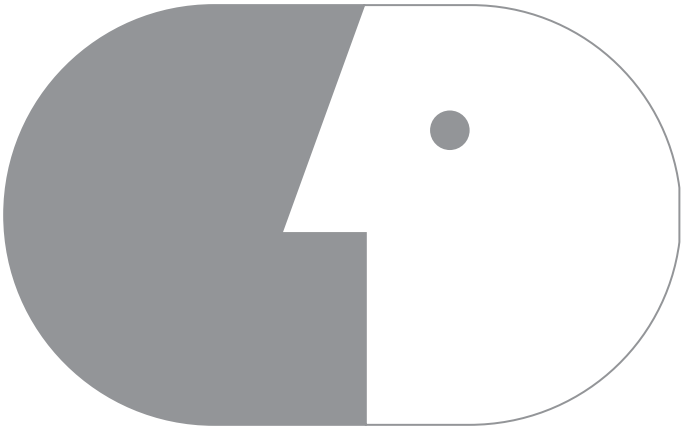
PATIENTS' PREFERENCE IN MIGRAINE



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PATIENTS' PREFERENCE IN MIGRAINE

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Contents

CHAPTER

1

General introduction and aim of this thesis

1. MIGRAINE DURING GP CONSULTATIONS

Headache is a problem for which patients occasionally attend a general practitioner (GP). Remarkable is that although headache has a high prevalence, occurs often frequently and has a high burden of illness, only a small proportion of people with headache visit the GP.
On a recent regular Monday in practice, my agenda shows 35 regular consultations (of which 5 are booked for double time), 12 consultations by telephone, 24 repeated prescriptions, 1 surgical intervention, 1 therapeutic injection and 2 home visits. Accidentally there are remarkably many headache patients this day. I would like to discuss these with you.

Consultations for headache:

I. In the morning one consultation about the attack treatment of migraine. Patient C.
II. Just before the morning coffee break authorization of a repeated prescription for the attack treatment of migraine for a patient using much attack treatment. Patient D.
III. At the end of the morning a telephone consultation about preventive therapy. Patient A.
IV. In the afternoon a patient makes a visit to start preventive therapy, after previous consultations about possible benefits. Patient B.

These patients give a good impression of how GPs encounter migraine, though in reality this is too many consultations on one day. One migraine patient each day would be more appropriate. My own general practice showed the following numbers of patients in 2008:

Headache patients 2008	Incidence (practice)	Incidence (/1000)	Prevalence (practice)	Prevalence* (/1000)
Migraine	99	58	126	74
Tension type headache	71	42	77	45
Undifferentiated headache	34	20	51	30
Cluster headache	2	1	4	2

** Prevalent headache patients consulting the GP for headache in one year*

In my practice, migraine was the 16th most prevalent disorder encountered in 2008. This corresponds with the average incidence/prevalence in general practice. According to the second Dutch national GP survey the migraine incidence in 2004 was 2.9 and the prevalence was 10.2 on an annual basis (male and female, /1000)[1]. Migraine is the most common disorder in the ICPC-chapter `N', the nervous system. Some examples of migraine compared to other disorders encountered by the GP from the same chapter (neurology) are as follows; GPs encounter migraine 3 times as frequently as epilepsy (prevalence 2.9/1000), 6 times as frequently as concussion (prevalence 1.8/1000), 1.4 times as frequently as tension type headache (prevalence 7.3/1000) and 132 times as frequently as cluster headache (pr evalence 0.3/1000).[1]

2. PREVENTIVE THERAPY FOR MIGRANE

Case A

Patient A is 44 year old male, suffering from migraine from the age of 7. He called the practice with some questions on preventive treatment for migraine. Every month he suffers from 3-4 attacks. Being a professional photographer, he frequently has to cancel appointments. He is reluctant against the daily use of tablets. He fears to go the same way as his old mother, who daily uses several prescription drugs. He also fears the side effects of prophylaxis.

The goal of preventive treatment of migraine is to reduce the attack frequency and thereby lowering the severity of the attacks. Limiting the burden of the disease and regaining of personally and socially functioning are the aims of preventive therapy. Nevertheless this treatment is not popular: only 7-19% of the patients who qualify for this therapy are effectively prescribed this treatment.[2-4] Several considerations play a role at the choice for preventive treatment. A first condition is when the frequency, intensity and duration of the attacks, in spite of optimum attack treatment, influence the quality of life seriously negative. A factor which also counts is that a high attack frequency and migraine with aura are associated with signs of cerebral damage on MRI[5], although it has not been shown yet that preventive treatment can prevent these white matter lesions effectively. Moreover preventive treatment has been designated when overuse of attack medication threatens and/or MOH develops. The relevance of this is once more underlined because chronic daily headache, mostly by over use of pain killers or triptans, comprehends in the Netherlands approximately 4% of the adult population.[6]

2.1 Qualitative studies on migraine prevention

Case B

Patient B is a 33 year old female, working in child nursery, suffering from migraine from the age of 10. The GP did offer her two years ago preventive therapy. At that point she told that she suffered frequently from migraine attacks. Attack medication helps rather well. She experiences more benefits from NSAID then from triptans. In general, she can continue her work after a couple of hours. She postponed the use of preventive medication each time and did not find her migraines worse enough. Nevertheless, now she has made an appointment to start with a preventive treatment.

Primary care is an important setting for the management of migraine and in many countries the majority of migraine consultations occur in this context. For example, in the Netherlands 95% of triptans are prescribed in primary care.
Despite the fact that that preventive therapy is a safe and effective intervention[7-9], only few of the migraine patients who qualify for preventive therapy receive it[10] and when they do adherence is modest.[7] This under-use is in contrast with the opinion of many patients. Some patients even express a desire for preventive therapy for infrequent headache. Both GPs and patients are reluctant to exploit the preventive possibilities.
We could study these issues in qualitative studies. In qualitative research – with some overstatement – it is not the number of patients that counts, but is the views, opinions and emotions as such. Focus group research does not provide a statistical overview of patients' opinions on migraine preventive therapy.Qualitative research on preventive therapy provides input for other studies on preventive therapy. For example, the items that have been identified can be further explored in questionnaires. It can support the preparation of intervention studies by providing input for the training for the participating physicians who have to offer the therapeutic interventions.[11,12] The results of qualitative studies can also be very helpful in developing continuous medical education (CME).
Qualitative research should be as carefully worked out as other forms of research.
Little is known about the opinions of GPs and patients on preventive migraine therapy or about the dimensions of the decision to introduce it. In order to reduce the unmet need of migraine patients, it is important to know why GPs are not prescribing preventive therapy and why patients are not asking for it.
Although migraine is embedded in a complex biopsychosocial context, there have only been few qualitative studies in the area. Reports have included patients' perceptions of migraine and chronic daily headache[13,14], the needs of migraine patients[15,16], migraine-related decision-making[17-19], the burden of migraine and impact on quality of life[20,21] patient experience and expectations of management.[22-24] However, none of these studies explores views on prevention.

2.3 Surveys on preventive therapy

Guidelines on migraine preventive therapy differ widely, with preventive treatment recommended for patients from two attacks per month up to twice a week. There is no objective threshold determining from which number of attacks or duration of the attacks a preventive treatment for migraine is indicated. The time spent with headache is the frequency multiplied by the duration of the attack. It is unclear whether patients regard this as the basis of their decision to accept preventive therapy. Other factors are also frequently mentioned, such as the response on attack treatment, avoidance of medication-overuse headache (MOH), the impact, subjective experienced burden, social non-functioning, absence at work, coping behaviour, etc.
At present, there are many thresholds used, generally established on basis of consensus under physicians. In a survey under specialists it was found that the indication for prescribing preventive medications was 3–4 attacks per month in 85.8% of physicians and at least 8 days of acute medication use per month in 64.3%.[25]

2.4 Opinion of the migraine patient

In the US, 50% of patients with migraine meet the criteria for use of preventive treatment, but only 5-12% actually uses it.[26] In the Netherlands, 12% of all patients with migraine use preventive treatment.[10] It is unknown to what extend patients with migraine consulting their GP are interested in using preventive therapy. That makes it interesting to investigate how many and which patients use preventive therapy in primary care, and how many patients would like to use this form of treatment in primary care or have interest in it (and should be actively informed by their GP). Another question that can be answered by using a questionnaire is how frequency, duration, severity, and impact of migraine attacks are related to the wish to use preventive treatment.
It is also unknown if patients with fewer than two attacks per month (the threshold used in many guidelines) would like to consider preventive treatment. Do patients feel sufficiently confident to approach their GP themselves for preventive therapy? How many patients prefer an active approach by their physician? A UK study reports that patients often do not consult their GP for their headache symptoms but still would like more help.[15]

2.5 Prevalence of preventive treatment

How effective attack treatment of migraine may be, the negative influence of the headache attacks on the daily living of the patient is most decreased when migraine patients successfully experience a reduction of the attack frequency. A recent US study showed that only 13% of the migraine patients who qualified for preventive treatment actually get this.[2,3] A study from 2002 on preventive migraine treatment in the Netherlands shows that 12% of the triptan or ergotamine users also use prevention therapy. Another study showed that 28% of the triptan and ergotamine users did ever start with preventive therapy.[4,10]

Guidelines on migraine treatment advice to start preventive therapy starting from two attacks each month up to 4 attacks each month[27,28].
The most often applied way to explore preventive therapy is to assess the numbers of patients using preventive treatments in drug databases.[10] To see if preventive therapy is sufficiently prescribed is determined by how frequent preventive medication is prescribed, and that finding is subsequently compared with the prevalence of migraine in the total population. Shortcomings of this approach are that it is actually unknown for which disorder medication (like NSAIDs) is prescribed. Therefore, sometimes only more headache-specific medication like triptans and ergotamines are included in such studies. In addition, medication used in the preventive treatment of migraine is also used for other indications, like heart disorders and epilepsy. Consequently, estimates based on this approach are often incorrect. Often, this approach doesn't reveal the number of patients who started with preventive therapy and later stopped using it, e.g. in which preventive therapy actually failed. It is also is unknown which part of the migraine patients visited their physician for migraine and the percentage of them receiving preventive therapy.
To gain more insight into preventive treatment of migraine we performed a population-based cohort study to estimate the incidence of migraine in the Netherlands and to assess preventive treatment approaches in Dutch general practice, covering the last 10 years.

3. ATTACK TREATMENT OF MIGRAINE

Case C

Patient C is a 44 year old female who suffers from migraine once or twice each month. Initially she always used ibuprofen. Five years ago she tried a triptan, but because of the side effects she never wanted to try it again. She has more than one severe migraine attack each month and wants information on the best way to treat attacks now. The use of ibuprofen only results in a decrease of headache severity, and she still has to stop all her activities during a migraine attack. Is nausea the problem for the lack of efficacy? Should another NSAID been given, accompanied with anti-emetics, or should a triptan be tried again?

Attack treatments for migraine range from simple analgesics to migraine-specific treatments. Before the introduction of the triptans, selective 5-HT_1 agonists, in the early 1990s, accepted attack treatments were paracetamol, acetylsalicylic acid, NSAIDs and ergots. Still many patients use this kind of medication and in most guidelines it is still the first step in attack treatment (except for ergotamines, the use of which has vanished). Many patients and prescribers learned the benefits of the triptans, but still there is no direct evidence that triptans treat migraines better than analgesics or NSAIDs. To compare the benefits of triptans versus analgesics or NSAIDs

Triptans*

Almotriptan	*tablet 12,5 mg*
Eleptriptan	*tablet 40 mg*
Frovatriptan	*tablet 2,5 mg*
Naratriptan	*tablet 2,5 mg*
Rizatriptan	*tablet 10 mg, melt tablet 10 mg, tablet 5 mg, melt tablet 5mg*
Sumatriptan	*nasal spray 10 mg, nasal spray 20 mg, injection 12 mg/ml 0,5 ml, suppository 25 mg, tablet 100 mg, tablet 50 mg*
Zolmitriptan	*tablet 2,5 mg, melt tablet 2,5 mg*

*available in the Netherlands

there are a number of approaches possible. One of them is to assess the efficacy in trials and to compare that. There are many trials of triptans and other classes of attack treatment compared to placebo. Triptans show only moderate efficacy (on average 30% pain free at 2 hours), as shown in the largest available review.[29] From the evidence based point of view it is most desirable to have results of head-to-head trials. There are some of these trials, also gathered in a review.[30,31] These trials show no clear superiority from one class of drugs above the other.
The question still is whether there is better efficacy of triptans or that others factors also determine the extent of triptan use, for example the substantial marketing by drug companies. Another attribute in the choice of attack treatment is the question whether the cost of triptans compared to NSAIDs justify the large use of triptans.[31] However, this attribute is getting less relevant, since the cost of triptans is lowering during the last years. The average price of a triptan tablet was in 2011 between 5 and 6 Euros and in 2013 a several generic triptans are in the Netherlands for under 25 cents per tablet.
A point of interest in this discussion is the disadvantage of trials in general, that trials compare large groups with each other, and don't show the response of individual patients. Clinical trials comparing migraine treatments traditionally use a parallel-group design. The endpoints are defined as headache free after two hours post dose, improvement of pain on a 4-point headache scale, etcetera. These study designs reveal the efficacy of attack treatment on a predetermined aspect on a predetermined outcome measure in a group and do not reveal individual or group preferences of the included patients.

3.1 Preference studies

To better answer this question is it necessary to assess the patients' preference for either one of the headache treatments, which can be done in so-called *"patients preference studies"*. Per sonal preference seems more relevant, especially when the disorder presents itself as attacks. The main difference is that now the endpoint focuses on the patient and is determined by the patient (patient centred endpoint). An important

endpoint for one person does not have to be of equal importance for another person. Some migraine patients, for example, may prioritize rapid onset of pain relief, while others may find it a more welcome experience that adverse events are absent. So in a preference study patients weight for themselves the benefits versus harms and are able to choose the individually optimal tailored attack treatment. Two or more treatments are compared in a randomized crossover design: patients use treatment A in the first attacks and then treatment B secondly in later attacks, or vice versa. The primary outcome measure is the proportion of patients preferring the one treatment to the other (are more satisfied with the one treatment above the other). The optimal design for preference studies is currently a debate, such as on how one should interpret the results when patients have no preference.[32,33]

3.2.1. Triptan versus NSAID

The triptan rizatriptan is the second most prescribed triptan in the Netherlands and has a good efficacy.[29] In the Netherlands it is a prescription only drug. Ibuprofen is widely used for migraine, probably still the most used treatment in migraine attacks the world nowadays, because it is everywhere available and shows good efficacy.[34-36] It is available in the Netherlands as OTC.

As mentioned before, in studies of triptans versus NSAIDs there are no benefits from one above the other.[30] There is one head-to-head study between rizatriptan and ibuprofen and this study shows no difference on the endpoint of 2 hour pain free[37].

3.2.2. Triptan versus analgesics

The triptan naratriptan is the fourth most prescribed triptan in the Netherlands. Paracetamol is an effective treatment for the attack treatment in children, adolescents and adults, with the remark, that most evidence for its efficacy is sometimes fairly old.[38-40] Traditionally paracetamol is the often used over the counter (OTC) painkiller in the Netherlands. There are no direct head to head studies of naratriptan with paracetamol.[41] Yet there are RCTs comparing paracetamol with other triptans, showing equal efficacy[42,43] or even more efficacy when used in combination with aspirin and caffeine.[44] A review on the use of paracetamol for migraine has been published, and it is a moderately effective intervention.[45]

4. TRIPTAN OVERUSE

Case D

Patient D is a 51 year old women, suffering from migraine from the age of 12. She did call the practice assistant for a repeated prescription of sumatriptan 100mg tablets. In the past she had migraine attack in average two times each month. The EPR (Electronic Patient Register) now shows that this would be the second prescription of 12 sumatriptan 100 mg tablets this month. The EPR also shows that Mrs. D received prescriptions for in total 36 tablets during last 3 months. Is this amount a risk for overuse? Should the patient be invited for consultation or should the prescription just be authorized?

