Patients' preference in migraine

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CHAPTER

10

Other

General discussion

GENERAL DISCUSSION

The studies in this thesis present existing gaps in our knowledge about migraine; gaps of knowledge of importance for primary care. The main conclusions are summarized in Chapter 11.
Headache, especially migraine, is a frequently presented complaint in general practice. This thesis covers an important issue, because patients often suffer much. Headaches have great impact on patients, because it's not just the pain, but headaches also affect social functioning and cause failure in various social roles (like school and work).

The preventive treatment is described in Part 1, chapters 2-6 of this thesis. In Part 2 two randomized controlled crossover trials (RCTs) between a triptan and a NSAID or analgesic are presented. These trials focus on the ongoing discussion which attack treatment is most effective in migraine. In Part 3 various aspects of medication overuse by triptans is presented. We studied how prevalent it is, which triptans are concerned, whether all triptans are equally involved, the extent in which it takes place and what the costs are.

The main characteristics of the studies in this thesis and the implications for practice and research will be highlighted and discussed. Some recommendations for future research are presented.

1. Preventive treatment for migraine

a. Moment of starting preventive treatment

No clear threshold or consensus when to start preventive treatment is found in literature (see Chapter 2). Mostly, the recommendations are based on the frequency of migraine. However, in the many published guidelines no supportive evidence has been provided for the recommended thresholds. There are no known studies exploring this issue. So, we'll have to conclude that there is little justification for the frequently chosen threshold of three attacks per month.
Nearly always physicians, not the patient, draw up these guidelines and they determine when to advise to start preventive treatment. We found that in fact the opinion of the patient, which we consider important, is poorly appreciated (Chapter 2). Given the importance of intrinsic motivation of the patient, making an authority-based decision based on only one single factor, such as frequency, cannot be recommended (Chapter 4, 5 and 6).
So, there is room for input from the patient. Our studies show that there is great diversity in patient desires. Not only impact, duration and/or severity of the attacks count, but issues as being negative about daily medication and patient's experienced effect of attack treatment, are also meaningful (Chapter 6).

Our recommendation is to discuss preventive treatment with the patient starting from two attacks per month. Then, together with the patient, can be decided to agree or disagree on initiation, and at what moment it should be done. The Dutch general practitioners Headache guideline recommends discussing preventive treatment from two or more attacks per month and, subsequently, to make a decision about the therapy in dialogue with the patient[1]. Therefore, the Dutch guideline is appropriate in this context. Also, in this guideline the patient's involvement is considered to be high.
In conclusion, there is no evidence for a rigorous threshold, because there is a large variation among patients on what conditions they are willing to start preventive therapy. Furthermore, factors which are important for the patient need to be considered explicitly in a conversation between physician and patient (Chapter 4, 5 and 6).

b. Effectiveness of preventive treatment

The review on preventive treatment (Chapter 2) demonstrates that preventive treatment of migraine is a worthwhile intervention, for which beta-blockers and anti-epileptic drugs can be used. It can be argued that preventive treatment will contribute to a much greater reduction in disease burden than can be established with attack treatment only. Preventive treatment does not ensure that headaches disappear completely, but great benefits can be gained. Especially for patients with a high disease burden preventive treatment can be of major importance (Chapter 2). Preventive treatment appears to be cost-effective in the primary care setting compared with attack treatment only[2].
Not many preventive studies have been performed in general practice. Consequently, the study population used in these reviews does not correspond with the population in general practice. There is also doubt whether the results of this review can be applied to general practice. This should be a reason for further investigation using the appropriate (primary care) population, like the recent study of Smelt et al.[3]. Our study (Chapter 3) in daily general practice also shows that preventive treatment can be well performed in general practice.
In conclusion, preventive therapy is presumably a suitable intervention in primary care and can generally be carried out properly. Consequently, GPs can offer this treatment to patients without hesitance.

c. Hesitation about preventive treatment in patients and physicians

However, many GPs are sceptical about the effectiveness of preventive treatment (Chapter 4). Moreover, the conclusions from the review and the observational study are contradicting (Chapter 2 and 3), since the review shows that preventive treatment is an effective intervention, but many GPs are doubting that.
Because about half the disease burden can be decreased, there is a large gain to be expected for patients with a high disease burden (Chapter 2).
Patients and GPs both have the same hesitations regarding preventive treatment of migraine. They largely use the same attributes in their decision to accept and/or to

advise preventive treatment (Chapter 4 and 5). This provides a good base for shared decision making. However, because some cognitions are incorrect, additional post-graduate teaching is needed.
GPs mention a complex of inhibitory and stimulating factors, sometimes based on views about migraine treatment, and sometimes based op process factors (Chapter 4).
Patients mention a comparable complex of factors, including the perceived burden of migraine and questions about autonomy and self-determination. Moreover, in their opinion the influence of the physician is the key factor (Chapter 5).
The hesitations against preventive treatment are often subjective in nature (Chapter 4 and 5). We expect that understanding the hesitations and the discussion of these hesitations with the patient can lead to more clarity and acceptance. This could be evaluated in further studies.
On average, there is a long delay between the diagnosis of migraine and the start of preventive treatment (Chapter 3). The motivation for preventive treatment arises only after a long period of perceived burden of disease and at an older age. For general practitioners, it is important to realize that the patient must be motivated to accept preventive treatment. However, this is often not the case at the moment making the diagnosis (Chapter 3). Consequently, the topic of prophylaxis, when indicated, should be raised in usual patient contacts.

