-3.12 (0.40)	212	-2.55 (0.36)	-0.81 (-1.68;0.06)	0.068
12 months	181	-4.01 (0.47)	202	-2.97 (0.41)	-1.23 (-2.45;-0.00)	0.050
Patients not using prophylaxis at baseline						
3 months	115	-2.83 (0.55)	135	-2.24 (0.46)	-1.22 (-2.15;-0.29)	0.010
6 months	118	-3.51 (0.48)	142	-2.69 (0.44)	-1.18 (-2.14;-0.21)	0.017
12 months	120	-4.14 (0.54)	137	-2.81 (0.48)	-1.59 (-2.85;-0.32)	0.014
Patients with ≥2 attacks per month at baseline						
3 months	130	-3.14 (0.51)	139	-2.13 (0.46)	-1.01 (-2.40;0.39)	0.157
6 months	128	-3.48 (0.45)	140	-2.35 (0.44)	-1.26 (-2.28;-0.24)	0.016
12 months	124	-4.33 (0.56)	137	-2.37 (0.48)	-2.02 (-3.35;-0.70)	0.003
Patients with no prophylaxis and with ≥2 attacks per month at baseline						
3 months	82	-3.05 (0.66)	88	-1.92 (0.51)	-1.31 (-2.83;0.20)	0.089
6 months	82	-3.82 (0.52)	90	-2.61 (0.54)	-1.37 (-2.64;-0.20)	0.035
12 months	81	-4.15 (0.61)	91	-2.15 (0.57)	-2.16 (-3.72;-0.60)	0.007

CI = confidence interval, SE = standard error

For patients with low levels of psychological distress (baseline K10 score ≤20), the change in HIT-6 score at six months was –1.51 (p=0.008), compared with 0.16 (p=0.494) for patients with increased psychological distress,[25] suggesting that psychological distress acted as an effect modifier.

No significant differences were found between the intervention and control groups in terms of the frequency, severity or duration of attacks, the number of days per month on which patients had headaches and absences from work (Table 4).

Sensitivity analyses after imputation of missing data did not substantially change the results (data not shown).

The intervention was not cost-effective (see Appendix 2).

INTERPRETATION

We found no clinically relevant effect of a proactive approach to migraine in primary care for patients who were taking two or more doses of triptan per month. Among patients not using prophylactic medication at baseline who had two or more attacks per month, we saw a significant but not clinically relevant difference. Patients with a

Table 4. Adjusted difference in average change in score for secondary outcomes between the intervention and control groups at follow-up at 3, 6 and 12 months corrected for clustering, age, sex and baseline score

	Intervention group		Control group			
	No. of respondents	Mean change (SE)	No. of respondents	Mean change (SE)	Between-group difference (95% CI)	p-value
Number of attacks/month:*						
3 months	173	-0.43 (0.16)	192	-0.41 (0.13)	-0.02 (-0.41;0.38)	0.939
6 months	171	-0.37 (0.17)	195	-0.48 (0.13)	0.07 (-0.33;0.46)	0.747
12 months	172	-0.83 (0.17)	193	-0.61 (0.15)	-0.29 (-0.63;0.04)	0.084
Headache days per month:$						
3 months	170	-0.44 (0.26)	190	-0.37 (0.25)	-0.06 (-0.67;0.54)	0.836
6 months	168	-0.51 (0.30)	195	-0.59 (0.20)	0.20 (-0.37;0.77)	0.492
12 months	168	-1.08 (-0.26)	191	-0.32 (0.26)	-0.72 (-1.37;-0.06)	0.033
Mean severity attacks:* #						
3 months	146	-0.07 (0.05)	164	-0.08 (0.04)	-0.04 (-0.14;0.06)	0.440
6 months	145	-0.71 (0.05)	163	-0.11 (0.04)	0.035 (-0.075;0.15)	0.529
12 months	136	-0.11 (0.05)	166	-0.03 (0.04)	-0.07 (-0.18;0.04)	0.220
Number of triptans used last month:						
3 months	122	-0.44 (0.34)	151	-0.47 (0.30)	0.10 (-0.70;0.90)	0.814
6 months	117	-0.81 (0.37)	145	-0.40 (0.35)	-0.14 (-0.72;0.44)	0.636
12 months	116	-1.72 (0.44)	144	-0.83 (0.32)	-0.79 (-1.68;0.1.04)	0.083
Absent from work (days/month):						
3 months	149	-0.08 (0.11)	165	-0.11 (0.13)	-0.02 (-0.28;0.23)	0.849
6 months	162	-0.01 (0.17)	185	-0.24 (0.09)	0.15 (-0.16;0.46)	0.333
12 months	142	0.04 (0.12)	166	-0.06 (0.11)	0.02 (-0.28;0.32)	0.883