Medication overuse headache (MOH) is the name for the problem that occurs, when headache patients start using more and more pain-killers or triptans for the treatment of headache attacks. If for a longer period the use exceeds a certain threshold, in some patients it is striking that more and more headaches appear and then eventually daily headache with variable intensity develops. The criteria for MOH have been established by the International Headache Society (IHS) and are based on observational research and consensus.[46] It is not the total number of used tablets per period, which is responsible for the arising of the daily headache. The most important parameter is the number of days that the painkillers are used per period. For painkillers and NSAIDs the critical threshold of use lies on 15 days per month and for triptans on 10 days per month and this should endure at least three consecutive months.[46] Little knowledge exists on how headache (as well tension type headache as migraine) transforms in MOH and on

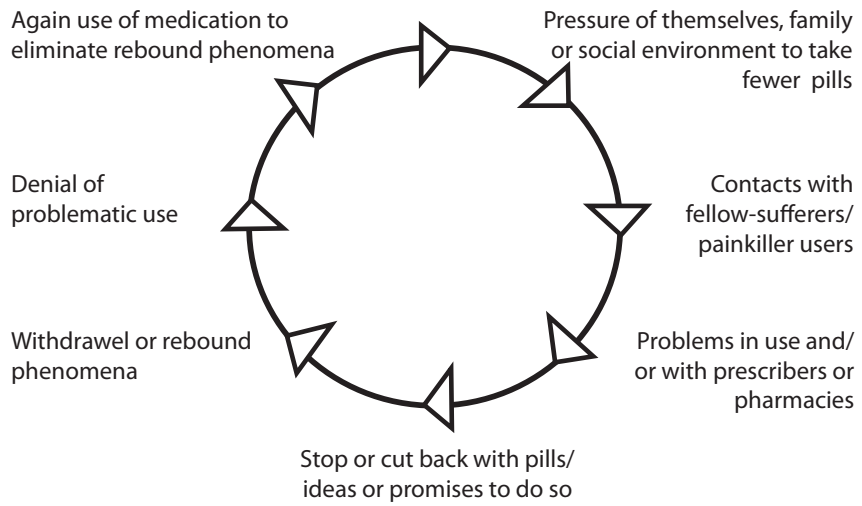

Figure 1. Aspects of addiction in medication overuse headache

which mechanisms the process is based. It is known that the migraine frequency plays an important role, as well as a low socio-economic status, overweight and psychiatric comorbidity.[6,47,48] More and more MOH is seen as a form of addiction or addictive behaviour, with corresponding characteristics of addiction.[49-53] See figure 1.
Because the threshold for triptan overuse differs from other classes of headache attack treatment, triptan overuse headache (TOH) is a separate diagnostic entity[46]. From the experience in headache clinics can be learned, that triptan continued use of 18 single doses per month or more leads almost always results in daily headache.[54]
MOH is increasingly recognized as a problem worldwide, with an estimated prevalence in the general population of 1-4%.[6,55] It is unknown whether the prevalence MOH is rising or that the problem gets more attention nowadays.
According to Dutch guidelines the best intervention in MOH is totally stopping with the drug causing it.[56,57] Other sources recommend several drugs to support the stopping with overuse.[58]
In general practice there is a problem in recognition of MOH because OTCs remain outside the direct observation of the GP. In addition, there is a problem at discovering overuse of triptans, in spite of the fact that these drugs are prescription only drugs (at least in the Netherlands). The main reasons for this are unfamiliarity with the risk of overuse of attack medication and problems with the arrangements for repeated prescriptions in general practice.
There are many studies on MOH, mostly in tertiary headache centers.[55,59-61] The prevalence of TOH is likely to increase with the expected increasing availability of OTC triptans (now UK, Germany, Romania) and the currently often advocated, but still unproven, instruction[62] to treat attacks as early as possible while the headache is still mild. TOH can have a major impact on the quality of life of migraine patients[48,63] and causes a considerable increase in cost.[59]
The assessment of the prevalence and associated cost of triptan-overuse and whether the risk of overuse differs among the seven available triptans has been not well mapped yet. In a small population-based study in Denmark 5% of sumatriptan-users used > 30 DDDs per month and were responsible for 38% of the total sumatriptan consumption and costs.[64] In two French studies, 25-30% of triptan users were overusers[65] and 12% became overusers (defined as ≥180 DDDs/yr.) within one year from starting using triptans.[66] In an Italian study a much lower rate of overuse was found (3.2%), but this is probably due to a low overall use of triptans in this country.[67]
A large scale observational study will provide insight in the prevalence of TOH and the individual role of the triptans.

5. AIMS AND STRUCTURE OF THE THESIS AND BRIEF DESCRIPTION OF THE CHAPTERS

The most important theme in this thesis is the "patient perspective", illustrated by the fact that patients' preference has been chosen as endpoint the two RCTs in this thesis.

This thesis is divided into three parts, described below.

5.1. Preventive treatment of migraine

The first part of this thesis presents migraine treatment on the theme of "preventive treatment of migraine in general practice", and contains five studies.

The first chapter of part I is a narrative 'umbrella' review on effectiveness of preventive therapy for migraine (Chapter 2). For the readers who are interested in a further elaboration on preventive therapy we refer to this chapter.

The second chapter of part I is an observational study in a large primary care database in the Netherlands (Chapter 3). To gain more insight to the potential impact and the preventive treatment of migraine, this chapter presents a population based cohort study, providing insight into the incidence of migraine and preventive treatment approaches in general practice during the last 11 years. Patients with migraine visit mostly the GP for migraine and preventive therapy is mostly initiated by them. Even when a specialist (neurologist of paediatrician) initiates the preventive therapy, the GP will carry it out. For this reason general practice is the best place to investigate the use of preventive therapy. Furthermore, in this situation can be assessed which percentage of patients with migraine call upon the GP and again which of those get prescriptions for preventive therapy.

Two qualitative studies, address how patients and GPs think and feel about preventive therapy (Chapter 4 and 5). Little is known about the opinions of GPs and patients on preventive treatment or on the inputs into the decision to introduce it. In order to reduce the unmet need of migraine patients, it is important to know why GPs are not prescribing preventive treatment and why patients are not asking for it.

Chapter 4 is a qualitative study that seeks to explore the ideas, motives and expectations of GPs on preventive migraine therapy.
The aim of chapter 5 is to explore the ideas, views, motives and expectations of migraine patients with regard to preventive therapy: the "patients' point of view".

Chapter 4 and 5 have the same design and provide different perspectives on the same topic.

Chapter 6 presents a cross-sectional survey conducted in three general practices with five GPs and reveals what patients in general practice think about preventive therapy. The first study aim was to investigate how many and which patients use preventive therapy, and how many patients would like to use this form of treatment. The second aim was to investigate how frequency, duration, severity, and impact of migraine attacks related to the patients' need for preventive treatment.

5.2. Attack treatment of migraine

This second part describes two RCTs with the patient preference as main endpoint (Chapter 7 and 8).
Chapters 7 and 8 describe a double-blinded double dummy, cross-over trials, on rizatriptan and ibuprofen (chapter 7) and on naratriptan and paracetamol (chapter 8). The aim of these studies was to evaluate; 1) the satisfaction of patients using a triptan in the attack treatment of migraine compared to the alternative medication, and 2) to evaluate whether a patient preference design is more sensitive to detect clinical relevant differences compared to the traditional study design using efficacy as the primary outcome measure.

5.3. Medication overuse

Part III (Chapter 9) of this thesis is a study in which the overuse of triptans is assessed in the GIP-Database, a database of the Dutch Health Care Insurance Board which includes the drug prescriptions of 6.7 million people (46% of the total Dutch population). For that purpose we defined two thresholds, a lower threshold from which up there is possible overuse, and a higher threshold, from which up there is almost certainly a diagnosis overuse. We assessed; 1) the prevalence and associated cost of triptan overuse in the Dutch general population; 2) the demographic characteristics of triptan overusers to identify possible risk factors; and 3) whether the risk of overuse differs among the seven available triptans.

6. FINAL CHAPTERS

Chapter 10 is general discussion and includes clinical implications, guiding and directions for further research. Chapter 11 is a summary of the main findings from this thesis in English. Chapter 11 is a summary in Dutch.

References

1. Linden van der M.W., Westert, G. P., Bakker de D.H., and Schellevis, F. G. Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk. Klachten en aandoeningen in de bevolking en in de huisartspraktijk. 2004. Utrecht/Bilthoven, NIVEL/RIVM. Tweede Nationale Studie.
2. Lipton RB, Bigal ME. Ten lessons on the epidemiology of migraine. *Headache* 2007; 47 Suppl 1S2-S9.
3. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 2007; 68(5):343-349.
4. Rahimtoola H, Buurma H, Tijssen CC, Leufkens HG, Egberts AC. Migraine prophylactic medication usage patterns in The Netherlands. *Cephalalgia* 2003;23(4):293-301.
5. Kruit MC, van Buchem MA, Hofman PA, Bakkers JT, Terwindt GM, Ferrari MD, Launer LJ. Migraine as a risk factor for subclinical brain lesions. *JAMA* 2004; 291(4):427-434.
6. Wiendels NJ, Knuistingh Neven A, Rosendaal FR, Spinhoven P, Zitman FG, Assendelft WJJ, Ferrari MD. Chronic frequent headache in the general population: prevalence and associated factors. *Cephalalgia* 2006;26(12):1434-1442.
7. Linde M, Jonsson P, Hedenrud T. Influence of disease features on adherence to prophylactic migraine medication. *Acta Neurol Scand* 2008.
8. Mulleners WM, Chronicle EP. Anticonvulsants in migraine prophylaxis: a Cochrane review. *Cephalalgia* 2008;28(6):585-597.
9. Victor S, Ryan SW. Drugs for preventing migraine headaches in children. *Cochrane Database Syst Rev* 2003;(4):CD002761.
10. Rahimtoola H, Buurma H, Tijssen CC, Leufkens HG, Egberts AC. Incidence and determinants of migraine prophylactic medication in the Netherlands. *Eur J Clin Pharmacol* 2002;58(2):149-155.
11. Donovan J, Mills N, Smith M, Brindle L, Jacoby A, Peters T, Frankel S, Neal D, Hamdy F. Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. Commentary: presenting unbiased information to patients can be difficult. *BMJ* 2002;325(7367):766-770.
12. Pope C, Mays N. Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. *BMJ* 1995;311 (6996):42-45.
13. Peters M, Abu-Saad HH, Vydelingum V, Dowson A, Murphy M. Migraine and chronic daily headache management: a qualitative study of patients' perceptions. *Scand J Caring Sci* 2004;18(3):294-303.
14. Peters M, Huijer Abu-Saad H, Vydelingum V, Dowson A, Murphy M. The patients' perceptions of migraine and chronic daily headache: a qualitative study. *J Headache Pain* 2005;6(1):40-47.

15. Belam J, Harris G, Kernick D, Kline F, Lindley K, McWatt J, Mitchell A, Reinhold D. A qualitative study of migraine involving patient researchers. *Br J Gen Pract* 2005; 55(511):87-93.
16. Cottrell CK, Drew JB, Waller SE, Holroyd KA, Brose JA, O'Donnell FJ. Perceptions and needs of patients with migraine: a focus group study. *J Fam Pract* 2002;51(2):142-147.
17. Peters M, Abu-Saad HH, Vydelingum V, Dowson A, Murphy M. Patients' decision-making for migraine and chronic daily headache management. A qualitative study. *Cephalalgia* 2003;23(8):833-841.
18. Ivers H, McGrath PJ, Purdy RA, Hennigar AW, Campbell MA. Decision making in migraine patients taking sumatriptan: an exploratory study. *Headache* 2000;40(2):129-136.
19. Meyer GA. The art of watching out: vigilance in women who have migraine headaches. *Qual Health Res* 2002;12(9):1220-1234.
20. Tenhunen K, Elander J. A qualitative analysis of psychological processes mediating quality of life impairments in chronic daily headache. *J Health Psychol* 2005;10 (3):397-407.
21. Ruiz dV, I, Gonzalez N, Etxeberria Y, Garcia-Monco JC. Quality of life in migraine patients: a qualitative study. *Cephalalgia* 2003;23(9):892-900.
22. Moloney MF, Strickland OL, DeRossett SE, Melby MK, Dietrich AS. The experiences of midlife women with migraines. *J Nurs Scholarsh* 2006;38(3):278-285.
23. Morgan M, Jenkins L, Ridsdale L. Patient pressure for referral for headache: a qualitative study of GPs' referral behaviour. *Br J Gen Pract* 2007;57(534):29-35.
24. Rozen TD. Migraine prevention: what patients want from medication and their physicians (a headache specialty clinic perspective). *Headache* 2006;46(5):750-753.
25. Stewart JT, Domenico D'A, Vicente B, Peter B, Andrew JD. Guidelines for Prescribing Prophylactic Medications for Migraine: A Survey Among Headache Specialist Physicians in Different Countries.
26. Diamond M, Dahlof C, Papadopoulos G, Neto W, Wu SC. Topiramate improves health-related quality of life when used to prevent migraine. *Headache* 2005;45 (8):1023-1030.
27. Couturier EG, Bomhof MA, Gooskens R, Keyser A, Mulleners WM. Richtlijnen diagnostiek en behandeling chronisch recidiverende hoofdpijn zonder neurologische afwijkingen. Utrecht, Nederlandse Vereniging voor Neurologie. 2008.
28. Grol MH, Neven AK, Pijnenborg L, Goudswaard AN. [Summary of the practice guideline 'Headache' from the Dutch College of General Practitioners]. *Ned Tijdschr Geneeskd* 2006;150(6):305-309.
29. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 2001;358 (9294):1668-1675.

30. Lipton RB, Bigal ME, Goadsby PJ. Double-blind clinical trials of oral triptans vs other classes of acute migraine medication - a review. *Cephalalgia* 2004;24(5):321-332.
31. Tfelt-Hansen P. Triptans vs other drugs for acute migraine. Are there differences in efficacy? A comment. *Headache* 2008;48(4):601-605.
32. Dahlof C. How to assess patient preference of migraine treatments. *Cephalalgia* 1999;19 Suppl 242-5.
33. Dowson AJ, Tepper SJ, Dahlof C. Patients' preference for triptans and other medications as a tool for assessing the efficacy of acute treatments for migraine. *J Headache Pain* 2005;6(3):112-120.
34. Suthisisang C, Poolsup N, Kittikulsuth W, Pudchakan P, Wiwatpanich P. Efficacy of low-dose ibuprofen in acute migraine treatment: systematic review and meta-analysis. *Ann Pharmacother* 2007;41(11):1782-1791.
35. Morillo LE. Migraine headache. *Clin Evid* 2004;(11):1696-1719.
36. Codispoti JR, Prior MJ, Fu M, Harte CM, Nelson EB. Efficacy of nonprescription doses of ibuprofen for treating migraine headache. a randomized controlled trial. *Headache* 2001;41(7):665-679.
37. Misra UK, Kalita J, Yadav RK. Rizatriptan vs. ibuprofen in migraine: a randomised placebo-controlled trial. *J Headache Pain* 2007;8(3):175-179.
38. Lipton RB, Baggish JS, Stewart WF, Codispoti JR, Fu M. Efficacy and safety of acetaminophen in the treatment of migraine: results of a randomized, double-blind, placebo-controlled, population-based study. *Arch Intern Med* 2000;160 (22):3486-3492.
39. Lipton RB, Stewart WF, Ryan RE, Jr., Saper J, Silberstein S, Sheftell F. Efficacy and safety of acetaminophen, aspirin, and caffeine in alleviating migraine headache pain: three double-blind, randomized, placebo-controlled trials. *Arch Neurol* 1998;55(2):210-217.
40. MacGregor EA, Wilkinson M, Bancroft K. Domperidone plus paracetamol in the treatment of migraine. *Cephalalgia* 1993;13(2):124-127.
41. Ashcroft DM, Millson D. Naratriptan for the treatment of acute migraine: meta-analysis of randomised controlled trials. *Pharmacoepidemiol Drug Saf* 2004;13(2):73-82.
42. Freitag F, Diamond M, Diamond S, Janssen I, Rodgers A, Skobieranda F. Efficacy and tolerability of coadministration of rizatriptan and acetaminophen vs rizatriptan or acetaminophen alone for acute migraine treatment. *Headache* 2008;48 (6):921-930.
43. Dowson A, Ball K, Haworth D. Comparison of a fixed combination of domperidone and paracetamol (Domperamol) with sumatriptan 50 mg in moderate to severe migraine: a randomised UK primary care study. *Curr Med Res Opin* 2000;16 (3):190-197.

44. Goldstein J, Silberstein SD, Saper JR, Elkind AH, Smith TR, Gallagher RM, Battikha JP, Hoffman H, Baggish J. Acetaminophen, aspirin, and caffeine versus sumatriptan succinate in the early treatment of migraine: results from the ASSET trial. *Headache* 2005;45(8):973-982.
45. Derry S, Moore RA. Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev* 2013; 4CD008040.
46. Silberstein SD, Olesen J, Bousser MG, Diener HC, Dodick D, First M, Goadsby PJ, Gobel H, Lainez MJ, Lance JW, Lipton RB, Nappi G, Sakai F, Schoenen J, Steiner TJ. The International Classification of Headache Disorders, 2nd Edition (ICHD-II)--revision of criteria for 8.2 Medication-overuse headache. *Cephalalgia* 2005;25 (6):460-465.
47. Bigal ME, Lipton RB. Clinical course in migraine: conceptualizing migraine transformation. *Neurology* 2008;71(11):848-855.
48. Wiendels NJ, van Haestregt A, Knuistingh Neven A, Spinhoven P, Zitman FG, Assendelft WJJ, Ferrari MD. Chronic frequent headache in the general population: comorbidity and quality of life. *Cephalalgia* 2006;26(12):1443-1450.
49. Lake AE, III. Screening and behavioral management: medication overuse headache--the complex case. *Headache* 2008;48(1):26-31.
50. Lundqvist C, Grande RB, Aaseth K, Russell MB. Dependence scores predict prognosis of medication overuse headache: a prospective cohort from the Akershus study of chronic headache. *Pain* 2012;153(3):682-686.
51. Olesen J, Bousser MG, Diener HC, Dodick D, First M, Goadsby PJ, Gobel H, Lainez MJ, Lance JW, Lipton RB, Nappi G, Sakai F, Schoenen J, Silberstein SD, Steiner TJ. New appendix criteria open for a broader concept of chronic migraine. *Cephalalgia* 2006;26(6):742-746.
52. Radat F, Creac'h C, Guegan-Massardier E, Mick G, Guy N, Fabre N, Giraud P, Nachit-Ouinekh F, Lanteri-Minet M. Behavioral dependence in patients with medication overuse headache: a cross-sectional study in consulting patients using the DSM-IV criteria. *Headache* 2008;48(7):1026-1036.
53. Lundqvist C, Aaseth K, Grande RB, Benth JS, Russell MB. The severity of dependence score correlates with medication overuse in persons with secondary chronic headaches. The Akershus study of chronic headache. *Pain* 2010;148(3):487-491.
54. Limmroth V, Katsarava Z, Fritsche G, Przywara S, Diener HC. Features of medication overuse headache following overuse of different acute headache drugs. *Neurology* 2002;59(7):1011-1014.
55. Diener HC, Limmroth V. Medication-overuse headache: a worldwide problem. *Lancet Neurol* 2004;3(8):475-483.
56. Katsarava Z, Fritsche G, Muessig M, Diener HC, Limmroth V. Clinical features of withdrawal headache following overuse of triptans and other headache drugs. *Neurology* 2001;57(9):1694-1698.

