Chapter 8

Summary and general discussion

OUTLINE OF THIS CHAPTER

The general aim of this thesis was to study how treatment of migraine in the primary care setting can be improved. For this reason, we conducted the Leiden Improvement of Migraine In primary care Treatment (LIMIT) study, in which we investigated whether a proactive approach towards migraine patients in primary care is effective in diminishing headache complaints. Although, we had good reasons to expect that the intervention would lead to a decrease in triptan use and in headache complaints, the study did not show a clinically relevant effect of the intervention.
First, this chapter presents the main findings of the individual studies included in this thesis. Then, I discuss two possible explanations for the ineffectiveness of the intervention of the LIMIT study, namely: incorrectness of the assumptions on which the study was based, and the limitations of the pragmatic study design. This reflection on the LIMIT study also includes the results of the other studies presented in this thesis. These studies dealt with reasons related to patients and general practitioners (GPs) for not starting preventive treatment, the effect of starting preventive medication on triptan use, the wishes of migraine patients concerning attack medication for migraine, the risk of behavioural change in pragmatic trials in primary care, and the minimally important change of the HIT-6 questionnaire. Finally, this chapter concludes by describing the possible added value of the work this thesis for daily primary care and makes some suggestions for future research.

SUMMARY OF MAIN FINDINGS

- A proactive approach towards migraine patients in general practice results in an increase in prophylactic agent prescriptions, but not in a decrease in headache complaints (Chapter 2).
- The decision of the individual patient and his/her general practitioner (GP) to start preventive treatment is not only determined by attack frequency, but also depends on the impact of the headache attacks on daily life and attitude towards preventive migraine medication (Chapter 3).
- The number of triptans prescribed decreases by 1.0 to 1.6 triptans per month during the six months after starting preventive treatment with propranolol or metoprolol. Compared with data from clinical trials, this decrease is smaller than expected (Chapter 4).
- The current outcome measures in migraine research do not adequately reflect the wishes of migraine patients. Patients want medication to work faster, to abolish

pain at an earlier stage, to make them able to function properly relatively quickly, and to prevent recurrence of the attack (Chapter 5).
- Different interpretations of the concept of usual care are used in pragmatic studies in primary care. Many researchers do not adequately report which information has been given to the caregivers and patients in the control group, making it difficult to evaluate the adequacy of the study design in terms of internal and external validity (Chapter 6).
- We estimated the between-group minimally important difference (MID) of the HIT-6 questionnaire, which is regularly used to compare groups of migraine patients. For a group of migraine patients in primary care we recommend to set this value at –1.5 points. For determination of differences within individuals, we estimated the within-person minimally important change (MIC) at –2.5 to –6 points (Chapter 7).

ASSUMPTIONS UNDERLYING THE LIMIT STUDY

We designed the LIMIT study because we assumed that there was considerable room for improvement in the treatment of migraine patients in the Netherlands by their GPs. From the literature, we had indications that preventive treatment was under-used[1-5] and that a substantial number of patients would be willing to try preventive treatment.[5] Also, we had indications that a considerable number of patients used triptans inadequately (e.g. taking triptans for tension-type or medication-overuse headache, or as a prevention against migraine attacks) and would therefore suffer from headache unnecessarily.[6-8] Below, I will comment on the contradiction between this favourable general picture from literature and the somewhat disappointing results of the LIMIT study concerning preventive medication and attack medication.

Room for improvement in preventive treatment

We assumed that there was room for improvement in the preventive treatment of migraine patients and that patients would be willing to try preventive medication. In the intervention group of the LIMIT study 28% of participants started preventive medication. This percentage was significantly higher compared to the control group, of which 14% of patients started preventive treatment.[9] However, only 43% of patients in the intervention group who, according to their baseline headache diary experienced two or more migraine attacks per month, started preventive medication. This percentage is lower than the 55% of patients who indicated to be willing to try preventive treatment in earlier research.[5] From previous studies, we knew that important factors in the decision-making process concerning medication use are the effectiveness of an agent, general fear of new interventions on their health problem,

fear of side-effects, drug dependency or fear of becoming a chronic patient, involvement in the decision-making process, and the physician taking the time to explain possible side-effects.[10-12] Therefore, these aspects were explicitly discussed in the training for GPs in the LIMIT study. In Chapter 3, patients stated that their main reasons for not starting preventive medication were: negative attitudes towards medication in general, fear of medication side-effects, previous unsuccessful attempts, attacks not being severe enough, and the impact of migraine on daily life being acceptable.[13] Thus, although under-treatment with preventive medication exists, patients were less willing to try preventive treatment than we had expected.