CI = confidence interval, SE = standard error

* Attacks of maximum 72 h, attacks recurring within 24 h are considered as a recurrence of the earlier attack

$ Days with at least 4 h of headache

On a 3-point scale (1=mild, 2=moderate, 3=severe)

low level of psychological distress appeared to derive more benefit from the intervention, but the effect was not clinically relevant. The intervention was not cost-effective. We saw no effect of the intervention on headache complaints at six months. The negative results could not be explained by selection bias, selective loss to follow-up of patients or behavioural changes in the physicians in the control group. However, there are some possible explanations for our results. First, the threshold of two or more prescribed doses of triptan per month proved too low when targeting patients who have two or more attacks of migraine each month. Second, many patients were already using prophylaxis, and room for improvement among these patients was less than expected. Third, the threshold of two or more attacks of migraine per month

might have been considered too low by either the patient or the general practitioner, resulting in a decision not to start prophylaxis. Finally, the effectiveness of the currently available prophylactic agents has not been convincingly proven. It is estimated that fewer than 50% of patients respond well to these treatments.[18,19]
Other studies suggested that an educational program for general practitioners leads to better diagnostic accuracy and better treatment of migraine. However, these studies did not measure the effect in terms of patient outcomes,[31] or they did not include a control group.[32] A recent study evaluating an educational intervention for general practitioners with the aim of increasing the use of prophylactic medications led to 30% of the patients receiving at least one prescription for a prophylactic agent after six months.[33] This result is similar to our findings.

Limitations

A possible limitation of our study is that the general practitioners and participants could not be blinded. Although physicians in the control group were not informed as to the content of the intervention, their participation in our study may have triggered them to update their knowledge on the treatment of migraine. In addition, patients may have been triggered to seek help for their condition. This attention bias may have led to an underestimation of the effect of the intervention.[16]
Another limitation is the pragmatic design of our study, which we chose to ensure external validity and to facilitate subsequent implementation. However, because we chose not to monitor the treatment given by the physicians, we were unable to influence the actual treatment that patients received. As such, participants may have received suboptimal treatment.

Conclusion

This intervention resulted in an increase in the prescribing of prophylactic treatments for migraine. However, we saw no clinically relevant beneficial effect of this approach on headache complaints at six months. It is possible that the intervention resulted in better treatment for patients not using prophylactic medication at baseline who had two or more attacks of migraine per month. Future interventions in primary care should target these patients. Also, it should be considered that an intervention might have less effect for patients with higher levels of psychological distress.

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APPENDIX 1: FRAMEWORK AND CONTENT OF THE INTERVENTION OF THE LIMIT STUDY

Background

The training was based on the learning cycle of Kolb.[1] According to this cycle effective and sustainable learning is the result of a process during which four phases act in coherence. These four phases are: concrete experience, reflective observation, abstract conceptualization and active experimentation. We facilitated different learning styles by using various teaching methods (theory, group discussion about example cases, reflection on group discussion, planning the intervention in own practice). To ensure the participants were well-prepared to bring the intervention into practice we used the Pyramid of Miller (knows, knows how, shows how, does) as a guide in the development of the training.[2]

First meeting

Introduction (30 min)

- Background of the LIMIT study
- Migraine: incidence, prevalence and disease burden

Diagnostic and treatment of migraine[3-7] (20 min)

- Diagnostic methods
  - o Distinction between migraine headache, tension-type headache, combinations of tension-type headache and migraine headache, drug-induced headache, and cluster headache.
  - o Use of a headache diary
- Migraine attack treatment
  - o Stepwise approach based on the headache guideline of the Dutch College of General Practitioners: 1) paracetamol + anti-emetic, 2) NSAID + anti-emetic, 3) triptan
  - o Use, adverse effects and contraindications of triptans
- Treatment for tension-type headache, migraine headache, and combinations of tension-type headache and migraine headache

Prophylaxis[8-14] (30 min)

- Indications
- Goals of prophylactic treatment
- Advantages of prophylactic treatment
- Perceptions of patients
- Prophylactics: beta-blocker / sodium valproate
  - o Titration scheme (see supplement 1, prophylaxis protocol)
  - o Adverse effects

  - Contraindications
  - Duration of prophylactic treatment
- Menstrual migraine
  - Definition
  - Treatment possibilities

Consultation (30 min)
- Role-play: start prophylaxis with an ambivalent patient.