57. Katsarava Z, Muessig M, Dzagnidze A, Fritsche G, Diener HC, Limmroth V. Medication overuse headache: rates and predictors for relapse in a 4-year prospective study. *Cephalalgia* 2005;25(1):12-15.
58. Evers S, Jensen R. Treatment of medication overuse headache - guideline of the EFNS headache panel. *Eur J Neurol* 2011;18(9):1115-1121.
59. Lampl C, Buzath A, Yazdi K, Sandor PS. Ergot and triptan overuse in Austria--an evaluation of clinical data and cost. *Cephalalgia* 2002;22(10):807-811.
60. Limmroth V, Katsarava Z. Medication overuse headache. *Curr Opin Neurol* 2004;17 (3):301-306.
61. Katsarava Z, Jensen R. Medication-overuse headache: where are we now? *Curr Opin Neurol* 2007;20(3):326-330.
62. Ferrari MD. Should we advise patients to treat migraine attacks early? *Cephalalgia* 2004;24(11):915-917.
63. Guitera V, Munoz P, Castillo J, Pascual J. Quality of life in chronic daily headache: a study in a general population. *Neurology* 2002;58(7):1062-1065.
64. Gaist D, Tsiropoulos I, Sindrup SH, Hallas J, Rasmussen BK, Kragstrup J, Gram LF. Inappropriate use of sumatriptan: population based register and interview study [see comments]. *BMJ* 1998;316(7141):1352-1353.
65. Perearnau P, Vuillemet F, Schick J, Weill G. [Patterns of prescription and usage of triptans in Alsace (France): misuse is frequent and avoidable]. *Rev Neurol (Paris)* 2006;162(3):347-357.
66. Lugardon S, Roussel H, Sciortino V, Montastruc JL, Lapeyre-Mestre M. Triptan use and risk of cardiovascular events: a nested-case-control study from the French health system database. *Eur J Clin Pharmacol* 2007;63(8):801-807.
67. Pavone E, Banfi R, Vaiani M, Panconesi A. Patterns of triptans use: a study based on the records of a community pharmaceutical department. *Cephalalgia* 2007.

Part 1

Preventive treatment of migraine

CHAPTER

2

Preventive therapy for migraine: a narrative 'umbrella' review

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ABSTRACT

Background

Migraine is a frequently occurring, disabling disorder. In addition to attack treatment, other useful interventions to reduce the burden of disease (such as preventive treatment) should be applied.

Methods

This is a narrative 'umbrella type' review of preventive migraine treatment based on a search in Medline and Embase. Also presented is an overview of indications for preventive treatment mentioned in guidelines (identified with the same search method), complemented with guidelines from the Guidelines International Network and the National Guideline Clearinghouse.

Results

According to most sources, patients with an average of two or more attacks per month, when using attack treatment, are eligible for preventive treatment. This decision is also based on the (average) duration of attack, severity of attacks, and the response to attack treatment. In the present guidelines there is only limited involvement of patients, whereas this is an essential condition for treatment continuation and success. Before starting prevention, the average attack frequency should be determined, preferably using a headache diary for 2-3 months, because of the highly variable frequency of migraine attacks. None of the currently available preventive medications (such as beta-blockers, sodium valproate, topiramate and candesartan) are specific for migraine. To obtain good outcome, preventive treatment should be titrated up step-by-step to the highest possible dose without side-effects. For about 50% of patients with preventive treatment, a 50% reduction in attack frequency can be achieved and the remaining attacks tend to become less severe.

Interpretation

Preventive treatment of migraine is a worthwhile intervention in primary care, for which beta-blockers and anti-epileptic drugs can be used. For many patients preventive treatment will contribute to a greater reduction in disease burden than can be established with attack treatment alone.

INTRODUCTION

Migraine is a complex, common and disabling disorder of the brain, and its mechanisms are still not completed elucidated [1]. The diagnosis of migraine is sometimes difficult to establish and should be based on the generally accepted criteria of the International Headache Society (IHS 2004) [2].

Preventive treatment of migraine may be considered when, despite optimal attack treatment, the frequency, intensity and duration of attacks severely affect the quality of life. Therefore, prior to initiating preventive treatment, the extent of disease burden should be established. This is difficult and it is not possible to base this on a single consultation. Retrospectively reported symptoms are often not adequately expressed; generally, the last or most violent attack remains strongest in the memory. Furthermore, establishing the migraine burden may be difficult because many patients have a combination of headache types, or have headache as a result of overuse of pain killers, ergotamine or triptans. A headache diary often provides outcome information [3,4], and is essential for revealing clues to the diagnosis, for estimation of use of pain killers, and for determining the frequency of attacks. For a valid estimation of the often strongly fluctuating attack frequency, the diary must be maintained for a period of (minimally) two months [5].

After starting preventive medication, it is recommended that the effectiveness of the treatment be assessed after at least two months use (with the exception of menstrual migraine) [6,7]. In case of preventive treatments, attention should be paid to attack treatment, either via prescribed attack treatment or by self-medication.

These (and other) problems show that it is not an easy decision to start preventive treatment for migraine. Similarly, it is can be difficult to choose between the options. Prior to the decision, it is necessary to establish: the benefits of preventive treatment (specified for all types of treatments), and the threshold from which patients will be eligible for preventive treatment.

This narrative 'umbrella' review aims to provide an overview of the outcome of current preventive treatments, and give an overview of the indications for preventive treatment from relevant guidelines.

METHODS

This review is based on an article previously published in Dutch [8]. For an overview of preventive interventions for migraine, Medline and Embase were searched using the terms migraine and preventive treatment (and synonyms thereof) . We searched for guidelines in the Guideline International Network (GIN) database and the National Guideline Clearinghouse [9,10]. For the present overview a selection was made based the relevance of the resources for the situation in the Netherlands. Because of the diversity in methodology, study endpoints, and drug application schemes and administration,

a systematic analysis of migraine preventive therapy as a whole could not be performed. Therefore, the findings are presented in the format of a so-called `umbrella' review, covering various treatment options.
Summary tables for the various medications were made using Review Manager, version 5.0.24.

Threshold for preventive therapy

The Dutch College of General Practitioners (NHG) guideline on headache, recommends a prevention threshold of two attacks and more [11], whereas the guideline of the Dutch Society of Neurologists states three attacks or more per month as threshold [12]. Other international guidelines provide a divergent range of recommendations (Table 1). Selection of the guidelines in Table 1 was mainly based on the relevance of the guideline (e.g. the number of patients to which it applies). In addition, we present guidelines that are mainly relevant for the Netherlands. We conclude that there is a large diversity in the content of the guidelines, as well as in the factors leading to a decision. The most frequently mentioned factors are:

- attack frequency;
- failure, poor response or side-effects of attack treatment;
- frequency or extent of use of attack treatment;
- reduced quality of life, or inability to perform activities of daily living;
- patient's preference.

Patient preference is mentioned in only a few guidelines. This is in contrast to current opinion that patient preference is a major factor in decision-making related to preventive treatment [1,13-16]. Less mentioned aspects of decision-making on prophylaxis are absenteeism, status after withdrawal of chronic pain treatment, costs of attack treatment, uncommon migraine forms, and frequent or long-lasting aura.

Effectiveness of preventive treatment

The available preventive medicines have not been specifically developed and registered for migraine, and all have other another intended indication. The anti-migraine effects are reported to be 'nicely tolerated'. The effectiveness for roughly all treatments is that in just over 50% of the patients the frequency decreases by 50% [6,7]. In addition, the remaining attacks often become less severe.
General practitioners (GPs) should address a number of potential pitfalls when initiating preventive treatment of migraine. Patients often have motivation problems, partly due to a lack of trust in the efficacy, and frustration when nevertheless attacks occur. Also, many patients resent the daily use of medication [14-16]. Other important pitfalls are a too rapid increase in dose, an insufficiently long or a too low dose, and the use of wrong or obsolete treatments.
A problem often encountered with beta-blockers prescribed for migraine is that they are sometimes changed by drugs belonging to another class (from a cardiovascular perspective), by e.g. cardiologists or internists, thereby losing the benefit for migraine.

Therefore, it is desirable that physicians/neurologists etc. other than GPs have a basic knowledge of the possibilities for preventive treatment of migraine. In addition, patients can also be educated to inform their other caretakers.

Preventive treatments for migraine

Beta-blockers
In the Netherlands, beta-blockers are the most used preventive drugs for migraine and are the first-line choice in the NHG Guideline on headache. The anti-migraine activity is supposed to rely on noradrenergic and serotonergic impact on the central nervous system. In a Cochrane review, 58 trials with a total of 5072 patients were analyzed, in which propranolol was compared 26 times to a placebo and 47 times to another preventive medicine [7]; the daily dosage in these studies ranged from 60-320 mg. Propranolol was more effective than placebo. However, no estimation was possibility of the relation between the effectiveness and dosages used each day [17-20].
The other beta-blockers (metoprolol, atenolol, bisoprolol and nebivolol) were also more effective than placebo, but these drugs do not seem to distinguish themselves from propranolol [21-33]. Because these drugs have less ß2-properties in comparison with propranolol, they may have less side-effects. Beta-blockers with intrinsic sympaticomimetic activity (acebutolol, oxprenolol and pindolol) are not effective in migraine. Side-effects of beta-blockers can be considerable and frequently lead to discontinuation. The occurrence of side-effects shows wide diversity. From the Cochrane review the average percentage of persons dropping-out because of side-effects is 17% [7]. In daily practice, this percentage is probably higher. In case of pregnancy there seem to be no teratogenic effects. Only propranolol and metoprolol are 'labelled' for migraine prevention in the Netherlands. (figure 1, p 30)

Anti-epileptics
The mechanism of anti-epileptics in the preventive treatment of migraine is unclear. Because of the considerable pharmacological impact of these drugs, several assumptions are made. It is assumed that the GABA neurotransmitter, NMDA receptors, catecholamine induced and opioid neurotransmitter systems, and calcium and sodium canals are involved. In the Netherlands two drugs of this group are frequently used: sodium valproate and topiramate. In the Cochrane review, 8 randomized controlled studies with sodium valproate and 7 with topiramate were summarized [6]. Sodium valproate showed to be consistently more effective than placebo [34]. The side-effects of sodium valproate should be taken seriously. In older patients cognitive impairments and Parkinsonism have been reported. The drug is not allowed during pregnancy.
(figure 2, p 31)

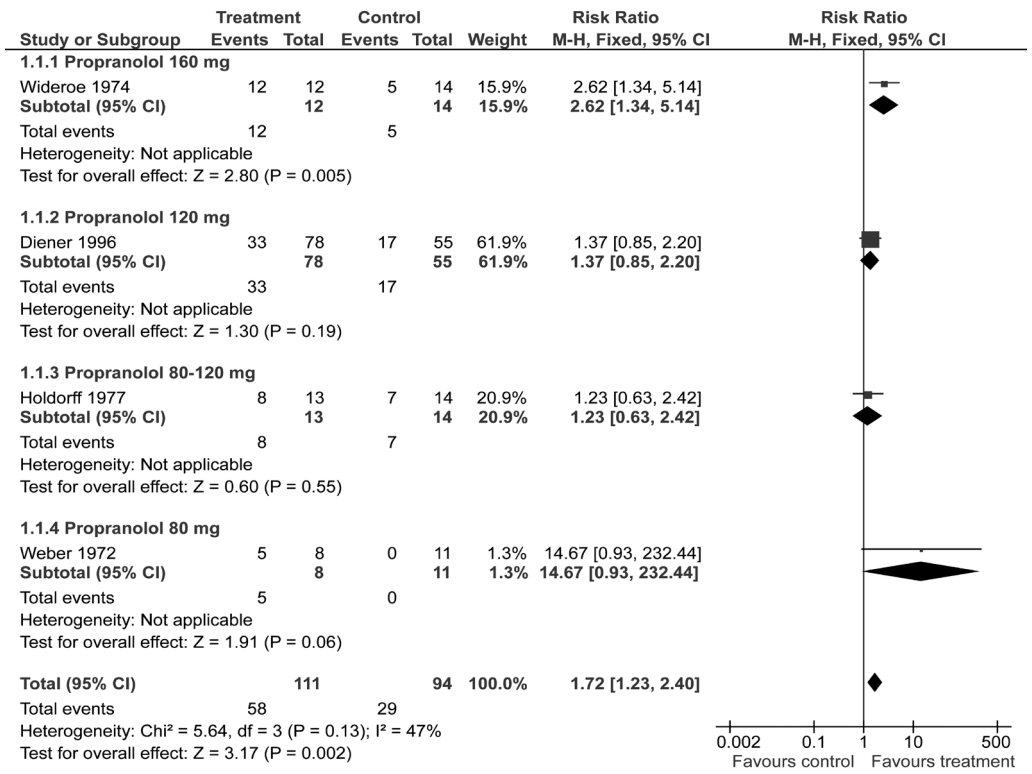

Figure 1. Number of responders in migraine preventive therapy with beta-blockers. Based on Linde K, Cochrane database of reviews 2009[7].

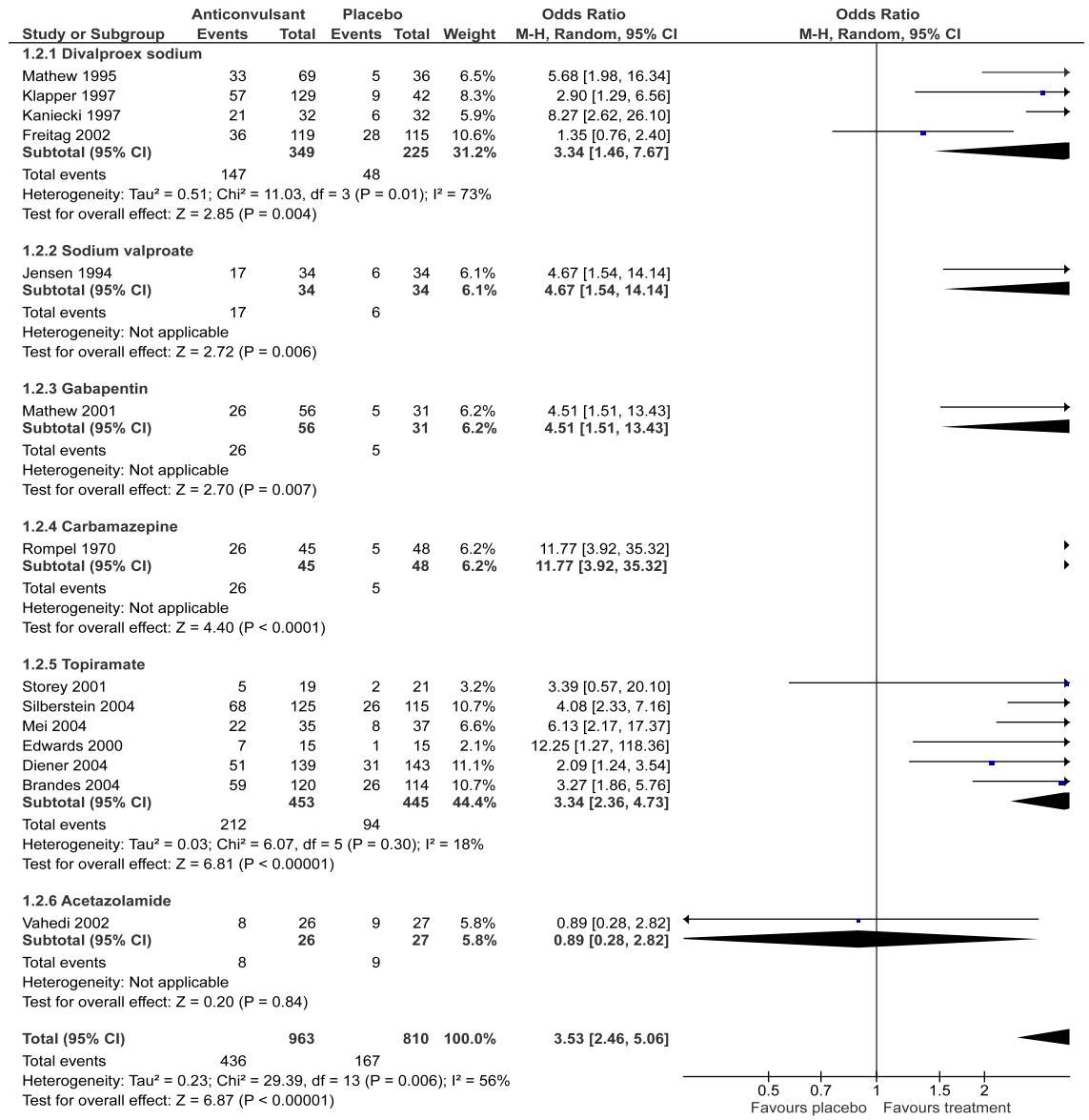

Figure 2. Number of responders in migraine preventive therapy with anti-convulsants. Based on Chronicle E, Cochrane database of reviews 2009[6].

