Brief intervention by general practitioners for medication-overuse headache, follow-up after 6 months: a pragmatic cluster-randomised controlled trial

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Abstract Medication-overuse headache (MOH) is a common health problem. Withdrawal of the overused medication is the treatment of choice. We investigated the long-term effectiveness of brief intervention (BI) for MOH patients in primary care. The BI for MOH in primary care study was a blinded, pragmatic, cluster-randomised controlled trial. 25,486 patients (age 18–50) from 50 general practitioners (GPs) were screened for MOH. GPs defined clusters and 23 GPs were randomised to receive BI training and 27 GPs to continue business as usual (BAU). The GPs assessed their MOH patients with the Severity of Dependence Scale, gave individual feedback about the risk of MOH and advice to reduce headache medication. Primary outcomes, assessed 6 months after the intervention, were reduction in headache and medication days/month. 42 % were screening responders. 2.4 % had self-reported MOH. A random selection of 104 patients with self-reported MOH were invited, 75 were randomised out of which 60 with a physician-defined MOH diagnosis were included. None were lost to follow-up. BI was significantly better than BAU regarding primary outcomes (p < 0.001–0.018). Headache and medication days were reduced by 5.9 (95 % CI 1.1–10.8) and 6.2 (1.1–11.3) more days/month in BI than BAU group. Chronic headache resolved in 63 and 11 % in the BI and the BAU group (p < 0.001). Headache-related disability was lower among those who detoxified. In conclusion, BI is an effective treatment in primary care with lasting effect 6 months after the intervention for MOH.

Trial Registration: ClinicalTrials.gov identifier: NCT01314768.

Keywords Medication-overuse headache · Migraine · Screening and brief intervention · General practice · Severity of dependence scale · Cluster-randomised trial

Introduction

Medication-overuse headache (MOH) accounts for approximately 50 % of all chronic headache, affects 1–2 % of the general population, has a large impact on quality of life, and is probably the most costly headache disorder [1–5]. It is regarded as a difficult condition to treat, and based on the lack of randomised controlled trials (RCTs), evidence-based treatment guidelines are so far not established [6, 7]. However, withdrawal of the overused medication is generally considered the first step as this often improves MOH [1, 6, 7]. A possible cause of MOH has been suggested to be lack of knowledge of the potential relationship between medication overuse and chronification of headache among both headache patients and their doctors [8, 9]. This is supported by the demonstration that simple information and advice may be enough to achieve headache...
Improvement in many MOH patients [10–12]. Even if initial management is successful, a further challenge is the high rates of relapse varying between 20 and 60% [1, 13–16]. We have recently shown that MOH can be treated, with good acceptability and short-term outcomes, by general practitioners (GPs) through a behavioural brief intervention (BI) [17]. Knowledge of long-term effects of this BI is essential for recommending implementation in primary care.

The aim of this pragmatic primary care study was to investigate if the effects of BI in terms of medication withdrawal and headache improvement last over 6 months.

Methods

Design and study setting

This was a blinded, pragmatic, cluster RCT in primary care. The CONSORT flow diagram and flow chart of the study design are shown in Figs. 1 and 2.

A detailed study protocol and further details and discussion of the methods have been published elsewhere and will only be briefly described here [17–19]. The study was undertaken in South-eastern Norway in 2011–2013.

Participants

General practitioners and patients

Eighteen continuous medical education (CME) groups were invited to a training course on the management of headache. Eight groups declined participation, thus ten CME groups with 50 GPs were included.

A short screening questionnaire for headache and medication use was posted to all 18–50-year-old patients (n = 25,486) on the 50 participating GPs’ patient lists. The response rate of the screening questionnaire was 42%. 259 (2.4%) patients screened positive for MOH (headache ≥15 days/month and headache medication ≥10 days/month) and were eligible to be evaluated for the clinical trial (Fig. 1). Inclusion into the study required that the revised diagnostic criteria of the International Classification of Headache Disorders (ICHD-II) for MOH were fulfilled after a clinical interview [20, 21]. The only exclusion criterion was insufficient language skills to participate in an interview in Norwegian. To avoid GPs declining to participate in the study due to workload, up to three randomly chosen MOH patients per GP were invited to the intervention study. Thus, a random selection of 104 patients with self-reported MOH were invited, 75 accepted the invitation and were randomised out of which the 60 patients with a physician-defined MOH diagnosis were included (Fig. 1).