Questions/discussion (10 min)

Second meeting

Drug-induced headaches[15-26] (30 min)
- Diagnosis of medication-overuse headache and triptan-overuse headache
- Risk factors
- Motivation of patients to stop using headache inducing substance
- Withdrawal protocol (see supplement 2, medication-induced headache protocol)
- Consequences of withdrawal for patients
- Follow-up of patients
- Long term results of withdrawal according to literature
- Prevention of medication-overuse headaches

Consultation (45 min)
- Role-play: patient with drug-induced headache

Action plan intervention (30 min)
- Patients who are prescribed ≥2 triptans per month are selected from the Electronic Patient Records
- Practice nurse invites the patients for an evaluation consultation
- Evaluation consultation consists of:
  - Make sure patient understands reason for the evaluation consultation
  - Discuss complaints, medication use and patient satisfaction with treatment
  - Evaluation of diagnosis and current treatment
  - Follow-up:
    - Patients with adequate treatment: continue treatment and advise patient to contact practice if attack frequency increases or if attacks become aggravated
    - Patients with inadequate attack treatment: improve attack treatment using tips provided in the training
    - Patients eligible for prophylaxis: discuss the possibility of prophylactic treatment (see supplement 1, prophylaxis protocol)

- Patients with medication–induced headache: discuss discontinuation of medication or other headache inducing substances (see supplement 2, medication-induced headache protocol)

- Report to researchers about evaluation consultation

Questions/discussion (15 min)

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SUPPLEMENT 1. PROTOCOL FOR MIGRAINE PROPHYLAXIS IN THE GENERAL PRACTICE

Step 1 Beta-blocker

In case of an indication for prophylaxis and no contraindications for the use of a beta-blocker then the preferred first method of treatment is a beta-blocker. The dosage is to be built up to the minimum effective dose using the schedule below. Propanolol and metoprolol have both been proven effective in the prevention of migraine attacks. The choice of drug is to be determined by the preference of and experience of the prescribing GP.

Propanolol

Starting dosage: 20 mg 2 dd
If effect is deemed insufficient, double dosage after two weeks: 40 mg 2dd
If effect is still deemed insufficient, double dosage after another two weeks: 80 mg 2dd
It is also possible to prescribe a retard tablet once a day.

Metoprolol

Starting dosage 50 mg 2 dd
If effect is deemed insufficient, double dosage after two weeks: 100 mg 2dd
It is also possible to prescribe metoprolol succinate once a day
It is also possible to prescribe a retard tablet once a day.

Follow-up

At least 6 months, preferably 9 – 12 months of prophylactic treatment. In mono-therapy and usual dosage for prophylaxis it is not necessary to taper off, medically speaking, however psychologically it can be useful.

Step 2. Sodium valproate (Depakine®)

Sodium valproate must be gradually built up due to the possibility of adverse effects if the therapy is immediately started with therapeutic dosages.

Week 1	1 dd 300 mg
Week 2	2 dd 300 mg
Week 3-6	3 dd 300 mg

If the effect is deemed insufficient, the dosage can be raised to maximally 2 dd 600 mg.

Follow-up

At least 6 months, preferably 9-12 months of prophylactic treatment. Taper off sodium valproate to 300 mg a week.