Topiramate has also been shown to improve headache better than placebo [35-38]. The optimum amount is 100 mg daily (in two doses), but many undesirable side-effects have been reported. At a daily dosage of 100 mg side-effects led to discontinuation in 23% of the patients [6]. The drug is not allowed during pregnancy. Two gabapentin trials showed a lowering of migraine attack frequency; however, these studies had methodological shortcomings [39]. After accusations of withholding scientific proof concerning the effectiveness of the drug, doubts related to gabapentin have increased [40]. For the remaining anti-epileptics (carbamazepine, lamotrigine, clonazepam) there is insufficient or no evidence [35,41-43]. In the Cochrane analysis it is concluded that anti-epileptics are an effective preventive treatment of migraine. However, only for sodium valproate and topiramate is there sufficient evidence to justify their use for the prevention of migraine attacks (topiramate is 'labelled' for this indication).

Other treatments in migraine prevention

Of the remaining treatments, flunarizine has been well studied. Nine placebo-controlled studies include a relatively small number of patients [44-52]. In 2 of 9 studies, no advantage of flunarizine was shown compared to placebo [48,49]. The remaining 7 studies showed an advantage. Flunarizine is effective in the prevention of migraine; however, the treatment is no longer popular because of the risk of serious side-effects, such as extrapyramidal dysfunction and drowsiness.

Pizotifen was evaluated in 11 placebo-controlled studies and showed improvement compared with placebo, except in children [53]. However, most of the studies were small, with often no more than 50 patients. Pizotifen is frequently not well tolerated and the most important side-effects are weight increase, fatigue and drowsiness. This means that when weighing the advantages and disadvantages, the result is often negative for pizotifen.

Methysergide has been registered for many years; however, because of the rare side-effects of retroperitoneal, pulmonary and/or endocardial fibrosis, the drug is only to be prescribed by experienced physicians and after very careful assessment.

Antidepressants are frequently prescribed for the treatment of migraine, especially in the USA. Because the evidence for SSRIs is moderate, they are not included in the Dutch guidelines. Amitriptyline can be considered in case of additional tension-type headache, and can be useful in some migraine patients. There is no evidence for the use of SSRIs in migraine [54].

There are studies with lisinopril (ACE inhibitor), candesartan and telmisartan (AII antagonist). The studies with lisinopril and candesartan show benefit, for telmisartan the primary endpoint was not significantly better (probably because of the too small numbers). In spite of the few side-effects of these drugs, the 'level of evidence' is still too low to recommend their large-scale use [55-57].

Acetylsalicylic acid has been used for migraine prevention and some researchers claim success. However, positive preventive effects do not occur in more than 20-26% of the patients and this does not exceed the placebo effect. Therefore, most researchers find

that acetylsalicylic acid is not indicated as preventive migraine therapy [23,58,59].

Three placebo-controlled trials investigated verapamil, but because the results are inconclusive [60-62] there is no place for its use in migraine.

Two placebo-controlled and three open studies in patients with episodic migraine show that the effects of botulinum toxin injections in frontal and occipital muscles do not differ from placebo [63-65]. Trials in patients with chronic migraine (migraine headache on ≥ 15 days/month), have shown that injections with onabotulinumtoxinA lead to a reduction of the impact of migraine [66]. However, whereas the therapeutic gain over placebo was statistically significant, the clinical significance was modest [67].

Riboflavin and coenzyme Q10 each have each been examined in a placebo-controlled study, both being positive. Based on these very limited data, these remedies are not yet recommended [68]. Four out of five controlled studies with tanacetum parthenium (feverfew) were positive [69]; the effectiveness is strongly dependent on the resorption of the obligatory preparation, which limits its practical usability.

Combination therapy in preventive treatment

A few studies explored the combination of different preventive treatments in patients who did not benefit from one single preventive. These studies sometimes include expert opinions or overviews [70-72], case reports or small series [73,74] and a few comparative trials [75-78]. Two studies show a benefit of combination therapy (topiramate plus nortriptyline; beta blocker plus topiramate) [75,76]. In two studies there was no added benefit of the combination (propranolol plus nortriptyline; flunarizine plus topiramate) [77-79]. At present, the use of a combination of different preventives remains uncertain.

Prevention in menstrually-related migraine

The acute treatment of menstrually-related migraine is identical to that of other migraine attacks. Some authors express a preference for naproxen, as this has a reasonable effect on the migraine as well as being effective for menstrual complaints [80].

Pure menstrual migraine attacks occur exclusively on days -2 to +3 of the menstruation period in at least two out of three menstrual cycles. and at on no other moments of the cycle [2].

In menstrually-related migraine all preventive therapies for migraine are applied [81-84]. Because only small studies are available on the efficacy of preventive treatment for menstrually-related migraines, current treatment is actually based on consensus [82-86]. Short-term prevention focuses only on days -2 before to +4 days after start of the menstruation) [83,84,86]. There is also a variation of this strategy, with duration up to 11 days (a somewhat older strategy, day -2 up to +9).

NSAIDs are an option for short-term prophylaxis in general practice, because there is a more or less reliable effect on migraine as well as on menstrual complaints [80,87,88]. As in attack treatment, naproxen is the most often used option [80].

Triptans are also an option in the short-term prophylaxis of migraine [89-96]. Several small studies have shown a consistent positive effect. As the duration of triptan use

does not exceed 6 days each month, medication overuse headache (MOH) is not likely to emerge. When there are also migraine attacks in between menstruations, and those attacks are also treated with triptans, there is a danger of developing MOH . This also applies when using NSAIDs, but for this medication class there is a greater margin. In addition, preventive treatment of menstrual migraines with triptans is relatively costly.

Estrogens are mainly used as short-term prophylaxis. Studies on preventive use of estrogens, especially percutaneous estradiol gel, still show considerable disagreement on effectiveness. Most trials with estrogens show robust effects [83], but some trials have disappointing results [84].

Another option is the continuous use of combined oral contraceptives [83,84,97]. The results are sometimes disappointing; only a proportion of patients respond well to this therapy. Often, when there is a good response to this intervention, there are breakthrough bleedings, resulting in termination of this therapy. A contemporary approach to breakthrough bleedings under continuous oral contraceptive use is that, at the start of a bleeding, a 7-day pause is started. However, it is unclear what the impact of this strategy is on the frequency of migraines.

Because migraine with aura is a risk factor for cerebrovascular accidents and this risk is increased when using oral contraceptives [98], recent guidelines advise not to prescribe oral contraceptives for patients with migraines, especially not for migraine with aura. Young women who have migraine with aura should be strongly advised to stop smoking, and to consider a form of birth control other than oral contraceptives [98].

Preventive treatment in case of medication overuse

The recommended action in case of MOH is withdrawal of the drug that is causing the headache [5,99-102]. In earlier definitions of the IHS classification [2] the disappearance or decrease of the headache after withdrawal was an obligatory criterion for MOH. In the present version, that requirement is replaced by the requirement that the headache should have developed or has markedly worsened during medication overuse. Many studies show a return of daily headache back to a less frequent episodic headache after withdrawal [99,103-120]. In the Netherlands, this knowledge has resulted in the consensus that withdrawal is the preferred approach [11,12]. It is unclear if this approach is sufficiently `evidence based', or just suits Dutch 'culture' (when you use too much of something, this cannot be good and you must stop). And, above all, in the Netherlands, for MOH it is recommended not to add extra drugs.

Some studies on interventions with specific medication have been done on MOH, with varying results. Four studies with topiramate showed a small but significant reduction in headache [121-124]. Studies with sodium valproate also showed relief [125,126]. Sometimes also naproxen is used because of the incorrect assumption that NSAIDs do not increase the risk of MOH [127]. Prednisolone has also been used to reduce withdrawal headache, but this is not supported by controlled clinical trials. Although the evidence is not conclusive [128], the recent European guideline of the European Federation of

Neurological Societies (EFNS) for the treatment of MOH mentions prednisolone for the treatment of withdrawal symptoms, based on three open-label studies and two placebo-controlled trials [129]. The three open-label trials claimed a beneficial effect of prednisolone on the severity and duration of withdrawal symptoms [130-132]. However, due to the low quality, these studies are not a proper basis for a guideline [133]. Of the two placebo-controlled trials, in the largest trial (n=102) prednisolone showed no benefit compared to placebo, and the other smaller trial (n=18) suggests some benefit of prednisolone [128,134]. According to the EFNS, prednisolone may have an advantage, because all other medications even cause MOH. However, it is doubtful whether this is the right argument when claims of efficacy are unsupported. The EFNS guideline also mentioned amitriptyline as a possible treatment for withdrawal symptoms; however, this is also not based on evidence, but on consensus [129].

There are no randomised direct comparisons between withdrawal with and without using supportive medication [111]. Drug intervention studies for MOH only show small improvements. On the other hand, the studies with withdrawal of the causing agent show a consistent effect [135-137].

In conclusion, withdrawal seems to be the best intervention and best matches the Dutch attitude regarding drug use in general. In addition, there is some evidence for the effectiveness of other strategies, such as behavioural therapies [138-147].

Many GPs have noted that MOH has some characteristics of addiction, comparable to alcohol or smoking addiction. Characteristic of MOH is that patients at the acute stage of withdrawal experience a strong increase in headache (rebound phenomenon). MOH patients often experience some results from attack medication; it can temporarily relieve the complaints. In general, patients do not recognize that the daily use of medication is the actual cause of the headache.

Comparative studies on preventive therapy

Many comparative studies between preventive treatments have been performed, with differing combinations, mainly with beta-blockers, sodium valproate, topiramate, flunarizine, pizotifen, methysergide, verapamil, nimodipine and amitriptyline [6,7,79,148-169]. In these studies, the most frequently used comparator is flunarizine [44,47,79,149-164]. As the use of flunarizine often leads to side-effects such as drowsiness, lethargy, weight gain, increased appetite, depression and extrapyramidal symptoms, these comparisons with flunarizine are of limited value for daily practice.

A point of interest is the comparison within the group of anti-epileptic drugs. Only one study has compared sodium valproate with topiramate, and showed a small advantage of topiramate; however, the daily dosages of both drugs were lower than usual [169]. For the remaining drugs no significant differences were shown.

DISCUSSION

In general, preventive treatment of migraine is a well accessible and at times useful intervention, but only when carried out correctly and carefully. As about half the disease burden can be decreased, there is a large gain for patients with a high disease burden. Preventive treatment for migraine is a tailor-made task, adapted to the individual patient. Table 2 presents a summary of the principles of preventive migraine treatment, and table 3 lists the treatments used.

Table 2. Principles of preventive treatment of migraine; recommendations based on the outcome of the present review

Basic principles of preventive migraine treatment	
Indication	– At least two or more attacks per month – Patient preference
Factors to take into account for indication	Attack intensity, duration, response to attack treatment, extent of attack medication, quality of life, and interference with patient activities
Important points	– Based on average attack frequency in three preceding months – Start with low dosage and titrate up step-by-step, until maximal accepted dose without side-effects – Always in combination with provision of attack treatment – Individualized approach to treatment type and dosage (avoid side-effects or interference with lifestyle) – Beta-blockers and anticonvulsants both well applicable in general practice
Duration	– At least 2-3 months before effect assessment – When effective, continuation for 9-12 months – In case of recurrence start preventive treatment again

'First choice' in preventive treatment are beta-blockers (propranolol and metoprolol) and anti-epileptic drugs (sodium valproate and topiramate). 'Second choice' preventives are those which have demonstrated some preventive effect, but with limited evidence. These treatments come into play when 'first choice' treatments are ineffective or not tolerated, and the patient is motivated for further attempts. 'Third choice' treatments have demonstrated preventive effect, but sometimes at the cost of severe side-effects, or only with important and specific terms and conditions. Botulinum toxin does not show convincing benefits in episodic migraine whereas in chronic migraine there can be some benefit; however, the therapeutic gain seems very modest [67].

Table 3. Available medications for the preventive treatment of migraine

	Drug	**Dosage (step by step titration)**
First choice	Propranolol	40-240 mg
	Metoprolol	100-200 mg
	Sodium -valproate	1000 - 1500 mg (mostly 50% compared to epilepsy, phasing out schedule necessary)
	Topiramate	50 bd (25-100 mg)
Second choice	Atenolol, bisoprolol, nebivolol	Regular dosage (titration)
	Candesartan	16 mg
	Lisinopril	5-10 mg
	Telmisartan	80 mg
Third choice (for physicians with special interest)	Pizotifeen	More dis- than advantages, weight gain
	Flunarizine	Rare side effects (extrapyramidal symptoms)
	Methysergide	Interval treatment, serious adverse events
	Amitriptyline	Conflicting evidence
Insufficient evidence, no proven efficacy, too many / serious side-effects	Gabapentin, lamotrigin, SSRIs, acetylsalicylic acid, verapamil, riboflavin, botulinum toxin, tenacetum partenium	

Table 1. Indications for preventive treatment of migraine addressed in guidelines

Organisation	Attack frequency / month	Attack intensity	Attack duration	Response to attack treatment	Extent of attack treatment	Quality of life	Interference with activities	Costs	Patient preference	Additional	Level of care covered*
Dutch College of General Practitioners [11]	2 or more	-	-	-	-	-	-	-	Yes, in agreement	Not in case of MOH	Primary
Domus Medica, Society of General Practitioners, Belgium [176]	2 or more	-	-	Yes	Yes#	-	Yes	-	Yes, willing-ness daily medication	Frequent, very long, or uncomfortable auras	Primary
Migraine in Primary Care Advisers (MIPCA), [177] *England*	4 or more	-	-	Yes	-	-	-	-		-	Primary
American Academy of Family Physicians [178]	2 or more	Yes	Yes#	Yes	> 2 days / week		-	Yes	Yes#	Uncommon migraine conditions	Primary
Dutch Society for Neurologists [12]	3 or more	Yes	-	Yes	> 8 days / month	-	-	-	-	-	Primary and secondary
EFNS (European Federation National Neurological Societies) [179]	2 or more	-	-	Yes	-	-	Yes	-	-	Frequent, very long, or uncomfortable auras	Primary and secondary
AAN (American Neurological Society) [180]	Yes#	-	-	Yes	Yes#	-	Yes	Yes	Yes, opinion on severity	Adverse effect attack treatment, uncom-mon migraine conditions	Primary and secondary
Canadian Medical Association [181]	3 or more	Yes		Yes	-	Yes	-	-	Yes#	-	Primary and secondary
Institute for Clinical Systems Improvement, USA [182]	3 or more	Yes	Yes	-	-	-	-		Yes	-	Primary, second-ary and tertiary
BASH guideline (British Association for the Study of Headache) [183]	Yes#	-	-	Yes	Yes#	-	Yes	-	Yes#	Not in case of MOH,	Primary, second-ary and tertiary
Scottish Intercollegiate Guidelines Network (SIGN) [184]	Yes#	-	-	Yes	-	-	Yes	-	-	Uncommon migraine conditions	Primary, second-ary and tertiary
National Agency of Accreditation and Evaluation in Health, France (ANAES) [185]	Yes#	Yes	-	-	> 6-8 dose / month		Yes	-	-	-	Primary, second-ary and tertiary
German Society for Neurology (DGN) [186]	3 or more	Yes	> 72 hours	Yes	Yes	Yes	Yes	-	-	Uncommon migraine conditions	Primary, second-ary and tertiary
German Migraine and Headache Society (DMKG) [187]	3 or more	-	> 72 hours	Yes	> 10 days / month	Yes	-	-	-	Uncommon migraine conditions	Primary, second-ary and tertiary

 # Unspecified. MOH = medication overuse headache

For combination treatment for prevention of migraine, the study results are so heterogeneous that no clear positioning is possible. At this time it seems not to be recommended to launch preventive combination therapy in primary care, something that might not apply to treatment-resistant cases in secondary or tertiary care.
In practice, first a well-founded diagnosis is needed, preferably based on a headache diary. Only when the patient is convinced of the advantages of preventive therapy can one expect patient compliance. The expectations of patient and physician should be realistic; if not, the probability of treatment failure increases. The dosage scheme must be appropriate for the social (including professional) context of the patient. The treatment choice is partially based on the co-morbidity. The dosage and way of administration must be clear and adequate. Especially for topiramate, slow level-up titration is extremely important. However, also for beta-blockers and certainly for sodium valproate slow level-up is recommend. The slogan is "start low and go slow".
The duration of the treatment before evaluation of its effectiveness should span at least two months. An effective treatment is continued for 6-12 months; after that, a trial of a run-down is advised. Should the frequency of migraine attacks increase, the duration of the treatment will be prolonged. Treatment results and the consequences of the run-down of prophylaxis should be evaluated with a headache diary
The two groups of medication successfully used in the preventive treatment of migraine are beta-blockers and anticonvulsants. However, it is difficult to compare these treatments because they have a totally different action and side-effects, and also different dosage regimens. Therefore, only a narrative review is possible
Also with regard to the indication for preventive therapy, only a narrative approach is possible.
Although there are more overall reviews on the preventive treatment of migraine [1,170-174], they are more superficial in nature, and are generally more positive about the application of preventive drugs in (general) practice than are the authors of this article. These latter reviews seem to lack critical appraisal. Authors often recommend antidepressants, whereas we think they have limited value because of their limited effectiveness. A major difference also lies in the frequent recommendation of SSRIs, which we do not advise. In general, many more drugs are recommended than are discussed in the present review [175].
In most recommendations, the threshold for starting preventive treatment is almost always authority based. Regarding indication, further research into the needs of the patient is warranted [16]. For many patients preventive treatment will contribute to a greater reduction in disease burden compared to attack treatment alone. Preventive treatment of migraine is a worthwhile intervention in primary care, for which both beta-blockers and anti-epileptic drugs can be effectively used.