d. Experiences with preventive treatment in daily practice

The low expectations of success of preventive treatment are in contrast with what GPs normally meet in daily practice. The lack of confidence in preventive treatment is not reflected in the prescription data from GPs. (Chapter 3).
Once the preventive treatment is started in general practice, it usually goes well. The frequently applied beta-blockers show to perform well. More than half (56%) of the patients is using preventive therapy during nine months or more (Chapter 3).
The actual percentage of Dutch migraine patients using preventive treatment is 13%. Though this percentage may seem low, it is also found as one-year prevalence in many other studies on preventive treatment[4-12]. From our study, it appears that many more patients have ever used preventive treatment. During a period of 11 years 44% of migraine patients have had with experience with preventive treatment (Chapter 3). That's a convenient percentage because it roughly corresponds to the percentage of migraine patients with two or more attacks per month[13].

e. Expectations and problems in the application of preventive treatment

Surprisingly, patients want preventive treatment more often than GPs are expecting (Chapter 4 and 6). Both the qualitative studies and the questionnaire study emphasize that the opinion of patients is crucial (chapters 4, 5, and 6). It is particularly important that the patient is motivated for preventive intervention. This is not only necessary for the acceptance of the treatment, but also stimulates proper compliance (Chapter 5). Our study reveals that many doctors underestimate the positive intentions of patients and their participation in a favorable way (Chapter 4).

It is also noticeable that only sparsely attack treatment is combined with preventive treatment. Preventive treatment is prescribed to only 4.8% of triptan users (Chapter 3). The non-users, despite of an indication, may simply use their attack treatment and, therefore, they are satisfied.
When considering prophylaxis, one has to realize that not every beta-blocker shows similarly good results. Propranolol shows a weaker performance than metoprolol and atenolol. Therefore, other beta-blockers should be preferred in general practice. Choosing the most appropriate beta-blocker is therefore an important issue (Chapter 3).
In daily practice often only one preventive attempt is carried out (Chapter 3). For other diseases, such as hypertension, it is entirely usual to apply several different treatments up to the point where an effective treatment has been found. We expect preventive treatment of migraine may improve when multiple attempts are made if the first attempt in has failed.
In conclusion, an active approach by GPs has to be pursued, emphasizing offering preventive treatment at the appropriate time for patients.

2. Attack treatment, triptan versus other attack treatments

a. Choice attributes and preference in attack treatment

Patients' choice for an attack treatment is based on a number of significant attributes of that treatment. Those choice attributes are different for everyone (Chapter 7 and 8). Based on these studies the most important attributes are: rapid onset of relief (31.6%), decrease severity of attack (17.5%), return to normal function (15.8%), complete pain free (14.0%) and no adverse events (8.8%).
Realizing this, it becomes apparent why patients choose differently. There is no outstanding attribute and, therefore, an effective endpoint applicable for everyone is not available. Thus, the optimal therapy varies, depending on the preferences of the patient.
To find out for which attack treatment patients have a preference was the main aim of the studies in chapter 7 and 8. In these studies the personal preference on a -5 to +5 (10 point) scale addressing various degrees, is the primary endpoint. Therefore, these RCTs can be characterized as post-treatment patient-preference trials, in which patients express preference after exposure to both treatments. Patient's preference is a so-called 'patient centered endpoint'.
One of the most remarkable findings in these RCTs is when patients express a preference for either triptan or NSAID / analgesic, that preference was strong. Some benefit more from the triptan and others benefit more from ibuprofen or paracetamol. There is only a small group benefiting from both, indicating they have no clear preference. In the naratriptan-paracetamol study actually all patients showed preference for one

of the treatments. The studies show that, as mentioned before, when patients don't benefit from NSAID or analgesic they often do respond to a triptan. Therefore, it makes really sense to actively monitor treatment response in all patients, because if there is no response to NSAIDs or analgesic patients should be motivated to consider the use of a triptan.
In conclusion, the main argument on which the choice of attack treatment should be based is the preference of the patient and not the relative effectiveness from population-based studies.