Intervention

Brief intervention (BI) course

GPs received a 1-day course on headache management by headache experts (CL and ESK). The course included a short presentation of the BI scheme, exemplified by role play. GPs in half of the CME groups received the BI course initially, while the others received it after the 6 months follow-up and were thus “business as usual” (BAU) controls.

Brief intervention (BI) vs. business as usual (BAU)

GPs allocated to the BI arm (n = 23) invited screening-positive MOH patients to a BI consultation. Using the Severity of Dependence Scale (SDS), GPs scored patients behaviour regarding their medication use [22, 23]. Based on their SDS score, patients were then informed about the individual risk of their headache being medication induced [22]. The BI then aimed towards achieving an explicit plan including a decision by the patient to cut down the offending medication, and an agreement about how the GP could offer relevant support. Explicit recommendations to reduce headache medication use and information about possible difficulties and gains were given. Importantly, the information that MOH usually “gets worse for 1–2 weeks before it improves” was underlined. The GPs could, in collaboration with the patients, decide whether rescue medication (another medication than that presently over-used and maximum for 2 days/week) and short-time sick leave were necessary. Prophylaxis was not prescribed as a part of the initially BI. The estimated time for the BI was 9–10 min in one single consultation.

GPs allocated to the BAU arm (n = 27) continued business as usual.

Follow-up assessments

Baseline and short-term assessment

The first follow-up assessment of the patients was at the blinded clinical interview 3 months after inclusion [17]. The ICHD-II criteria with revisions were applied and baseline data were collected retrospectively [20, 21].
Sample from GPs list 18-50 years N= 26 841

Study population n=25 486

Responders n=10 579

Self-reported MOH n=259

Invited into main study n=104

No response n=26 Declined n=1 Non-eligible new illness n=2

Participants n=75

Cluster-randomisation based on GP

BI group n=30

BAU group n=45

Lost to follow-up n=1

Baseline

BI group n=29

Self-reported MOH in BAU n=44

Not MOH based on ICHD-II n=5

3 months follow-up BI group ICHD-II MOH n=24

BAU group ICHD-II MOH n=36

6 months follow-up BI group ICHD-II MOH n=24

BAU group ICHD-II MOH n=36
**Six months follow-up**

Six months after inclusion, patients were interviewed by telephone by a headache expert (ESK). A short semi-structured questionnaire was used to collect the data systematically. Patients who did not reply to multiple telephone contacts were sent a written questionnaire.

**Randomisation and blinding**

The CME groups were the randomisation units, each GP and his/her patients' defining one cluster. All GPs and patients were blinded as to study design, group allocation and outcome evaluation. The investigator group was blinded to patient group, intervention and treatment.

**Outcomes**

All outcomes were pre-specified in the study protocol [18]. The permission from the Regional Committee for Medical Research Ethics was given based on the possibility of a cross-over from the BAU group to the intervention group if the main outcomes at 3 months showed significant treatment effects. Thus, to evaluate the intervention in a longer perspective than 3 months, but still in the initially RCT design, the present blinded 6 months follow-up was added. Though this time point was not pre-specified, the outcomes were the same [18]. Primary outcomes were reduction in headache days/month and medication days/month. Secondary outcomes were proportion in number of patients with chronic headache, medication overuse, and 25 and 50 % reduction in headache days/month. Additionally, headache-related disability was measured by the Migraine Disability Assessment (MIDAS) questionnaire and the Headache Impact Test (HIT-6) [24, 25].

**Statistics**

Power calculations suggested a sample size of >18 patients per arm to give sufficient power for the main outcomes (80 % power, 5 % significance level, intra-class correlation coefficient estimated at 0.5) (see [18, 19] for details).

All patients who met the inclusion criteria of a physician-defined MOH diagnosis were analysed at all time points and in the treatment group to which they had been randomised.