References

1. Goadsby PJ, Sprenger T. Current practice and future directions in the prevention and acute management of migraine. *Lancet Neurol* 2010;9(3):285-298.
2. Headache classification subcommittee of the International Headache Society. The International Classification of Headache Disorders. *Cephalalgia* 2004;24(supplement 1):8-160.
3. Nappi G, Jensen R, Nappi RE, Sances G, Torelli P, Olesen J. Diaries and calendars for migraine. A review. *Cephalalgia* 2006;26(8):905-916.
4. Phillip D, Lyngberg A, Jensen R. Assessment of headache diagnosis. A comparative population study of a clinical interview with a diagnostic headache diary. *Cephalalgia* 2007;27(1):1-8.
5. Dekker F, Wiendels N, de Valk V, van der Vliet C, Knuistingh Neven A, Assendelft WJJ, Ferrari MD. Triptan overuse in the Dutch general population: A nationwide pharmaco-epidemiology database analysis in 6.7 million people. *Cephalalgia* 2011;31(8):943-952.
6. Mulleners WM, Chronicle EP. Anticonvulsants in migraine prophylaxis: a Cochrane review. *Cephalalgia* 2008;28(6):585-597.
7. Linde K, Rossnagel K. Propranolol for migraine prophylaxis. *Cochrane Database Syst Rev* 2004;(2):CD003225.
8. Mulleners WM, Haan J, Dekker F, Ferrari MD. [Preventive treatment for migraine.]. *Ned Tijdschr Geneeskd* 2010;154(29):A1512.
9. Guidelines International Network. 4-10-2011. 1-11-2011. www.g-i-n.net.
10. National Guideline Clearinghouse. 2011. 1-11-2011. www.guideline.gov.
11. Grol MH, Neven AK, Pijnenborg L, Goudswaard AN. [Summary of the practice guideline 'Headache' from the Dutch College of General Practitioners]. *Ned Tijdschr Geneeskd* 2006;150(6):305-309.
12. Couturier EG, Bomhof MA, Gooskens R, Keyser A, Mulleners WM. Richtlijnen diagnostiek en behandeling chronisch recidiverende hoofdpijn zonder neurologische afwijkingen. Utrecht, Nederlandse Vereniging voor Neurologie. 2008.
13. D'Amico D, Tepper SJ. Prophylaxis of migraine: general principles and patient acceptance. *Neuropsychiatr Dis Treat* 2008;4(6):1155-1167.
14. Dekker, F., Knuistingh Neven, A., Andriesse, B., Kernick, D., Ferrari, M. D., and Assendelft, W. J. J. Prophylactic treatment of migraine; the patient's view, a qualitative study. *BMC Fam Pract* 2012;13(1):13.
15. Dekker, F., Knuistingh Neven, A, Andriesse, B, Kernick, D., Ferrari, MD, and Assendelft, W. J. J. Prophylactic treatment of migraine by general practitioners: a qualitative study. *Br J Gen Pract* 2012;62(597):268-274..
16. Kol CM, Dekker F, Neven AK, Assendelft WJ, Blom JW. Acceptance or rejection of prophylactic medicine in patients with migraine: a cross-sectional study. *Br J Gen Pract* 2008;58(547):98-101.
17. Wideroe TE, Vigander T. Propranolol in the treatment of migraine. *Br Med J* 1974;2 (5921):699-701.

18. Diener HC, Foh M, Iaccarino C, Wessely P, Isler H, Strenge H, Fischer M, Wedekind W, Taneri Z. Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. The Study group. *Cephalalgia* 1996;16(6):441-447.
19. Holdorff B, Sinn M, Roth G. [Propranolol for prophylaxis of migraine (author's transl)]. *Med Klin* 1977;72(25):1115-1118.
20. Weber RB, Reinmuth OM. The treatment of migraine with propranolol. *Neurology* 1972;22(4):366-369.
21. Schellenberg R, Lichtenthal A, Wohling H, Graf C, Brixius K. Nebivolol and metoprolol for treating migraine: an advance on beta-blocker treatment? *Headache* 2008;48(1):118-125.
22. Siniatchkin M, Andrasik F, Kropp P, Niederberger U, Strenge H, Averkina N, Lindner V, Stephani U, Gerber WD. Central mechanisms of controlled-release metoprolol in migraine: a double-blind, placebo-controlled study. *Cephalalgia* 2007;27(9):1024-1032.
23. Diener HC, Hartung E, Chrubasik J, Evers S, Schoenen J, Eikermann A, Latta G, Hauke W. A comparative study of oral acetylsalicyclic acid and metoprolol for the prophylactic treatment of migraine. A randomized, controlled, double-blind, parallel group phase III study. *Cephalalgia* 2001;21(2):120-128.
24. Sandor PS, Afra J, Ambrosini A, Schoenen J. Prophylactic treatment of migraine with beta-blockers and riboflavin: differential effects on the intensity dependence of auditory evoked cortical potentials. *Headache* 2000;40(1):30-35.
25. Hesse J, Mogelvang B, Simonsen H. Acupuncture versus metoprolol in migraine prophylaxis: a randomized trial of trigger point inactivation. *J Intern Med* 1994; 235(5):451-456.
26. Worz R, Reinhardt-Benmalek B, Foh M, Grotemeyer KH, Scharafinski HW. [Prevention of migraine using bisoprolol. Results of a double-blind study versus metoprolol]. *Fortschr Med* 1992;110(14):268-272.
27. Gerber WD, Diener HC, Scholz E, Niederberger U. Responders and non-responders to metoprolol, propranolol and nifedipine treatment in migraine prophylaxis: a dose-range study based on time-series analysis. *Cephalalgia* 1991;11(1):37-45.
28. Grotemeyer KH, Scharafinski HW, Schlake HP, Husstedt IW. Acetylsalicylic acid vs. metoprolol in migraine prophylaxis--a double-blind cross-over study. *Headache* 1990;30(10):639-641.
29. Steiner TJ, Joseph R, Hedman C, Rose FC. Metoprolol in the prophylaxis of migraine: parallel-groups comparison with placebo and dose-ranging follow-up. *Headache* 1988;28(1):15-23.
30. Olsson JE, Behring HC, Forssman B, Hedman C, Hedman G, Johansson F, Kinnman J, Palhagen SE, Samuelsson M, Strandman E. Metoprolol and propranolol in migraine prophylaxis: a double-blind multicentre study. *Acta Neurol Scand* 1984; 70(3):160-168.

31. Kangasniemi P, Hedman C. Metoprolol and propranolol in the prophylactic treatment of classical and common migraine. A double-blind study. *Cephalalgia* 1984;4(2):91-96.
32. Andersson PG, Dahl S, Hansen JH, Hansen PE, Hedman C, Kristensen TN, de Fine OB. Prophylactic treatment of classical and non-classical migraine with metoprolol--a comparison with placebo. *Cephalalgia* 1983;3(4):207-212.
33. van de Ven L.L., Franke CL, Koehler PJ. Prophylactic treatment of migraine with bisoprolol: a placebo-controlled study. *Cephalalgia* 1997;17(5):596-599.
34. Hering R, Kuritzky A. Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. *Cephalalgia* 1992;12(2):81-84.
35. Brandes JL, Saper JR, Diamond M, Couch JR, Lewis DW, Schmitt J, Neto W, Schwabe S, Jacobs D. Topiramate for migraine prevention: a randomized controlled trial. *JAMA* 2004;291(8):965-973.
36. Edwards KR, Potter DL, Wu SC, Kamin M, Hulihan J. Topiramate in the preventive treatment of episodic migraine: a combined analysis from pilot, double-blind, placebo-controlled trials. *CNS Spectr* 2003;8(6):428-432.
37. Silberstein SD, Neto W, Schmitt J, Jacobs D. Topiramate in migraine prevention: results of a large controlled trial. *Arch Neurol* 2004;61(4):490-495.
38. Storey JR, Calder CS, Hart DE, Potter DL. Topiramate in migraine prevention: a double-blind, placebo-controlled study. *Headache* 2001;41(10):968-975.
39. Di Trapani G, Mei D, Marra C, Mazza S, Capuano A. Gabapentin in the prophylaxis of migraine: a double-blind randomized placebo-controlled study. *Clin Ter* 2000; 151(3):145-148.
40. Landefeld CS, Steinman MA. The Neurontin legacy--marketing through misinformation and manipulation. *N Engl J Med* 2009;360(2):103-106.
41. Stensrud P, Sjaastad O. Clonazepam (rivotril) in migraine prophylaxis. *Headache* 1979;19(6):333-334.
42. Steiner TJ, Findley LJ, Yuen AW. Lamotrigine versus placebo in the prophylaxis of migraine with and without aura. *Cephalalgia* 1997;17(2):109-112.
43. Ghose K, Niven BE, Berry D. A double-blind crossover comparison of the effects of vigabatrin with placebo in the prevention of migraine headache. *J Headache Pain* 2002;3(2):79-85.
44. Louis P. A double-blind placebo-controlled prophylactic study of flunarizine (Sibelium) in migraine. *Headache* 1981;21(6):235-239.
45. Frenken CW, Nuijten ST. Flunarizine, a new preventive approach to migraine. A double-blind comparison with placebo. *Clin Neurol Neurosurg* 1984;86(1):17-20.
46. Mentenopoulos G, Manafi T, Logothetis J, Bostantzopoulou S. Flunarizine in the prevention of classical migraine: a placebo-controlled evaluation. *Cephalalgia* 1985;5 Suppl 2135-140.
47. Sorensen PS, Hansen K, Olesen J. A placebo-controlled, double-blind, cross-over trial of flunarizine in common migraine. *Cephalalgia* 1986;6(1):7-14.

48. Thomas M, Behari M, Ahuja GK. Flunarizine in migraine prophylaxis: an Indian trial. *Headache* 1991;31(9):613-615.
49. al Deeb SM, Biary N, Bahou Y, al JM, Khoja W. Flunarizine in migraine: a double-blind placebo-controlled study (in a Saudi population). *Headache* 1992;32(9):461-462.
50. Diamond S, Schenbaum H. Flunarizine, a calcium channel blocker, in the prophylactic treatment of migraine. *Headache* 1983;23(1):39-42.
51. Sorge F, Marano E. Flunarizine v. placebo in childhood migraine. A double-blind study. *Cephalalgia* 1985;5 Suppl 2145-148.
52. Sorge F, De SR, Marano E, Nolano M, Orefice G, Carrieri P. Flunarizine in prophylaxis of childhood migraine. A double-blind, placebo-controlled, crossover study. *Cephalalgia* 1988;8(1):1-6.
53. Gillies D, Sills M, Forsythe I. Pizotifen (Sanomigran) in childhood migraine. A double-blind controlled trial. *Eur Neurol* 1986;25(1):32-35.
54. Moja PL, Cusi C, Sterzi RR, Canepari C. Selective serotonin re-uptake inhibitors (SSRIs) for preventing migraine and tension-type headaches. *Cochrane Database Syst Rev* 2005;(3):CD002919.
55. Schrader H, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. *BMJ* 2001;322(7277):19-22.
56. Tronvik E, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. *JAMA* 2003;289(1):65-69.
57. Diener HC, Gendolla A, Feuersenger A, Evers S, Straube A, Schumacher H, Davidai G. Telmisartan in migraine prophylaxis: a randomized, placebo-controlled trial. *Cephalalgia* 2009.
58. Bensenor IM, Cook NR, Lee IM, Chown MJ, Hennekens CH, Buring JE. Low-dose aspirin for migraine prophylaxis in women. *Cephalalgia* 2001;21(3):175-183.
59. Buring JE, Peto R, Hennekens CH. Low-dose aspirin for migraine prophylaxis. *JAMA* 1990;264(13):1711-1713.
60. Solomon GD, Scott A.F. Verapamil and propranolol in migraine prophylaxis: a double-blind, crossover study. *Headache* 1986;26325.
61. Solomon GD, Steel JG, Spaccavento LJ. Verapamil prophylaxis of migraine. A double-blind, placebo-controlled study. *JAMA* 1983;250(18):2500-2502.
62. McGoon MD, Vlietstra RE, Holmes DR, Jr., Osborn JE. The clinical use of verapamil. *Mayo Clin Proc* 1982;57(8):495-510.
63. Obermann M, Diener HC. Is botulinum toxin useful in treating headache? No. *Curr Treat Options Neurol* 2009;11(1):24-31.
64. Evers S, Vollmer-Haase J, Schwaag S, Rahmann A, Husstedt IW, Frese A. Botulinum toxin A in the prophylactic treatment of migraine--a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2004;24(10):838-843.

65. Evers S, Rahmann A, Vollmer-Haase J, Husstedt IW. Treatment of headache with botulinum toxin A--a review according to evidence-based medicine criteria. *Cephalalgia* 2002;22(9):699-710.
66. Lipton RB, Varon SF, Grosberg B, McAllister PJ, Freitag F, Aurora SK, Dodick DW, Silberstein SD, Diener HC, DeGryse RE, Nolan ME, Turkel CC. Onabotulinumtoxin A improves quality of life and reduces impact of chronic migraine. *Neurology* 2011;77(15):1465-1472.
67. Robertson CE, Garza I. Critical analysis of the use of onabotulinumtoxinA (botulinum toxin type A) in migraine. *Neuropsychiatr Dis Treat* 2012;835-48.
68. Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis. A randomized controlled trial. *Neurology* 1998;50(2):466-470.
69. Silberstein SD, Goadsby PJ. Migraine: preventive treatment. *Cephalalgia* 2002; 22(7):491-512.
70. Evans RW, Pascual J, Lainez MJ, Leira R. Bending the rule of monotherapy for migraine prevention? *Headache* 2005;45(6):748-750.
71. Krymchantowski AV, Bigal ME. Polytherapy in the preventive and acute treatment of migraine: fundamentals for changing the approach. *Expert Rev Neurother* 2006;6(3):283-289.
72. Peterlin BL, Calhoun AH, Siegel S, Mathew NT. Rational combination therapy in refractory migraine. *Headache* 2008;48(6):805-819.
73. Krymchantowski AV, da Cunha JC. Low-Dose Topiramate Plus Sodium Divalproate for Positive Responders Intolerant to Full-Dose Monotherapy. *Headache* 2011.
74. Pascual J, Leira R, Lainez JM. Combined therapy for migraine prevention? Clinical experience with a beta-blocker plus sodium valproate in 52 resistant migraine patients. *Cephalalgia* 2003;23(10):961-962.
75. Krymchantowski AV, da Cunha JC, Bigal ME. Topiramate plus nortriptyline in the preventive treatment of migraine: a controlled study for nonresponders. *J Headache Pain* 2012;13(1):53-59.
76. Pascual J, Rivas MT, Leira R. Testing the combination beta-blocker plus topiramate in refractory migraine. *Acta Neurol Scand* 2007;115(2):81-83.
77. Domingues RB, Silva AL, Domingues SA, Aquino CC, Kuster GW. A double-blind randomized controlled trial of low doses of propranolol, nortriptyline, and the combination of propranolol and nortriptyline for the preventive treatment of migraine. *Arq Neuropsiquiatr* 2009;67(4):973-977.
78. Luo N, Di W, Zhang A, Wang Y, Ding M, Qi W, Zhu Y, Massing MW, Fang Y. A randomized, one-year clinical trial comparing the efficacy of topiramate, flunarizine, and a combination of flunarizine and topiramate in migraine prophylaxis. *Pain Med* 2012;13(1):80-86.
79. Bordini CA, Arruda MA, Ciciarelli MC, Speciali JG. Propranolol vs flunarizine vs flunarizine plus propranolol in migraine without aura prophylaxis. A double-blind trial. *Arq Neuropsiquiatr* 1997;55(3B):536-541.