Although recommended in the Dutch GP guidelines, the GPs did not discuss the possibility of preventive treatment in almost 50% of the patients who were a potential candidate for preventive treatment. The main reason for not discussing the possibility of preventive treatment was that the GPs had low expectations about the efficacy of this preventive medication.[13] This is perhaps understandable, as the effectiveness of preventive medication is indeed limited. In Chapter 4 we observed that the effect of starting propranolol or metoprolol for preventive treatment of migraine in daily practice has a relatively small effect on triptan use as compared to data from clinical trials.

Thus, we can conclude that under-treatment with preventive medication does exist but that starting preventive medication encounters resistance in both patients and GPs, partly caused by the presumed disappointing effect of preventive medications.

Room for improvement in attack treatment

We assumed that a proactive intervention by their own GP would convince patients to lower their medication use; this assumption was based on earlier studies aimed at reducing the overuse of other medications in primary care (e.g. benzodiazepines and anti-depressive drugs) which showed that a proactive intervention led to a reduction in the use of medications.[14;15] In the population of the LIMIT study, 8% of the patients received ≥12 triptan prescriptions each month, and thus probably suffered from medication induced headache. Indeed, medication-overuse headache was diagnosed in seven of these patients, who were then advised to stop all pain medications. However, although five of these patients lowered their use of pain medications, none of them stopped using them completely.[9] Thus, although GPs had received training on how to motivate patients with medication overuse headache to start withdrawal, in practice it seems relatively difficult to convince patients to actually do this.

Another issue concerning attack treatment is the limited effectiveness of the available medication on patients' complaints. In our Delphi study (Chapter 5), we found that patients wish their headache to disappear within about 30 minutes; however, research shows that more than 50% migraine patients do not notice any benefit

of their medication in the first hour after treatment.[16] Also, we found that the currently recommended measures in migraine research do not adequately reflect the wishes of migraine patients. The most important outcome measure used in studies on the effectiveness of migraine treatment is whether the patient is pain-free, and free of nausea and photo/phonophobia within two hours after taking the medicine.[17] However, the patients themselves want the medication to work faster, to abolish pain at an earlier stage, to make them able to function properly relatively quickly, and to prevent recurrence of the attack.

Thus, there seems to be room for improvement in the use of attack medication, especially prevention of overuse, as well regarding the wish of patients for more effective medication.

LIMITATIONS OF THE PRAGMATIC STUDY DESIGN

For the LIMIT study, we used a pragmatic study design in which we stayed as close to daily practice as possible. We chose this design to ensure external validity and, thus, the generalisability of the results. However, a pragmatic design has inherent risks of bias.[18] A first issue, that of non-adherence (i.e. GPs not carrying out the study protocol as designed by the researchers), has been discussed in the preceding paragraph. Below, I discuss the issues of behavioural change in the control group and the outcome measurement.

Behavioural change in the control group

We compared the effect of the intervention with 'usual care' as normally provided by GPs in the Netherlands. However, in a study setting, it is difficult to ensure that a control group receives genuine usual care comparable to everyday practice. Various actions by the researchers can influence the behaviour of the caregivers and patients (Chapter 6).[19] In the LIMIT study, we tried to avoid changes in the behaviour of GPs in the control group by using cluster randomisation. In this way, we prevented a learning effect in the GPs that usually appears when they have to provide usual care to one patient and an intervention to another. Also, we provided GPs in the control group with as little information as possible about the intervention to prevent behavioural change among these GPs. Nevertheless, their participation in the study may have triggered them to update their knowledge on the treatment of migraine and may have led to an underestimation of the effect of the intervention.

Regarding the patients in the control group of the LIMIT study, they received as little information about the study as possible. They were only 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 GP. Nevertheless, they 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.
Thus, the outcomes of the LIMIT study may have been negatively affected by changes in the behaviour of the GPs and patients in the control group.