Categorical data were presented as frequencies and percentages, while means were used for continuous data. When assessing the differences between BI and BAU groups, 95 % confidence intervals (CI) were calculated. Since the patients were recruited through their GP, there might be a cluster effect present in the data. According to an intra-class correlation coefficient (ICC), the level of clustering in outcome variables within GP was high. Moreover, due to repeated measurements on the same patient over time, observations are likely to be correlated. Therefore, to assess the difference in trend from baseline to 6 months follow-up in primary outcomes between BI and BAU groups, a hierarchical regression model with random effects for intercepts and time was fitted (SAS MIXED procedure). Such a model accounts for both cluster effect within GP and intra-patient correlations in time. First- and second-order time components were entered as fixed effects to assess a possibly non-linear time trend. In addition, a dummy variable identifying the group (BI or BAU)
was entered as fixed effect. Interaction between the indicator variable and time was considered and left in the model if significant. A significant interaction term suggests statistically significant differences between the groups. The differences in BI and BAU groups at 6 months were assessed by a hierarchical regression model with fixed effect for dummy identifying the group as well as random intercepts. The model was further adjusted for age, gender and presence of migraine. Significance level of \( p < 0.025 \) was used for the primary outcomes (Bonferroni corrected for two main outcomes). For all other outcomes, the level of significance was set at 5 %.

All statistical analyses were conducted using SAS version 9.3 and SPSS version 22.0.

**Ethics and data security**

The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services. Patients received written information and GPs received both oral and written information before they consented.

**Results**

**Sample characteristics**

All 60 patients included were available for the 6 months follow-up. Mean follow-up time was 6.5 months.

The BI (\( n = 24 \) patients) and BAU (\( n = 36 \) patients) group were comparable regarding demographics (age, gender, marital status, education and income; data not shown) and clinical characteristics at baseline (Table 1). The GPs in the two groups were also comparable [17]. The mean age of the 60 patients was 42.1 years (95 % CI 40.2–43.9), 87 % (76–93) were women and 70 % (58–80) had co-occurrence of migraine (48 % episodic and 22 % chronic migraine). The patients had had chronic headache for an average of 16.6 (13.9–19.3) years and the mean duration of medication overuse was 8.7 (7.3–10.2) years.

**Outcomes**

*Unadjusted outcome analyses*

After 6 months, the BI had significantly reduced headache and medication days/month compared to BAU (Table 1; Fig. 3). One patient in the BI group relapsed into medication overuse (combination analgesics) between 3 and 6 months.

Simple analgesics were most commonly overused at baseline and most patients in the BI group had withdrawn from these drugs, but also overuse of triptans and combination analgesics had stopped (Table 1). There was no difference in prophylactic medication use between the groups, but overall more patients had started prophylaxis (Table 1).

No adverse events or side effects were reported, except from temporary withdrawal headache after detoxification.

**Adjusted primary outcomes analyses and time trends**

At 6 months, headache days/month were reduced by on average 5.9 (1.1–10.8) and medication days/month by 6.2 (1.1–11.3) days/month in the BI compared to the BAU group (Table 2a). In addition, BI was significantly better than BAU to reduce number of headache and medication days compared to baseline (Table 2a).

The (second order) time trend model also supported a non-linear time-dependent improvement in BI versus BAU. The improvement was clear at 3 months but continued up to 6 months with further improvement in both headache and medication days. The model estimate gave 6.2 headache days/month and 10.4 medication days/month less in BI than BAU at 6 months with the time trend-adjusted model (Table 2b).

**Secondary outcomes analyses**

At 6 months, 71 % (17/24) of the BI group were without medication overuse compared to 22 % (8/36) in the BAU group (Table 1). Furthermore, 63 % (15/24) of the BI group and 11 % (4/36) of BAU no longer had chronic headache at 6 months follow-up (Table 1). In addition, 42 % of patients in the BI group had a reduction of headache days/month of more than 50 % and nearly 60 % improved by at least 25 % (Table 1). Figure 3 shows that the major difference between the study arms appeared prior to the 3 months time point, with a tendency, however insignificant, for further improvement rather than relapse to previous headache and medication pattern between 3 and 6 months.

The MIDAS was incomplete and could not be analysed for one BI patient and three BAU patients. HIT-6 was incomplete for one BI patient.