80. Sances G, Martignoni E, Fioroni L, Blandini F, Facchinetti F, Nappi G. Naproxen sodium in menstrual migraine prophylaxis: a double-blind placebo controlled study. *Headache* 1990;30(11):705-709.
81. Allais G, Sanchez Del RM, Diener HC, Benedetto C, Pfeil J, Schauble B, van OJ. Perimenstrual migraines and their response to preventive therapy with topiramate. *Cephalalgia* 2010.
82. Pringsheim T, Davenport WJ, Dodick D. Acute treatment and prevention of menstrually related migraine headache: evidence-based review. *Neurology* 2008;70 (17):1555-1563.
83. MacGregor EA. Menstrual migraine. *Curr Opin Neurol* 2008;21(3):309-315.
84. Loder E, Rizzoli P, Golub J. Hormonal management of migraine associated with menses and the menopause: a clinical review. *Headache* 2007;47(2):329-340.
85. Allais G, Bussone G, De LC, Mana O, Benedetto C. Advanced strategies of short-term prophylaxis in menstrual migraine: state of the art and prospects. *Neurol Sci* 2005;26 Suppl 2s125-s129.
86. Brandes JL. The influence of estrogen on migraine: a systematic review. *JAMA* 2006;295(15):1824-1830.
87. Al-Waili NS. Treatment of menstrual migraine with prostaglandin synthesis inhibitor mefenamic acid: double-blind study with placebo. *Eur J Med Res* 2000;5 (4):176-182.
88. Von Seggern RL, Mannix LK, Adelman JU. Rofecoxib in the prevention of perimenstrual migraine: an open-label pilot trial. *Headache* 2004;44(2):160-165.
89. Newman L, Mannix LK, Landy S, Silberstein S, Lipton RB, Putnam DG, Watson C, Jobsis M, Batenhorst A, O'Quinn S. Naratriptan as short-term prophylaxis of menstrually associated migraine: a randomized, double-blind, placebo-controlled study. *Headache* 2001;41(3):248-256.
90. Guidotti M, Mauri M, Barrila C, Guidotti F, Belloni C. Frovatriptan vs. transdermal oestrogens or naproxen sodium for the prophylaxis of menstrual migraine. *J Headache Pain* 2007;8(5):283-288.
91. Newman LC, Lipton RB, Lay CL, Solomon S. A pilot study of oral sumatriptan as intermittent prophylaxis of menstruation-related migraine. *Neurology* 1998;51 (1):307-309.
92. Silberstein SD, Elkind AH, Schreiber C, Keywood C. A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. *Neurology* 2004; 63(2):261-269.
93. Tuchman MM, Hee A, Emeribe U, Silberstein S. Oral zolmitriptan in the short-term prevention of menstrual migraine: a randomized, placebo-controlled study. *CNS Drugs* 2008;22(10):877-886.
94. Mannix LK, Savani N, Landy S, Valade D, Shackelford S, Ames MH, Jones MW. Efficacy and tolerability of naratriptan for short-term prevention of menstrually related migraine: data from two randomized, double-blind, placebo-controlled studies. *Headache* 2007;47(7):1037-1049.

95. Brandes JL, Poole A, Kallela M, Schreiber CP, MacGregor EA, Silberstein SD, Tobin J, Shaw R. Short-term frovatriptan for the prevention of difficult-to-treat menstrual migraine attacks. *Cephalalgia* 2009;29(11):1133-1148.
96. Moschiano F, Allais G, Grazzi L, Usai S, Benedetto C, D'Amico D, Roncolato M, Bussone G. Naratriptan in the short-term prophylaxis of pure menstrual migraine. *Neurol Sci* 2005;26 Suppl 2s162-s166.
97. Edelman AB, Gallo MF, Jensen JT, Nichols MD, Schulz KF, Grimes DA. Continuous or extended cycle vs. cyclic use of combined oral contraceptives for contraception. *Cochrane Database Syst Rev* 2005;(3):CD004695.
98. Schurks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. *BMJ* 2009;339b3914.
99. Mathew NT, Kurman R, Perez F. Drug induced refractory headache--clinical features and management. *Headache* 1990;30(10):634-638.
100. Wiendels NJ, Knuistingh Neven A, Rosendaal FR, Spinhoven P, Zitman FG, Assendelft WJJ, Ferrari MD. Chronic frequent headache in the general population: prevalence and associated factors. *Cephalalgia* 2006;26(12):1434-1442.
101. Wiendels NJ, van der Geest MC, Knuistingh Neven A, Ferrari MD, Laan LAEM. Chronic daily headache in children and adolescents. *Headache* 2005;45(6):678-683.
102. Wiendels NJ, van Haestregt A, Knuistingh Neven A, Spinhoven P, Zitman FG, Assendelft WJJ, Ferrari MD. Chronic frequent headache in the general population: comorbidity and quality of life. *Cephalalgia* 2006;26(12):1443-1450.
103. Baumgartner C, Wessely P, Bingol C, Maly J, Holzner F. Longterm prognosis of analgesic withdrawal in patients with drug- induced headaches. *Headache* 1989;29(8):510-514.
104. Bigal ME, Rapoport AM, Sheftell FD, Tepper SJ, Lipton RB. Transformed migraine and medication overuse in a tertiary headache centre--clinical characteristics and treatment outcomes. *Cephalalgia* 2004;24(6):483-490.
105. Diener HC, Dichgans J, Scholz E, Geiselhart S, Gerber WD, Bille A. Analgesic-induced chronic headache: long-term results of withdrawal therapy. *J Neurol* 1989;236(1):9-14.
106. Fritsche G, Eberl A, Katsarava Z, Limmroth V, Diener HC. Drug-induced headache: long-term follow-up of withdrawal therapy and persistence of drug misuse. *Eur Neurol* 2001;45(4):229-235.
107. Hering R, Steiner TJ. Abrupt outpatient withdrawal of medication in analgesic-abusing migraineurs. *Lancet* 1991;337(8755):1442-1443.
108. Katsarava Z, Fritsche G, Muessig M, Diener HC, Limmroth V. Clinical features of withdrawal headache following overuse of triptans and other headache drugs. *Neurology* 2001;57(9):1694-1698.
109. Katsarava Z, Limmroth V, Finke M, Diener HC, Fritsche G. Rates and predictors for relapse in medication overuse headache: A 1- year prospective study. *Neurology* 2003;60(10):1682-1683.

110. Katsarava Z, Muessig M, Dzagnidze A, Fritsche G, Diener HC, Limmroth V. Medication overuse headache: rates and predictors for relapse in a 4-year prospective study. *Cephalalgia* 2005;25(1):12-15.
111. Krymchantowski AV, Moreira PF. Out-patient detoxification in chronic migraine: comparison of strategies. *Cephalalgia* 2003;23(10):982-993.
112. Pini LA, Cicero AF, Sandrini M. Long-term follow-up of patients treated for chronic headache with analgesic overuse. *Cephalalgia* 2001;21(9):878-883.
113. Relja G, Granato A, Bratina A, Antonello RM, Zorzon M. Outcome of medication overuse headache after abrupt in-patient withdrawal. *Cephalalgia* 2006;26(5):589-595.
114. Rossi P, Di Lorenzo C, Faroni J, Cesarino F, Nappi G. Advice alone vs. structured detoxification programmes for medication overuse headache: a prospective, randomized, open-label trial in transformed migraine patients with low medical needs. *Cephalalgia* 2006;26(9):1097-1105.
115. Schnider P, Aull S, Baumgartner C, Marterer A, Wober C, Zeiler K, Wessely P. Long-term outcome of patients with headache and drug abuse after inpatient withdrawal: five-year follow-up. *Cephalalgia* 1996;16(7):481-485.
116. Suhr B, Evers S, Bauer B, Gralow I, Grotemeyer KH, Husstedt IW. Drug-induced headache: long-term results of stationary versus ambulatory withdrawal therapy. *Cephalalgia* 1999;19(1):44-49.
117. Tribl GG, Schnider P, Wober C, Aull S, Auterith A, Zeiler K, Wessely P. Are there predictive factors for long-term outcome after withdrawal in drug-induced chronic daily headache? *Cephalalgia* 2001;21(6):691-696.
118. Warner JS. Prolonged recovery from rebound headaches. *Headache* 2001;41(8):817-822.
119. Young WB. Medication Overuse Headache. *Curr Treat Options Neurol* 2001;3(2):181-188.
120. Zeeberg P, Olesen J, Jensen R. Probable medication-overuse headache. *Neurology* 2006.
121. Silvestrini M, Bartolini M, Coccia M, Baruffaldi R, Taffi R, Provinciali L. Topiramate in the treatment of chronic migraine. *Cephalalgia* 2003;23(8):820-824.
122. Mei D, Ferraro D, Zelano G, Capuano A, Vollono C, Gabriele C, Di TG. Topiramate and triptans revert chronic migraine with medication overuse to episodic migraine. *Clin Neuropharmacol* 2006;29(5):269-275.
123. Silberstein SD, Lipton RB, Dodick DW, Freitag FG, Ramadan N, Mathew N, Brandes JL, Bigal M, Saper J, Ascher S, Jordan DM, Greenberg SJ, Hulihan J. Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. *Headache* 2007;47(2):170-180.
124. Diener HC, Bussone G, Van Oene JC, Lahaye M, Schwalen S, Goadsby PJ. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2007;27(7):814-823.
125. Landy SH, Baker JD. Divalproex ER prophylaxis in migraineurs with probable chronic migraine and probable medication-overuse headache: a case series. *Pain Pract* 2004;4(4):292-294.

126. Freitag FG, Diamond S, Diamond ML, Urban GJ. Divalproex in the long-term treatment of chronic daily headache. *Headache* 2001;41(3):271-278.
127. Dodick DW, Silberstein SD. How clinicians can detect, prevent and treat medication overuse headache. *Cephalalgia* 2008;28(11):1207-1217.
128. Boe MG, Mygland A, Salvesen R. Prednisolone does not reduce withdrawal headache: a randomized, double-blind study. *Neurology* 2007;69(1):26-31.
129. Evers S, Jensen R. Treatment of medication overuse headache - guideline of the EFNS headache panel. *Eur J Neurol* 2011;18(9):1115-1121.
130. Bonuccelli U, Nuti A, Lucetti C, Pavese N, Dell'Agnello G, Muratorio A. Amitriptyline and dexamethasone combined treatment in drug-induced headache. *Cephalalgia* 1996;16(3):198-200.
131. Krymchantowski AV, Barbosa JS. Prednisone as initial treatment of analgesic-induced daily headache. *Cephalalgia* 2000;20(2):107-113.
132. Trucco M, Meineri P, Ruiz L, Gionco M. Medication overuse headache: withdrawal and prophylactic therapeutic regimen. *Headache* 2010;50(6):989-997.
133. Evers S, Marziniak M. Clinical features, pathophysiology, and treatment of medication-overuse headache. *Lancet Neurol* 2010;9(4):391-401.
134 Pageler L, Katsarava Z, Diener HC, Limmroth V. Prednisone vs. placebo in withdrawal therapy following medication overuse headache. *Cephalalgia* 2008;28 (2):152-156.
135. Andrasik F, Grazzi L, Usai S, Buse DC, Bussone G. Non-pharmacological approaches to treating chronic migraine with medication overuse. *Neurol Sci* 2009;30 Suppl 1S89-S93.
136. Boe MG, Salvesen R, Mygland A. Chronic daily headache with medication overuse: a randomized follow-up by neurologist or PCP. *Cephalalgia* 2009;29(8):855-863.
137. Boe MG, Salvesen R, Mygland A. Chronic daily headache with medication overuse: predictors of outcome 1 year after withdrawal therapy. *Eur J Neurol* 2009;16 (6):705-712.
138. Blanchard EB, Andrasik F, Appelbaum KA, Evans DD, Myers P, Barron KD. Three studies of the psychologic changes in chronic headache patients associated with biofeedback and relaxation therapies. *Psychosom Med* 1986;48(1-2):73-83.
139. Blanchard EB, Appelbaum KA, Guarnieri P, Morrill B, Dentinger MP. Five year prospective follow-up on the treatment of chronic headache with biofeedback and/or relaxation. *Headache* 1987;27(10):580-583.
140. Blanchard EB, Steffek BD, Jaccard J, Nicholson NL. Psychological changes accompanying non-pharmacological treatment of chronic headache: the effects of outcome. *Headache* 1991;31(4):249-253.
141. Blanchard EB, Taylor AE, Dentinger MP. Preliminary results from the self-regulatory treatment of high-medication-consumption headache. *Biofeedback Self Regul* 1992;17(3):179-202.
142. Grazzi L, Andrasik F, D'Amico D, Leone M, Usai S, Kass SJ, Bussone G. Behavioral and pharmacologic treatment of transformed migraine with analgesic overuse: outcome at 3 years. *Headache* 2002;42(6):483-490.

143. Lake AE, III. Behavioral and nonpharmacologic treatments of headache. *Med Clin North Am* 2001;85(4):1055-1075.
144. Primavera JP, III, Kaiser RS. Non-pharmacological treatment of headache: is less more? *Headache* 1992;32(8):393-395.
145. Rains JC, Penzien DB, McCrory DC, Gray RN. Behavioral headache treatment: history, review of the empirical literature, and methodological critique. *Headache* 2005;45 Suppl 2S92-109.
146. Rollnik JD, Karst M, Fink M, Dengler R. Coping strategies in episodic and chronic tension-type headache. *Headache* 2001;41(3):297-302.
147. Scharff L, Turk DC, Marcus DA. Psychosocial and behavioral characteristics in chronic headache patients: support for a continuum and dual-diagnostic approach. *Cephalalgia* 1995;15(3):216-223.
148. Couch JR, Hassanein RS. Amitriptyline in migraine prophylaxis. *Arch Neurol* 1979; 36(11):695-699.
149. Louis P, Spierings EL. Comparison of flunarizine (Sibelium) and pizotifen (Sandomigran) in migraine treatment: a double-blind study. *Cephalalgia* 1982;2 (4):197-203.
150. Worz R, Drillisch C. [Migraine prevention by a calcium channel blocker. Results of a double-blind study of flunarizine vs. pizotifen]. *MMW Munch Med Wochenschr* 1983;125(32-33):711-714.
151. Rascol A, Montastruc JL, Rascol O. Flunarizine versus pizotifen: a double-blind study in the prophylaxis of migraine. *Headache* 1986;26(2):83-85.
152. Cerbo R, Casacchia M, Formisano R, Feliciani M, Cusimano G, Buzzi MG, Agnoli A. Flunarizine-pizotifen single-dose double-blind cross-over trial in migraine prophylaxis. *Cephalalgia* 1986;6(1):15-18.
153. Lucking CH, Oestreich W, Schmidt R, Soyka D. Flunarizine vs. propranolol in the prophylaxis of migraine: two double-blind comparative studies in more than 400 patients. *Cephalalgia* 1988;8 Suppl 821-26.
154. Ludin HP. Flunarizine and propranolol in the treatment of migraine. *Headache* 1989;29(4):219-224.
155. Lutschg J, Vassella F. [The treatment of juvenile migraine using flunarizine or propranolol]. *Schweiz Med Wochenschr* 1990;120(46):1731-1736.
156. Shimell CJ, Fritz VU, Levien SL. A comparative trial of flunarizine and propranolol in the prevention of migraine. *S Afr Med J* 1990;77(2):75-77.
157. Gawel MJ, Kreeft J, Nelson RF, Simard D, Arnott WS. Comparison of the efficacy and safety of flunarizine to propranolol in the prophylaxis of migraine. *Can J Neurol Sci* 1992;19(3):340-345.
158. Diener HC, Matias-Guiu J, Hartung E, Pfaffenrath V, Ludin HP, Nappi G, De BF. Efficacy and tolerability in migraine prophylaxis of flunarizine in reduced doses: a comparison with propranolol 160 mg daily. *Cephalalgia* 2002;22(3):209-221.
159. Grotemeyer KH, Schlake HP, Husstedt IW. [Prevention of migraine with metoprolol and flunarizine. A double-blind crossover study]. *Nervenarzt* 1988;59(9):549-552.

160. Sorensen PS, Larsen BH, Rasmussen MJ, Kinge E, Iversen H, Alslev T, Nohr P, Pedersen KK, Schroder P, Lademann A, . Flunarizine versus metoprolol in migraine prophylaxis: a double-blind, randomized parallel group study of efficacy and tolerability. *Headache* 1991;31(10):650-657.
161. Steardo L, Marano E, Barone P, Denman DW, Monteleone P, Cardone G. Prophylaxis of migraine attacks with a calcium-channel blocker: flunarizine versus methysergide. *J Clin Pharmacol* 1986;26(7):524-528.
162. Lamsudin R, Sadjimin T. Comparison of the efficacy between flunarizine and nifedipine in the prophylaxis of migraine. *Headache* 1993;33(6):335-338.
163. Bussone G, Cerbo R, Martucci N, Micieli G, Zanferrari C, Grazzi L, Fabbrini G, Cavallini A, Granella F, Ambrosoli L, Mailland F, Poli A, Manzoni G. Alpha-dihydroergocryptine in the prophylaxis of migraine: a multicenter double-blind study versus flunarizine. *Headache* 1999;39(6):426-431.
164. Mitsikostas DD, Polychronidis I. Valproate versus flunarizine in migraine prophylaxis: a randomized, double-open, clinical trial. *Funct Neurol* 1997;12(5):267-276.
165. Mathew NT. Prophylaxis of migraine and mixed headache. A randomized controlled study. *Headache* 1981;21(3):105-109.
166. Bank J. A comparative study of amitriptyline and fluvoxamine in migraine prophylaxis. *Headache* 1994;34(8):476-478.
167. Bulut S, Berilgen MS, Baran A, Tekatas A, Atmaca M, Mungen B. Venlafaxine versus amitriptyline in the prophylactic treatment of migraine: randomized, double-blind, crossover study. *Clin Neurol Neurosurg* 2004;107(1):44-48.
168. Bonuso S, Di SE, Barone P, Steardo L. Timed-release dihydroergotamine in the prophylaxis of mixed headache. A study versus amitriptyline. *Cephalalgia* 1983;3 Suppl 1175-178.
169. Shaygannejad V, Janghorbani M, Ghorbani A, Ashtary F, Zakizade N, Nasr V. Comparison of the effect of topiramate and sodium valporate in migraine prevention: a randomized blinded crossover study. *Headache* 2006;46(4):642-648.
170. Dodick DW, Silberstein SD. Migraine prevention. *Pract Neurol* 2007;7(6):383-393.
171. Bigal ME, Lipton RB. The preventive treatment of migraine. *Neurologist* 2006;12 (4):204-213.
172. Pringsheim T, Davenport WJ, Becker WJ. Prophylaxis of migraine headache. *CMAJ* 2010;182(7):E269-E276.
173. Barbanti P, Aurilia C, Egeo G, Fofi L. Migraine prophylaxis: what is new and what we need? *Neurol Sci* 2011;32 Suppl 1S111-S115.
174. Fenstermacher N, Levin M, Ward T. Pharmacological prevention of migraine. *BMJ* 2011;342d583.
175. Antonaci F, Dumitrache C, De C, I, Allena M. A review of current European treatment guidelines for migraine. *J Headache Pain* 2010;11(1):13-19.
176. van Leeuwen, E., Paemeleire, K., van Royen, K, Goossens, M., and Dirven, K. Aanpak van migraine in de huisartsenpraktijk. 2010. Domus Medica, Vereniging van huisartsen. www.domusmedica.be.