Outcome measurement

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] We measured the effect after 3, 6, and 12 months. We chose this outcome measure, and measurement after a certain period of time, instead of outcome measures like attack frequency or an extensive headache diary directly after the intervention, because we wanted to measure the effect of the intervention on patients' lives more than on clinical parameters. However, we were confronted with the fact that subjective outcome measures, like the HIT-6 questionnaire, are more difficult to interpret and to validate.[18,22] In contrast to clinical parameters, the meaning of changes in scores on health status questionnaires is not intuitively apparent. In order to interpret change scores of these questionnaires one needs to determine the within-person minimally important change (MIC) and the between-group minimally important difference (MID). The within-person MIC reflects the magnitude of change in a questionnaire score that reflects a relevant change in a patient's condition. The between-person MID evaluates the difference in mean change scores of two groups that are followed over time, e.g. in a randomised trial. The within-person MIC and between-group MID can be assessed by two types of methods classified as 'anchor-based' and 'distribution-based' methods, respectively. In anchor-based methods an external criterion, the so-called 'anchor', is used to determine what patients (or their clinicians) consider important improvement or deterioration. In contrast, distribution-based methods are based on statistical characteristics of the sample.[23] In general, anchor-based methods are preferred over distribution-based methods, because anchor-based methods take into account the relevance of the measured change for the patient.[24-26]
In Chapter 7 we determined the MIC and MID of the HIT-6 questionnaire using an anchor based approach, to determine what patients considered an important improvement or deterioration. However, we found a low correlation of the change scores on the HIT-6 questionnaire with the anchor question, indicating uncertainty in the determination of these values.
Also, the MID we found in the study population of the LIMIT study (-1.5 points) was lower than the MID that we used as predetermined cut-off for clinical relevance for the LIMIT study, namely -2.3 points.[9] In that light, the outcomes of our trial could

be interpreted differently. Namely, at 12 months the differences in change scores between the control group and the intervention group were more than -1.5 points for several subgroups (not using prophylaxis at baseline, experiencing 2 or more attacks at baseline, or not using prophylaxis at baseline and experiencing 2 or more attacks each month). Therefore, if we had used this later determined lower MID instead of the MID we derived from previous research we could have concluded that, in these subgroups, the intervention did have a clinically relevant effect after 12 months.
Therefore, the fact that we did not find a clinically relevant effect of our intervention, may have been partly explained by uncertainty in the interpretation of the change scores of the HIT-6 questionnaire.

WHAT THIS THESIS ADDS

In this thesis we observed that there is indeed room for improvement in the treatment of migraine in primary care, especially among patients not using preventive treatment and experiencing two or more attacks each month. However, there is no need to advise GPs to invite all patients who receive prescriptions for two or more triptans each month to have an evaluation consultation, as this produces insufficient effect on headache outcomes and costs. However, it is important to pay special attention to patients who are a possible candidate for preventive treatment, as some patients might substantially benefit from preventive treatment, but do not use it. When discussing the possibility of preventive treatment, GPs can benefit from the results of the study in Chapter 3 and keep the possible barriers in mind, namely: negative attitudes towards medication in general, fear of medication side-effects, previous unsuccessful attempts, attacks not being severe enough, and the impact of migraine on daily life being acceptable. Also, GPs need to be sure that they do not deny patients a possibly effective treatment because of their own negative ideas towards preventive medication.
In addition, from this thesis we learned that, when designing pragmatic studies in primary care, there are methodological issues that make it harder to prove the effectiveness of an intervention. First, the outcomes of pragmatic studies in primary care can be negatively affected by changes in the behaviour of the GPs and patients in the control group. Second, the quality of life outcome measures that are often used in this type of research are more difficult to validate and interpret than the more robust outcome measures that are used in clinical trials.

FUTURE RESEARCH

From this thesis we can conclude that two main problems are encountered when aiming to improve migraine treatment in general practice, namely: barriers towards change in medication use among migraine patients and their GPs, and a disappointing effectiveness of migraine treatments (attack medication and preventive treatment) in general.

In my opinion, in migraine research we need to concentrate on the two major tasks. First, we should focus on ways to make the most efficient use of the currently available resources by: 1) identifying patient groups that will benefit most from the current treatment options, by studying which patients do and do not benefit from them, and the reasons for this; 2) improving consulting techniques with special attention paid to the barriers that patients have against the use of preventive medication and the correct use of attack medication; 3) education of GPs with specific focus on the barriers found in the GPs themselves, namely their low expectation of medication efficacy.

Secondly, we have to continue our search for more effective treatments of migraine, regarding both attack and preventive treatment. The present research has also revealed that we should a better understanding of the wishes of the patients as a possible starting point, by specifically focusing on patient-oriented outcomes.

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