There were no significant differences in headache-related disability measured by the MIDAS questionnaire between the BI (65.6, 95 % CI 35.2–96.1) and BAU (83.1, 60.5–105.6). There was no difference in mean HIT-6 score between the groups BI (63.0, 60.9–65.1) vs. BAU (63.4, 61.1–65.7). However, the MIDAS was significantly lower in detoxified patients in the BI group (48.8, 17.7–79.9) vs. the total BAU group (83.1, 60.5–105.6).
Discussion

BI in the management of MOH in primary care has an effect that lasts at least 6 months after the intervention. Only one patient relapsed over 6 months.

Strengths are the design, the high external and internal validity with inclusion of representative GPs and patients from a large population sample. Our cluster RCT adheres to the CONSORT statement for cluster-randomised, pragmatically designed and non-pharmacological intervention studies [26, 27]. Outcomes followed guidelines from the International Headache Society [28–30].

All Norwegian citizens are listed with a GP, and the included 50 GPs were representative of Norwegian GPs [31]. The age range of the patients was chosen to avoid co-morbidity of other interfering non-headache medication and disorders. The 42 % responder rate and possible risk of selection bias has not affected the sample of MOH patients compared to previous epidemiological studies with higher responder rates [5].

Intervention studies require willingness to cooperate and may lead to selection bias of both GPs and patients. However, the pre-study invitation and information did not mention any intervention. In addition, participants in the two study arms were randomly assigned and comparable. Thus, selection bias is probably of minor significance.

Even though the sample of included patients may seem small, it met pre-required power calculations for the main outcomes. Thus, we suggest our results to be both representative and valid.

Table 1 Baseline, 3 and 6 months follow-up data of the brief intervention (BI) and business as usual (BAU) group. Descriptive data

<table>
<thead>
<tr>
<th></th>
<th>Brief Intervention (N = 24)</th>
<th>Business as usual (N = 36)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 months follow-up</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>3 months follow-up</td>
</tr>
<tr>
<td>Headache days/month, mean (95 % CI)</td>
<td>24.8 (22.5–27.0)</td>
<td>17.4 (13.2–21.5)</td>
</tr>
<tr>
<td>Medication days/month, mean (95 % CI)</td>
<td>23.8 (21.4–26.1)</td>
<td>13.4 (8.8–18.0)</td>
</tr>
<tr>
<td>Proportion of patients (95 % CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without medication overuse</td>
<td>0 (0–14)</td>
<td>67 (47–82)</td>
</tr>
<tr>
<td>Without chronic headache</td>
<td>0 (0–14)</td>
<td>50 (31–69)</td>
</tr>
<tr>
<td>With ≥25 % reduction in headache days/month relative–baseline</td>
<td>0 (0–14)</td>
<td>58 (39–76)</td>
</tr>
<tr>
<td>With ≥50 % reduction in headache days/month relative–baseline</td>
<td>0 (0–14)</td>
<td>33 (18–53)</td>
</tr>
<tr>
<td>Prophylactic headache medication % (95 % CI)</td>
<td>13 (4–31)</td>
<td>17 (7–36)</td>
</tr>
<tr>
<td>Main headache diagnoses % (95 % CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication-overuse headache</td>
<td>100 (86–100)</td>
<td>33 (18–53)</td>
</tr>
<tr>
<td>Chronic tension-type headache</td>
<td>0 (0–14)</td>
<td>17 (7–36)</td>
</tr>
<tr>
<td>Chronic migraine</td>
<td>0 (0–14)</td>
<td>0 (0–14)</td>
</tr>
<tr>
<td>Episodic TTH and/or migraine</td>
<td>0 (0–14)</td>
<td>50 (31–69)</td>
</tr>
<tr>
<td>Main type overused medication % (95 % CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple analgesics</td>
<td>63 (43–79)</td>
<td>17 (7–36)</td>
</tr>
<tr>
<td>Triptans</td>
<td>13 (4–31)</td>
<td>0 (0–14)</td>
</tr>
<tr>
<td>Combination of acute analgesics</td>
<td>0 (0–14)</td>
<td>0 (0–14)</td>
</tr>
<tr>
<td>Opioids</td>
<td>4 (1–20)</td>
<td>4 (1–20)</td>
</tr>
</tbody>
</table>
The headache classification ICHD-II was recently revised to ICHD-III beta, but this does not affect the specific MOH diagnosis [32]. However, patients with additional chronic migraine should be classified as both MOH and chronic migraine in the new classification [32]. In the present study, 22% of the included MOH patients would have had a chronic migraine diagnosis in addition to a MOH diagnosis with the new criteria [32]. In a recent multicentre treatment study from tertiary care, the corresponding proportion with chronic migraine was 45% [33]. As in studies of MOH from secondary/tertiary care, co-occurrence of migraine was the main primary headache disorder and present in 70% of our MOH patients [1, 2].