SUPPLEMENT 2. PROTOCOL DRUG WITHDRAWAL IN THE GENERAL PRACTICE

- Once the diagnosis has been made the patient can make an appointment the GP about when to start the withdrawal
- Withdrawal will be undergone in an ambulatory setting without any drugs, except occasionally prokinetic agents for nausea/vomiting
- During a separate consultation the procedure will be explained and the GP will discuss which problems may occur
    - o After abrupt discontinuation of the drugs the headaches will get worse during 1-2 weeks. After that the patient will hit a plateau after which the symptoms will begin to dissipate. After 2 months an improvement can usually be seen, although sometimes this can take up to three months.
    - o If the treatment was originally given for chronic headache, this headache may disappear or the original headache may come back but less frequently. This headache will require adequate treatment.
- At the agreed moment the patient will abruptly stop using all painkillers, triptans, ergotamine, combination painkillers and caffeine containing products.
- Advise the patient to stay well hydrated.
- After a week, at the end of the rebound phase, the GP will contact the patient to check and if necessary provide the patient with support, moral or otherwise.
- Four weeks later the GP will schedule a consultation with the same goal.
- For triptans the expected timeframe for headache relief is about 2 months after withdrawal, for other analgesics after 3 months. At that moment the GP may decide to start prophylactic therapy.
- Relapse must be prevented by minimizing the attack treatment to well under the critical dosage for developing medication-overuse headache and maybe start prophylactic treatment as well (at least 2 to 3 months after the withdrawal from the headache inducing drugs).

APPENDIX 2: COST-EFFECTIVENESS ANALYSIS

Methods

The cost-effectiveness analysis was based on the imputed dataset. The costs were calculated from a societal perspective during the 1-year follow-up. Costs were converted to 2010 price levels using the standard Dutch consumer price index.[1] The intervention costs consisted of costs of development of the training materials, costs of the training (trainer, location, travel costs, GPs' investment of time), and the implementation costs (inviting the patients, etc). The cost of GP consultations and prescriptions were calculated based on standard cost prices[2], and cost of medication was based on information from the Dutch Health Care Insurance Board (www.medicijnkosten.nl). Medication costs based on the prescription data from the EPR were comparable to the medication costs based on self-reported medication use in the headache diaries. The medication costs presented here are based on the prescription data from the EPR. Cost of absence from work was calculated with the value per hour based on age and gender-specific national averages.[2] Unpaid labour was compared with the unpaid labour at baseline; any difference in hours of unpaid labour was valued at the costs of informal care (€ 9.22 per hour).[2]

Group differences in quality-adjusted life years (QALYs) were analysed using the independent-samples t-test, and group differences in costs were analysed using the bootstrap method. The cost utility analysis compared societal costs to QALYs based on the Dutch EQ-5D tariffs.[3]

Results

The average costs per patient in the intervention group were € 504 (95% confidence interval € 379 to € 629) higher than the average costs in the control group. This was mainly due to the costs of the GP training and the intervention consultations (Table 1). The non-healthcare costs per patient in the intervention group (€ 767) were comparable to those in the control group (€ 703). The societal costs per patient (i.e. the sum of healthcare and non-healthcare costs) are higher for the intervention group than for the control group. However, due to the large standard deviations this difference is not significant (difference € 568; 95% confidence interval € -1126 to € 2261).

The QALYs estimates over one year showed no difference between the intervention and the control group.

Combination of higher societal costs and less favourable QALY outcomes in the intervention group result in a low probability (between 0.2 and 0.3) that the intervention is cost effective compared to the control group for acceptable values of the willingness to pay.

Table 1. Mean cost per patient in the intervention and control group in the first year after randomisation

Cost item	Intervention group n=233	Control group n=257	Difference	
	Costs (€)	Costs (€)	Costs (€)	p-value*
Intervention	410	0	410	-
development	54	0	54	
training GP	299	0	299	
implementation GP	57	0	57	
GP consult – total (SD)	222 (207)	149 (149)	73	0.00
– headache (SD)	44	17	27	0.00
Triptan (SD)	357 (728)	345 (412)	12	0.88
Prophylaxis (SD)	61 (128)	43 (97)	18	0.10
Analgesic (SD)	47 (72)	56 (87)	-9	0.21
Total healthcare cost (SD)	1098 (833)	594 (525)	504	0.00
Productivity costs (SD)	719 (1441)	646 (1386)	73	0.61
Unpaid labour (SD)	48 (8761)	57 (7574)	-9	0.99
Total non-healthcare cost (SD)	767 (8761)	703 (7484)	64	0.95
Total societal cost (SD)	1865 (8786)	1297 (7545)	568	0.63

* Bootstrap method, correcting for non-response using multiple imputation

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