b. The role of impact in attack treatment

The height of the MIDAS-score did correspond with the expressed preference in de rizatriptan-ibuprofen study. However, this was only the case in a subgroup of patients with a strong preference for one of two treatments, not in the entire study population. Our two studies here differ. In the rizatriptan-ibuprofen study the patient outcome was largely influenced by the pre-measured impact of the MIDAS-core in favor of rizatriptan in the specified subgroup with strong preference. It was striking in the naratriptan-paracetamol study this was not the case at all. Migraine patients with high or low impact showed an equal preference for the triptan or paracetamol. In conclusion, the pre-measured impact did not have a consequent influence on the outcome in our studies. We advise to study this aspect in other preference studies.

c. Preference trials versus 'regular' trials

One of the differences between usual study designs and the preference studies in Chapter 7 and 8 is that these studies evaluated three successive attacks on each of the studied medications. Mostly only one attack is treated in comparative studies between two different attack treatments[14,15]. We think in daily practice, an evaluation more attacks is preferable. Only one attack doesn't sufficiently predict the general pattern, since in our studies the two-hour pain-free attack rate for the first treated attack differed from the total pain-free attack rate.
During the development of this thesis, the discussion which endpoint is best to compare attack treatment in migraine is actively held within the IHS[16,17]. The former vision of the IHS the two-hour pain-free period should be the primary endpoint[18,19]. Sustained pain-free is also a well-accepted endpoint. Now discussions are held about combining the 'two-hour pain free' and the 'sustained pain free' endpoint. A disadvantage is that those endpoints do not take into account what patients expect from therapy. In research with 'regular' RCT-design and with classical endpoints such as 2-hour pain-free, the patients preference disappears into nothingness. This can be considered as a general disadvantage of RCTs.
Patients make their own assessments based on several attributes and their reasons for preferences vary widely, see the above paragraphs. Therefore, a preference study better demonstrates the views of the patients. They are best aware which of the advantages or disadvantages are most important or most annoying for themselves. In other words: patients choose their own endpoint. Satisfaction with a self-preferred endpoint provides also the biggest chance on satisfaction with attack treatment for the individual.
However, with use preference trials it is not possible to determine the general effectiveness and / or efficacy between two active migraine treatments Then trials with classic endpoints continue to be more valuable.In conclusion, 'preference' (PTPP) trials are relatively new and should potentially be a more valid approach to detect clinical meaningful differences between established treatments (Chapter 7 and 8).

d. Strategy in attack treatment for migraine

Patients are well able, upon request, to present their preferences between two attack treatments. They can present their preferences between analgesics, NSAIDs and triptans in an excellent way (Chapter 7 and 8). Furthermore, they can also present their preferences between different triptans[20-26].
A practical strategy should be that the patient uses a drug for three consecutive attacks, after which an appropriate choice can be made, namely continuation or change (according to the selected method in the "preference trials" Chapter 7 and 8). Because multiple attributes contribute to that choice, at least three consecutive attacks are desirable to gain insight. Several known effective treatments (paracetamol, NSAIDs, triptans, and several of the latter category) can best be tested one by one using this strategy. Because migraine attacks occur one after the other for years, there is plenty of time in each patient to find out what works best.

3. Extent of triptan overuse

a. Extent and recognition of overuse

Medication overuse and especially triptan overuse is a common problem in the Netherlands (Chapter 9), often resulting in chronic daily headache with high disease burden. The costs of triptan use and overuse in this large-scale research turned out to be higher than in earlier (smaller) studies. Triptan overuse entails high cost, estimated between the 23% and 47% percent of the total cost of triptans (Chapter 9).
When some 'number crunching' is performed, the question arises whether triptans in the Netherlands do induce more headaches than they cure.
Triptan overuse is a common problem at national level. However, in a single general practice it concerns only a few patients. Of all medication overuse only triptan overuse is well known by GPs. .Consequently, overuse of analgesics and NSAIDs resulting in chronic daily use is mostly unknown to the GP. We recommend to pay more attention to this in guidelines and (post-graduate) education.

b. Opinions and recommendations with respect to overuse

All interventions that can help to reduce the magnitude of this problem are a welcome contribution.

Possibly, maximizing the reimbursed triptans to 15 to 20 DDDs per month would very likely indicate and discourage excessive overuse. It could induce prophylaxis more easily and, thereby, possibly reduce the amount of overuse and related headache burden.

The current electronic prescribing systems can monitor drug treatment much better, but they still are unable to alert for triptan overuse. A modification of the electronic prescribing systems and feedback systems for medication overuse headache is needed and could result in more health benefits (e.g. NHGdoc). Monitoring for triptan use is a prerequisite, accompanied by an increase in awareness in GPs, practice assistants, but also in pharmacists.

In conclusion, based on this thesis it is worthwhile paying attention to the prevention of MOH during consulting hours when headache is discussed and when an attack treatment is prescribed.

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