In RCTs, most participants tend to improve [34–36]. We know from a previous MOH study that an interview such as the 3 months follow-up here may in itself have affected the outcome [10]. To counteract this possible assessment effect, no specific information about MOH was given during the 3-month interview. However, similarities between screening, intervention and non-intended advice may have played a role since at least four patients in the BAU group changed behaviour through the study protocol. The change in outcome between 3 and 6 months, thus justifies our attempt to avoid direct patient contact prior to the first 3 months follow-up. The difference between the arms after the intervention, however, remained significant despite a possible general assessment effect. The change we observed points out the importance of controlling for this in all treatment studies on MOH.

In the present study, BI was better than BAU 6 months after the intervention. The results add further weight to the argument of attempting initial withdrawal in primary care, and that this does not lead to a higher relapse rate.

Even though there is a selection towards more centrally acting drugs and difficult-to-treat patients in secondary/tertiary care, it is noteworthy that the duration of chronic headache and medication overuse in our sample is comparable to that of other studies of withdrawal and early

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**Fig. 3 a** Proportion of patients (% with 95% CI) with medication overuse and B) proportion of patients (% with 95% CI) with chronic headache at baseline, 3 and 6 months follow-up for the brief intervention (solid) and business as usual (dashed) arm. Unadjusted data.

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been learned [38]. and that other non-pharmacological strategies may have of central sensitisation as well as a positive feedback loop tion to the assessment effect. These include normalisation 6 months may have several possible explanations in addi-

To sum up, for many MOH patients, patient education, detoxification and follow-up can be done in primary care where the majority of patients are already treated. A raised awareness of MOH among GPs may also serve a prophylactic purpose in preventing overuse of headache medica-

tions suggests that in primary care, prophylactics may be necessary for only a minority. The trend for further improvement between 3 and 6 months may have several possible explanations in addition to the assessment effect. These include normalisation of central sensitisation as well as a positive feedback loop and that other non-pharmacological strategies may have been learned [38].

With a short BI based on a single consultation mainly with behavioural advice, as opposed to lengthy in-hos-

tants, one risk may be an increased relapse rate. Studies from secondary/tertiary care have reported 20–60 % relapse rates of detoxified patients within the first year after withdrawal, but only few relapse after 12 months [1, 13–15]. The low relapse rate found in the present study concurs with the idea that patients with mainly simple analgesics and triptan overuse in primary care may represent a less “severe” MOH group than those seen in clinic populations or in countries with higher usage of centrally active pain killers and higher proportions of chronic migraine. In addition, the study-related contacts every third month may well have contributed towards the low relapse rate in our study.

As this was a pragmatic study, we do not know exactly how the individual GPs shaped their intervention and follow-up strategy. A previous Norwegian study supports that patients initially detoxified as in-patients by a neurologist can be followed up by their GP [16]. Our study also strongly suggests that the withdrawal itself can be done by the GP.


to the low relapse rate in our study.

We started prophylactic medication after the intervention, thus this cannot explain our results. The clear effect on headache frequency and disability of only reducing offending medi-

Another possibility was that in the BI group patients had been treated with more effective prophylactic medication, whereas in the BAU group patients were either not treated or treated with less effective medication. Hence, the reduction in headache days for the BI group could be explained by changes in medication treatment. However, the subgroup analysis of patients with detoxification and follow-up can be done in primary care where the majority of patients are already treated. A raised awareness of MOH among GPs may also serve a prophylactic purpose in preventing overuse of headache medica-

The 6 months efficacy results presented here confirm the findings from other observational studies of simple advice for MOH from neurologist settings where 60–90 % were detoxified [11, 12]. That MOH patients are heavily disabled is supported by the high disability scores seen in the present study. However, the subgroup analysis of patients with successful withdrawal in the BI group shows a significantly lower MIDAS disability score as seen in other treatment studies of MOH [4]. Only three patients in the BI group had started prophylactic medication after the intervention, thus this cannot explain our results. The clear effect on headache frequency and disability of only reducing offending medications suggests that in primary care, prophylactics may be necessary for only a minority.