177. Dowson AJ, Lipscombe S, Sender J, Rees T, Watson D. New guidelines for the management of migraine in primary care. *Curr Med Res Opin* 2002;18(7):414-439.
178. Modi S, Lowder DM. Medications for migraine prophylaxis. *Am Fam Physician* 2006;73(1):72-78.
179. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sandor PS. EFNS guideline on the drug treatment of migraine - report of an EFNS task force. *Eur J Neurol* 2006;13 (6):560-572.
180. Lewis D, Ashwal S, Hershey A, Hirtz D, Yonker M, Silberstein S. Practice parameter: pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. *Neurology* 2004;63 (12):2215-2224.
181. Pryse-Phillips WE, Dodick DW, Edmeads JG, Gawel MJ, Nelson RF, Purdy RA, Robinson G, Stirling D, Worthington I. Guidelines for the diagnosis and management of migraine in clinical practice. Canadian Headache Society. *CMAJ* 1997;156(9):1273-1287.
182. Diagnosis and Treatment of Headache. 2011. Institute for Clinical Systems Improvement (ICSI). 1-10-2011. www.icsi.org.
183. MacGregor, E. A., Steiner, T. J., and Davies, P. T. Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type, Cluster and Medication-Overuse Headache. 2010. British Association for the Study of Headache (BASH). 1-10-2011. www.bash.org.uk.
184. Diagnosis and management of headache in adults. 2008. Scottish Intercollegiate Guidelines Network (SIGN). 1-10-2011. www.sign.ac.uk.
185. Geraud G, Lanteri-Minet M, Lucas C, Valade D. French guidelines for the diagnosis and management of migraine in adults and children. *Clin Ther* 2004;26(8):1305-1318.
186. Therapie der Migräne. 2008. Deutsche Gesellschaft für Neurologie. 1-10-2011. www.dgn.org.
187. Evers, S., May, A., Fritsche, G., Kropp, P., Lampl, C., Limmroth, V., Malzacher, V., Sandor, P. S., Straube, A., and Diener, H. C. Akuttherapie und Prophylaxe der Migräne. 2008. Deutschen Migräne- und Kopfschmerzgesellschaft. 1-10-2011. www.dmkg.de.

CHAPTER 3

Preventive treatment for migraine in primary care, a population based study in the Netherlands

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ABSTRACT

Background
Preventive treatment of migraine contributes to reducing the impact of migraine but its extent of use in routine care is unknown.

Objective
To assess current use, previous use, duration and course of preventive treatment of migraine in Dutch general practice.

Methods
Retrospective cohort study, for period between 1997 and 2007, in the Interdisciplinary Processing of Clinical Information (IPCI) database, a GP research database in The Netherlands (source population over half million subjects). All prevalent and incident migraine patients (N = 7367) were included.

Results
About 13% of all migraine patients currently use preventive therapy and almost half of the migraine patients have prior use. Of those starting with preventive treatment 56% (95%CI: 54.3-64.7) still used it after 9 months. There was a long delay between migraine diagnosis and preventive treatment start. 44% (95%CI 43.0-45.7) started preventive therapy in the study period.

Conclusion
This large primary care database study shows that a limited number of patients are current users of preventive treatment, but many patients have prior use. After diagnosis there is often an extended time before preventive treatment is applied. Also there is often only one attempt. The continuation in time seems appropriate. Preventive therapy in migraine still deserves focus.

INTRODUCTION

Migraine is a common, chronic, incapacitating neurovascular disorder, characterized by attacks of severe headache, autonomic nervous system dysfunction, and in some patients, an aura involving neurological symptoms[1]. The mean one-year prevalence in adults aged 18 – 65 years of migraine is over 10% (10.9% in the Americas and 14.8% in Europe)[2].
An important treatment goal is reducing the attack frequency. Preventive treatment includes beta-blockers and anti-epileptics and is recommended in guidelines[3-6]. In the Netherlands preventive treatment with propranolol or metoprolol is recommended for patients with an attack rate of two or more attacks per month[3,4].
Several studies into preventive treatment for migraine suggest large under-treatment. A telephone survey in the US showed that only 13% of the migraine patients who qualified for preventive treatment actually received treatment[7,8]. An earlier questionnaire study showed similar low numbers (5% and 12.4%) for preventive treatment use[9,10], although an additional 17.2% of patients used medication with potential antimigraine effects for other indications[10]. In France use of preventive treatment was estimated at 6%[11]. In a small Dutch study in general practice 8% of the migraine patients used preventive medication[12]. Recently, we described a Dutch pharmacy record study comprising 6.2 million people, showing that 19% of the triptan users at some moment also take preventive medication[13]. Most studies on preventive migraine treatment use suffer from methodological shortcomings and differ amongst each other. In pharmacy records, the indication for drug prescribing is usually lacking, as a result of which the medication may be prescribed for other reasons (like hypertension). Questionnaire studies in the general population also may have included inappropriate migraine diagnoses and misclassify frequent attack treatment as preventive treatment[11].
For patients, the frequency of the migraine attacks is the most important consideration in the decision for preventive treatment[12]. Preventive treatment is also indicated when exuberant use of attack medication is imminent and when there is a risk of medication overuse headache (MOH), which has a population prevalence of 4% in adults[14,15]. Data on triptan use in the Netherlands suggest that triptans possibly cause more headache than that they cure[13]. For policy making and optimizing routine care a valid estimate of the proportion of migraine patients receiving preventive treatment is necessary. We performed a population based cohort study in a general practitioners' research database in the Netherlands to gain more insight into preventive treatment of migraine in primary care.

METHODS

Setting

The study was conducted in the Integrated Primary Care Information (IPCI) database, a longitudinal general practice research database in the Netherlands. The IPCI database is maintained by the Department of Medical Informatics of the Erasmus MC, University Medical Centre Rotterdam in the Netherlands. The database contains longitudinal data from computer-based patient records of more than 150 GPs throughout the Netherlands. Presently, the database comprises data on more than 800,000 subjects, of whom the age and gender distribution is similar to the Dutch population. The registration uses the International Classification of Primary Care (ICPC)[16,17] to register patient symptoms and diagnoses, although these can also be entered as free text. Prescription data include product name, quantity dispensed, dosage regimens, strength and indication. As of 1996, drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification scheme recommended by the World Health Organisation (WHO)[18]. GPs who participate in the IPCI project are not allowed to use paper-based records.

The IPCI database system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research[19]. The Scientific and Ethical Advisory Group of the IPCI project approved the study (number 05/92).

Study period and study population

We used data of all individuals with at least one year of follow-up data available in the database between January 1996 and December 2007 (n = 478,584). One year of data was needed to validly assess medical history and treatment history. Study entry was defined as the date at which one year of follow-up was accumulated or 1st January 1996 whichever was latest. Follow-up lasted until the end of the study period, end of patient registration with GP practice, death or last IPCI data delivery, whichever came first. Within the study population we identified a sub-cohort of patients with newly detected migraine (incident diagnosis).

Ascertainment of migraine

GPs have a diagnostic code for migraine (ICPC-code N89). Additional potential cases were identified in the database through an inclusive string search on free text ('migrain*'). The presence and date of diagnosis of migraine were evaluated by a manual review of the electronic patient record of all the potential cases by the principal investigator (FD). Our case definition relied on the IHS-classification[20]. As typical migraine symptoms we considered attack frequency, duration of the headache, (unilateral) location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs), nausea or vomiting, photophobia and phonophobia, the existence of precipitating aura, shooting, burning pain. We accepted GP diagnoses if they recurred in the patient record and if typical migraine symptoms were present.

The index date was defined as the date of diagnosis of migraine. If the index date was on or after the start of follow-up the migraine was classified as incident. In other cases the migraine was considered as prevalent.

We distinguished two categories of migraine as abstracted from the database, namely 'uncertain migraine' and 'certain migraine'. Uncertain migraine comprised patients who expressed symptoms of migraine or had sporadic attacks, or were labelled by the physician as having migraine, but only visited the GP once for that reason. These patients had incomplete symptoms or were one time only indistinct associated with migraine in the whole research period (no preventive therapy). Uncertain migraine was not included in our analysis. This category has to be distinguished from 'probable migraine' from the IHS-classification.[20] Migraine was classified as 'certain migraine' if the headaches features corresponded to the IHS criteria for migraine.[20] We further detailed certain migraine according to presence of aura and considered menstrually-related migraine (MRM) as a subgroup of certain migraine. Patients with typical aura without headache and patients with medication-overuse headache were considered separate from certain migraine.

Migraine treatment

Treatment details extracted from the database comprised the date of prescribing, full ATC-code, drug name, strength, dose instructions and primary indication for the prescription. As attack treatment we considered drugs mentioned in Dutch guidelines (paracetamol, acetylsalicylic acid, NSAIDs, triptans, ergots) and as preventive treatment we considered agents which are mentioned in Dutch Guidelines or are officially approved preventive treatment (beta blockers without intrinsic sympathomimetic activity, valproic acid, topiramate, pizotifen, amitriptyline and flunarizine)[3,4].

Analysis

We calculated age and gender specific incidence rates of different types of migraine by dividing the number of incident cases by the total accumulated follow-up time. Ninety-five percent confidence intervals (95%CI) were calculated assuming a Poisson distribution. We used Kaplan-Meier analysis to calculate the time to preventive treatment start following migraine diagnosis in patients who had not used any of the preventive treatment agents before. Kaplan-Meier analysis was also used to estimate the11-year cumulative incidence of treatment initiation following migraine diagnosis.

To assess duration of treatment we assessed the proportion of patients still using the initial medication in periods of 3, 6, 9 and 12 months following treatment start. Proportions were calculated by dividing the number of patients remaining on initial treatment divided by the number of patients still in follow-up at the end of the concerned period. All the analyses were conducted using SPSS for windows version 15.0 (SPSS Inc., Chigaco, USA).

RESULTS

The total amount of follow-up time for the 472,033 subjects in the study population without migraine at baseline was 1,855,904 person years with an average of 3.9 person years per subject (SD: 2.99). We identified 7,525 first-time diagnoses of migraine or related headache disorders, of which 5,134 were certain migraine, 2081 uncertain migraine, and 152 typical aura without headache (AWoH) and 158 medication overuse headache (MOH) (Figure 1). Menstrually-related migraine (MRM) was found in 712 patients (table 1). Migraine patients were predominantly female (75%) and mostly between 30 and 40 years of age (table 1). The overall incidence rate of migraine over the entire study period, including uncertain cases, was 4.05 per 1000 person years (95%CI: 3.96-4.15). Considering certain migraine only the incidence rate was 2.8 per 1000 person years (95%CI: 2.7-2.8).

Treatment of migraine

Out of 5,134 migraine patients, 684 (13.3%, 95%CI: 12.4-14.3) received preventive treatment prescription at any time during the study period, most of them without ever receiving attack treatment in the study period (no attack treatment out of 684: n = 501, 73.2%, 95%CI: 69.7-76.5) and consisting of a single type (n = 552, 80.7%, 95%CI: 77.5-83.6). Of all patients receiving preventive therapy 21 patients (3.1%, 95%CI: 2.0-4.7) had two or more preventive therapies (figure 1).

Among patients diagnosed as having migraine with aura 11.2% (95%CI: 9.40-13.30) were prescribed preventive treatment. Migraine patients without aura received preventive treatment in 13.2 % (95%CI: 8.3-20.1) and in patients for whom the presence of aura was not mentioned the percentage of receiving preventive treatment was 13.1 % (95%CI: 12.1-14.2). The odds ratio (OR) for having received preventive treatment in patients with aura versus patients not having aura or aura not specified was 0.87 (95%CI: 0.70-1.08)). Typical aura without headache was recorded for 152 cases of whom 24 (15.8 %, 95%CI: 10.6-222.8) received preventive treatment (table 2).

Of the 1936 migraine patients using triptan, 92 (4.8%, CI: 3.87-5.52) also used preventive medication. Of the 1,080 NSAID users 45 (4.2%, 95%CI: 3.09-5.58) also had preventive medication.

The average age for prescribing attack treatment was 38.1 (SD 14.6) years and for preventive treatment 42.3 (SD 15.4) years.

The Kaplan-Meier analysis showed that first time preventive treatment prescriptions were issued mostly within the first two years following diagnosis but continued to be issued at a lower steady rate thereafter (figure 3). The cumulative incidence of ever having used preventive treatment within a study period of 11 years (average 3.9 person years (SD: 2.99)) was 44.3% (95% CI 43.0-45.7). For women this was 47.0% (95% CI 43.4-48.6) and for male 36.1% (95% CI 33.4-38.9).

The average time lapse between starting attack treatment and starting preventive treatment was 4.3 years during this 11 year study period. Patients started preventive migraine treatment at a high average age: 38.1 for males and 42.3 years for females.

Among patients starting preventive treatment many had discontinued that treatment within three months, after which the percentage of users stabilized. The average proportion of patients still using preventive treatment after 9 months of first start was 55.6% (95%CI: 54.9-60.1) but strongly varied by treatment. Patients using beta-blockers were most likely to continue treatment (59.6% after nine months, 95%CI 54.3-64.7) whereas patients using pizotifen were least likely to continue (37.0% after nine months, 95%CI 26.2-49.1). Among patients using beta-blockers prolonged use after nine months was 77.8% (95CI 62.5-88.3) for atenolol, 62.6% (95CI 53.4-71.0) for metoprolol and 50.3% (95CI 42.6-58.0) for propranolol. For patients using amitriptyline or valproic acid the numbers were too small to make reliable estimates.

We also studied the extent to which patients continued to use initial, prescribed attack treatment. The drop in attack treatment use was much larger than the drop in preventive treatment. After 9 months the proportion still receiving prescriptions for a triptan was 26.7% (95%CI: 20.4-34.3) (not available as OTC in the Netherlands) and for NSAIDs 26.8% (95%CI: 24.5-29.3) (available as OTC).

DISCUSSION

In a large Dutch longitudinal general practice research database we found that the percentage of all migraine patients receiving preventive treatment in the Netherlands was 13.3% (95%CI: 12.4-14.3). Approximately 56% of those starting preventive treatment, continued on it for a prolonged period of time (i.e. 9 months), suggesting good treatment effect and acceptable side-effects. The duration of first preventive treatment use was much longer than that for first attack treatment. In the vast majority of patients only one type of preventive treatment was tried, which may be due to the fact that the current guideline recommends only beta blockers as preventive treatment.[3]

The large time lapse between starting attack- and preventive treatment of 4.3 years and the high average age on start (male 38.1 and female 42.3 years) points out the at the start of preventive therapy the burden of migraine often is already past its highest peak throughout life[1]. This underlines the reluctance to accept the daily use of preventive medication[21].

The number of new patients receiving preventive treatment remained stable over the study years. And as the incidence of new cases of migraine decreased over the years, there was a relative increase in the use of preventive treatment (data not shown).

We found no significant differences in migraine treatment prescribing between different types of migraine, or between presence and absence of aura. We neither found a relation between prescribing of preventive treatment and that of attack treatment (see figure 1); only a small proportion of patients receiving preventive treatment also received prescriptions for attack treatment.