The trend for further improvement between 3 and 6 months may have several possible explanations in addition to the assessment effect. These include normalisation of central sensitisation as well as a positive feedback loop and that other non-pharmacological strategies may have been learned [38]. With a short BI based on a single consultation mainly with behavioural advice, as opposed to lengthy in-hos-

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To sum up, for many MOH patients, patient education, detoxification and follow-up can be done in primary care where the majority of patients are already treated. A raised awareness of MOH among GPs may also serve a prophylactic purpose in preventing overuse of headache medica-

Table 2 Primary outcomes (2a) Hierarchical linear regression (without time trend) showing difference in primary outcomes between the brief intervention (BI) and business as usual (BAU) group at 6 months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Change from baseline</th>
<th>p value</th>
<th>Mean difference in number of days between BI and BAU groups, crude (95 % CI)</th>
<th>Change from baseline</th>
<th>p value</th>
<th>Mean difference in number of days between BI and BAU groups, adjusted (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache days/month</td>
<td>-8.3 (-4.2 to -12.4)</td>
<td>&lt;0.001</td>
<td>-5.9 (-10.8 to -1.1)</td>
<td>-8.3 (-4.2 to -12.4)</td>
<td>&lt;0.001</td>
<td>-5.9 (-10.8 to -1.1)</td>
</tr>
<tr>
<td>Medication days/month</td>
<td>-8.9 (-12.5 to -1.3)</td>
<td>0.018</td>
<td>-6.2 (-11.3 to -1.1)</td>
<td>-8.9 (-12.5 to -1.3)</td>
<td>0.018</td>
<td>-6.2 (-11.3 to -1.1)</td>
</tr>
<tr>
<td>Change from baseline (headache days/month)</td>
<td>-5.5 (-1.9 to -9.2)</td>
<td>0.004</td>
<td>-5.5 (-1.7 to -9.4)</td>
<td>-5.5 (-1.9 to -9.2)</td>
<td>0.004</td>
<td>-5.5 (-1.7 to -9.4)</td>
</tr>
</tbody>
</table>

*Regression coefficients adjusted for age, gender, and co-occurrence of migraine

Table 2 Primary outcomes (2b) Hierarchical linear mixed models with 2nd order time trend showing estimated mean headache and medication days/month in brief intervention and business as usual groups at different time points

<table>
<thead>
<tr>
<th>Time</th>
<th>Headache days/month, mean (95 % CI)</th>
<th>Medication days/month, mean (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Brief intervention</td>
<td>Business as usual</td>
</tr>
<tr>
<td>Baseline</td>
<td>24.6 (21.5–27.7)</td>
<td>25.3 (22.7–27.9)</td>
</tr>
<tr>
<td>3 months</td>
<td>19.6 (16.7–22.4)</td>
<td>23.0 (20.6–25.5)</td>
</tr>
<tr>
<td>6 months</td>
<td>16.5 (13.3–19.6)</td>
<td>22.7 (20.1–25.3)</td>
</tr>
</tbody>
</table>
with this, such patients should still be referred to a neurologist.

Acknowledgments The authors want to express our sincere gratitude to all participating patients and GPs, without them the study would not have been possible. Thanks also for logistic help from the research administration at Akershus University Hospital.

Compliance with ethical standards

Funding This study is supported by grants from the University of Oslo, the Research Centre at Akershus University Hospital and the South-Eastern Norway Regional Health Authority. The funding sources had no role in the design of the study; the collection, analysis, and interpretation of the data, preparation of the manuscript; or the decision to submit the manuscript for publication.

Conflicts of interest All authors have completed the ICMJE uniform disclosure form and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 2 years; no other relationships or activities that could appear to have influenced the submitted work.

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