The attack frequency at which patients are recommended to start preventive therapy varies widely in guidelines[22,23]. The Dutch guidelines recommend preventive therapy in case of two or more attacks per month in primary care[3] or advises preventive treatment in case of three of more attacks per month in secondary care[4].
Our rate of 13% preventive treatment is in line with studies in other countries[7,9-12,24-27]. Some studies, however, reported a lower frequency of use[25,28]. Others have estimated that 5-83% of the migraine patient qualifies for preventive treatment[8,10,29]. One study in the same population as ours claims much higher numbers for prevention[30]. However this study is performed in a high selective population of patients referred to a neurologist and as the presented data do not correspond with previous studies[12,24,25], this study is of questionable importance to compare preventive treatment with.
Our study period covers 11 years with in average for 3.9 person years availability, whereas most previous studies reported the actual number of patients per year. It shows that when cumulated over a longer period many more patients, 44.3% of all patients, have tried preventive treatment, which is well above previous estimates[7,9-12,24-27].
In the recent study by Berger et al, based on a US health insurance claims database, continued use was lower. For example, for beta-blocker use after 6 months continued use was 43.1%, compared to 59.6% in ours. However, there were various differences with our study. We used the volume of prescriptions, not only on the simple amount of prescriptions. Our inclusion is based on a validated method for diagnosis and their inclusion was also based on medication use as such (leading to higher numbers of patients). Finally their research period was shorter (2 years)[28].
Preventive treatment is prescribed to only 4.8% of triptan users and to 4.2% of the NSAID users (applies only to prescribed medication, not to OTCs). This finding differs from other studies in which triptan users have more preventive medication.[13,25] However, other studies are usually not based on clinical diagnosis.
In this study, using observational primary care information, misclassification of migraine may have occurred. False negative misclassification could have occurred if patients did not seek GP attention or if they were treated solely by a specialist. As neurologists in the Netherlands are treating 3% of migraine patients, the possible under presenting of severe migraine patients will likewise only be small[13]. Of the 478,585 eligible people in the database we identified 7525 certain and possible new migraine patients at an incidence rate of 4.05 per 1000 person years. These findings may not apply to the overall migraine population. In the electronic patient record many characteristics of migraine, such as the presence of aura and relation to the menstrual period is often insufficiently described. This most likely explains the low proportion of patients with aura (20.5%) and the probable under-reporting of MRM migraine (9.1%) and typical aura without headache (3.0%).
As preventive treatment for AWoH is not applicable or controversial, we did not include this diagnosis in our study. However, we included the MOH, since we had sufficient observation time for each subject to reliably assess the temporal relationship between medication overuse and diagnosis of migraine (usually migraine, rarely tension type headache, as recorded in the EPR). Including patients with MOH in the analysis may have caused some contamination by tension-type headache but given the numbers it will not have a major impact on the estimates.

This study shows a long-lasting and continued use for 9-12 months of preventive medication in 56% of patients starting on preventive medication for migraine. Although this real life study can not be compared with studies in an experimental setting, in our study the frequency of treatment withdrawal is much higher, especially for beta blockers[31]. In usual care treatment withdrawal can be interpreted, at least for a part, as non-response. The response rate in experimental trials is around 50%, which is in line with the withdrawal rate in our study[31]. The guideline compliance in our study was much better than in an older study (1995-1998)[25].

The absence of differences in treatment patterns between types of migraine and between population subgroups suggest that this study gives no indication for extra attention in the area of preventive treatment for any specific group of patients.
Despite many efforts to improve the treatment of migraine and an otherwise well used headache guideline in the Netherlands which promotes preventive treatment, there is much room for improvement. The compliance with treatment guidelines has improved, but the actual number of patients with preventive treatment remains low.
Qualitative research could give more insight into the reasons behind the little use of preventive medication in younger migraine patients, the extended duration between diagnosis and start of preventive treatment, and why and how prescribed attack treatment interferes with preventive treatment (e.g. whether patient and physicians only accept one treatment for one illness at the same time).
This may point the way for better explanation and defending of preventive treatment to expand the use of it, also by encouraging more than one attempt using alternative medication.
Although compliance of preventive treatment has improved and many patients have experience with it, preventive treatment still needs attention in primary care. Further research into underlying reasons and motives of patients and physicians is desirable. Firstly most gain would be made when more patients would consult their GPs when they have migraine attacks an so more often migraine would be diagnosed. And secondly if this was more often and/or repeated followed by active inviting migraine patients for a personal consultation to discuss preventive treatment there even was more improvement.

CLINICAL IMPLICATIONS

- A limited number of patients are current users of preventive treatment (13%), but many patients have prior use (44%).
- After diagnosis there is often an extended time before preventive treatment is applied, in average over 4 years.
- Often there is only one attempt in preventive therapy.
- The continuation in time of preventive treatment equals study-level.

References

1. Ferrari MD. Migraine. *Lancet* 1998;351(9108):1043-1051.
2. Atlas of headache disorders and resources in the world 2011. 2011. World Health Organization. 22-7-2011.
3. Grol MH, Neven AK, Pijnenborg L, Goudswaard AN. [Summary of the practice guideline 'Headache' from the Dutch College of General Practitioners]. *Ned Tijdschr Geneeskd* 2006;150(6):305-309.
4. Couturier EG, Bomhof MA, Gooskens R, Keyser A, Mulleners WM. Richtlijnen diagnostiek en behandeling chronisch recidiverende hoofdpijn zonder neurologische afwijkingen. Utrecht, Nederlandse Vereniging voor Neurologie. 2008.
5. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sandor PS. EFNS guideline on the drug treatment of migraine - report of an EFNS task force. *Eur J Neurol* 2006; 13(6):560-572.
6. Modi S, Lowder DM. Medications for migraine prophylaxis. *Am Fam Physician* 2006;73(1):72-78.
7. Lipton RB, Bigal ME. Ten lessons on the epidemiology of migraine. *Headache* 2007;47 Suppl 1S2-S9.
8. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 2007; 68(5):343-349.
9. Lipton RB, Scher AI, Kolodner K, Liberman J, Steiner TJ, Stewart WF. Migraine in the United States: epidemiology and patterns of health care use. *Neurology* 2002;58(6):885-894.
10. Diamond S, Bigal ME, Silberstein S, Loder E, Reed M, Lipton RB. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention study. *Headache* 2007; 47(3):355-363.
11. Lucas C, Chaffaut C, Artaz MA, Lanteri-Minet M. FRAMIG 2000: medical and therapeutic management of migraine in France. *Cephalalgia* 2005;25(4):267-279.
12. Kol CM, Dekker F, Neven AK, Assendelft WJ, Blom JW. Acceptance or rejection of prophylactic medicine in patients with migraine: a cross-sectional study. *Br J Gen Pract* 2008;58(547):98-101.

13. Dekker F, Wiendels N, de Valk V, van der Vliet C, Knuistingh Neven A, Assendelft WJJ, Ferrari MD. Triptan overuse in the Dutch general population: A nationwide pharmaco-epidemiology database analysis in 6.7 million people. *Cephalalgia* 2011;31(8):943-952.
14. Wiendels NJ, Knuistingh Neven A, Rosendaal FR, Spinhoven P, Zitman FG, Assendelft WJJ, Ferrari MD. Chronic frequent headache in the general population: prevalence and associated factors. *Cephalalgia* 2006;26(12):1434-1442.
15. Wiendels NJ, van Haestregt A, Knuistingh Neven A, Spinhoven P, Zitman FG, Assendelft WJJ, Ferrari MD. Chronic frequent headache in the general population: comorbidity and quality of life. *Cephalalgia* 2006;26(12):1443-1450.
16. Okkes I, Jamoulle M, Lamberts H, Bentzen N. ICPC-2-E: the electronic version of ICPC-2. Differences from the printed version and the consequences. *Fam Pract* 2000;17(2):101-107.
17. International Classification Committee of WONCA. ICPC-2 International Classification of Primary care, second ed. Oxford, Oxford University Press. 1998.
18. World Health Organisation, Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment. 1998. Oslo.
19. Vlug AE, van der LJ, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, van Bemmel JH. Postmarketing surveillance based on electronic patient records: the IPCI project. *Methods Inf Med* 1999;38(4-5):339-344.
20. Headache classification subcommittee of the International Headache Society. The International Classification of Headache Disorders. *Cephalalgia* 2004;24(supplement 1):8-160.
21. Dekker F, Knuistingh NA, Andriesse B, Kernick D, Reis R, Ferrari MD, Assendelft WJ. Prophylactic treatment of migraine; the patient's view, a qualitative study. *BMC Fam Pract* 2012;13(1):13.
22. Schuurmans A, van WC. Pharmacologic treatment of migraine. Comparison of guidelines. *Can Fam Physician* 2005;51838-843.
23. Antonaci F, Dumitrache C, De C, I, Allena M. A review of current European treatment guidelines for migraine. *J Headache Pain* 2010;11(1):13-19.
24. Rahimtoola H, Buurma H, Tijssen CC, Leufkens HG, Egberts AC. Incidence and determinants of migraine prophylactic medication in the Netherlands. *Eur J Clin Pharmacol* 2002;58(2):149-155.
25. Rahimtoola H, Buurma H, Tijssen CC, Leufkens HG, Egberts AC. Migraine prophylactic medication usage patterns in The Netherlands. *Cephalalgia* 2003; 23(4):293-301.
26. Cevoli S, D'Amico D, Martelletti P, Valguarnera F, Del BE, De SR, Sarchielli P, Narbone M, Testa L, Genco S, Bussone G, Cortelli P. Underdiagnosis and undertreatment of migraine in Italy: a survey of patients attending for the first time 10 headache centres. *Cephalalgia* 2009.
27. Lafata J, Tunceli O, Cerghet M, Sharma K, Lipton R. The use of migraine preventive medications among patients with and without migraine headaches. *Cephalalgia* 2009.

28. Berger A, Bloudek LM, Varon SF, Oster G. Adherence with migraine prophylaxis in clinical practice. *Pain Pract* 2012;12(7):541-549.
29. Valade D, Lanteri-Minet M, Radat F, Mekies C, Lucas C, Vives E, Joubert JM, Geraud G. Clinical determinants of migraine preventive treatment: contribution of SMILE, an observational survey of primary care migraine management in France. *Cephalalgia* 2010;30(10):1207-1213.

Tables
'Preventive treatment for migraine in primary care, a population based study

	Total		**Total cases migraine (certain + uncertain)**		**Uncertain migraine**	
Total	**N = 2340980 n (%)**		**N = 7367 n (%)**		**N = 2081 n (%)**	
Sex						
Male	1162830	(49.7)	1859	(25.2)	566	(26.7)
Female	1178150	(50.3)	5508	(74.8)	1515	(72.3)
Age						
0-10	247506	(10.6)	258	(3.5)	90	(4.3)
10-19	274523	(11.7)	880	(11.9)	256	(12.3)
21-29	321827	(13.7)	1388	(18.8)	396	(19.0)
31-39	391838	(16.7)	1826	(24.8)	497	(23.9)
41-49	361684	(15.5)	1665	(22.6)	450	(21.6)
51-59	303424	(13.0)	872	(11.8)	249	(12.0)
61-70	270737	(11.6)	294	(4.0)	83	(4.0)
71+	169441	(7.2)	184	(2.5)	61	(2.9)

All certain migraine				**AWoH†**		**MOH#**	
		Subgroup MRM*					
N = 4975 n (%)		**N = 712 n (%)**		**N = 152 n (%)**		**N = 158 n (%)**	
1213	(24.4)			55	(36.2)	*25*	*(15.8)*
3762	(75.5)	712		97	(63.8)	*133*	*(84.2)*
167	(3.4)	-		1	(0.7)	-	-
607	(12.2)	36	(5.1)	5	(3.3)	*12*	*(7.6)*
947	(19.0)	135	(19.0)	12	(7.9)	*33*	*(20.9)*
1238	(24.9)	288	(40.4)	34	(22.4)	*57*	*(36.1)*
1162	(23.4)	220	(30.9)	30	(19.7)	*23*	*(14.6)*
557	(11.2)	33	(4.6)	39	(25.7)	*27*	*(17.1)*
191	(3.8)	-	-	16	(10.5)	*4*	*(2.5)*
106	(2.1)	-	-	15	(9.9)	*2*	*(1.3)*

Table 1. Characteristics of the incident migraine, medication overuse and typical aura without headache in general practice

* MRM (= Menstrually-related migraine is a subgroup of certain migraine. † AWoH (Typical aura without headache) and # MOH (Medication-overuse headache) are not part of the total migraine (= all certain migraine).

30. Zielman R, Veenstra P, Zwet E, Berg J. How general practitioners treat migraine patients: evaluation of a headache guideline. *Cephalalgia* 2012;32(12):908-915.
31. Linde K, Rossnagel K. Propranolol for migraine prophylaxis. *Cochrane Database Syst Rev* 2004;(2):CD003225.

Table 2. Use of preventive treatment in migraine

	Migraine (certain)										**AWoH**		**MOH**	
	All*		**With and without aura**						**MRM**					
			Un-specified		**MA+**		**MA-**		**(sub-group)**					
Total	5134		3989		1053		144		712		152		158	
Preventive (%)	**684**	(12.9)	**523**	(13.1)	**118**	(11.4)	**19**	(13.2)	**72**	(3.8)	**24**	(15.79)	**15**	(9.5)
Specification preventive medication														
Propranolol	240	(35.1)	192	(36.7)	38	(32.2)	6	(31.6)	12	(44.4)	4	(16.7)	7	(46.7)
Metoprolol	177	(25.9)	133	(25.4)	31	(26.3)	3	(15.8)	7	(25.9)	1	(41.7)	2	(13.3)
Other beta blockers	87	(12.7)	59	(11.3)	21	(18.8)	1	(5.3)	4	(14.8)	6	(25.0)		-
AII-antagonists	7	(1.1)	6	(1.1)	1	(0.8)	-	-			-	-		-
Verapamil	6	(0.9)	5	(1.0)	1	(0.8)	-	-			-	-		-
Valproic acid	16	(2.3)	8	(1.5)	4	(3.4)	3	(15.8)	-	-	1	(4.2)	2	(13.3)
Topiramate	2	(0.3)	2	(0.4)	-	-	-	-	-	-	-	-	-	-
Pizotifen	80	(11.7)	63	(12.0)	16	(13.6)	1	(5.3)	-	-	-	-	2	(13.3)
Clonidine	29	(4.4)	23	(4.4)	2	(1.7)	4	(21.1)	1	(3.7)	1	(4.2)	-	-
Flunarizine	9	(1.3)	7	(1.3)	-	-	-	-	1	(3.7)	2	(38)	-	-
Methysergide	3	(0.4)	2	(0.4)	1	(0.8)	-	-	-	-	-	-	-	-
Amitriptyline	36	(5.3)	31	(5.9)	4	(3.4)	1	(5.3)	2	(7.4)	-	-	2	(13.3)

Numbers of patients (percentage). MA+= migraine with aura. MA-= migraine without aura, MRM= menstrually-related migraine (as mentioned in EPR, both regular and pure). AWoH = Typical aura without headache (migraine sans migraine). MOH= medication overuse headache. *Without AWoH, including MOH.

Figures

'Preventive treatment for migraine in primary care, a population based study

Figure 1. Process of identification of preventive migraine cases in the Integrated Primary Care Information (IPCI) database

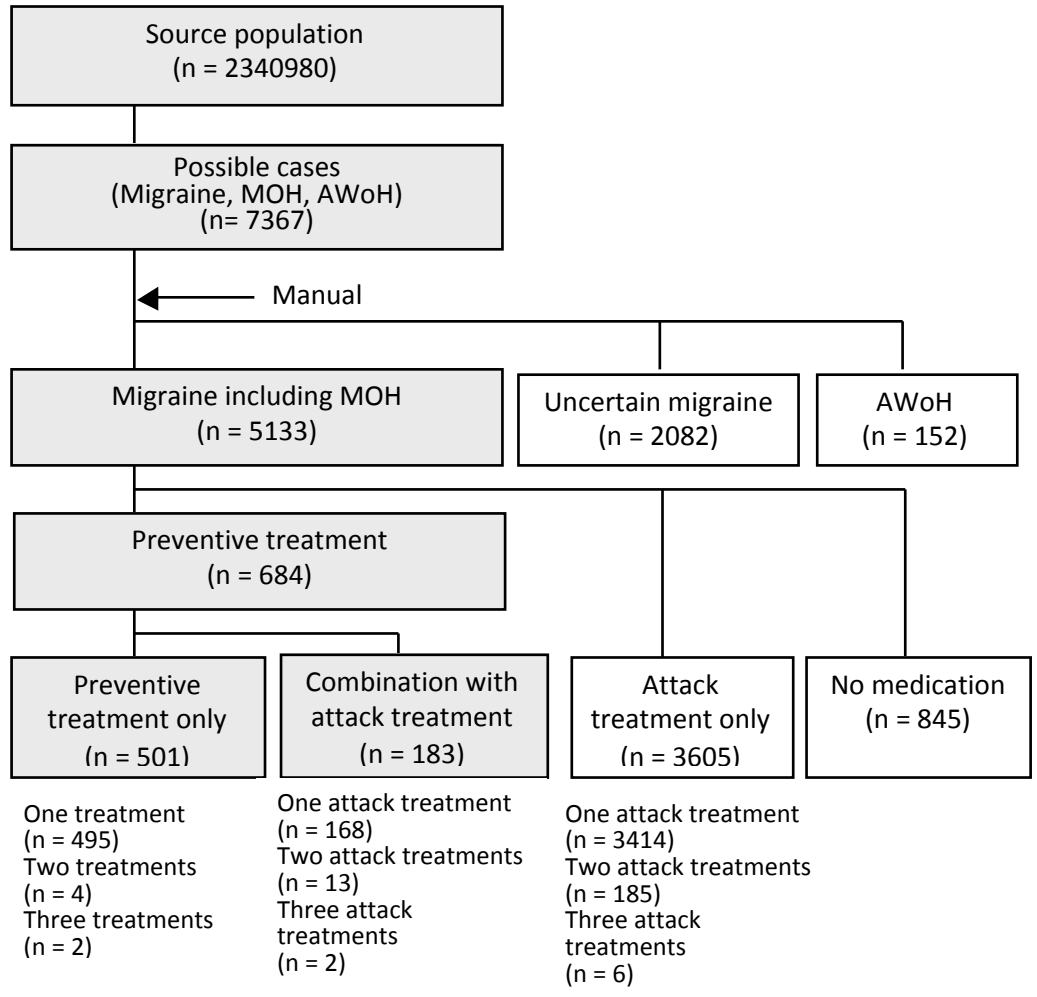
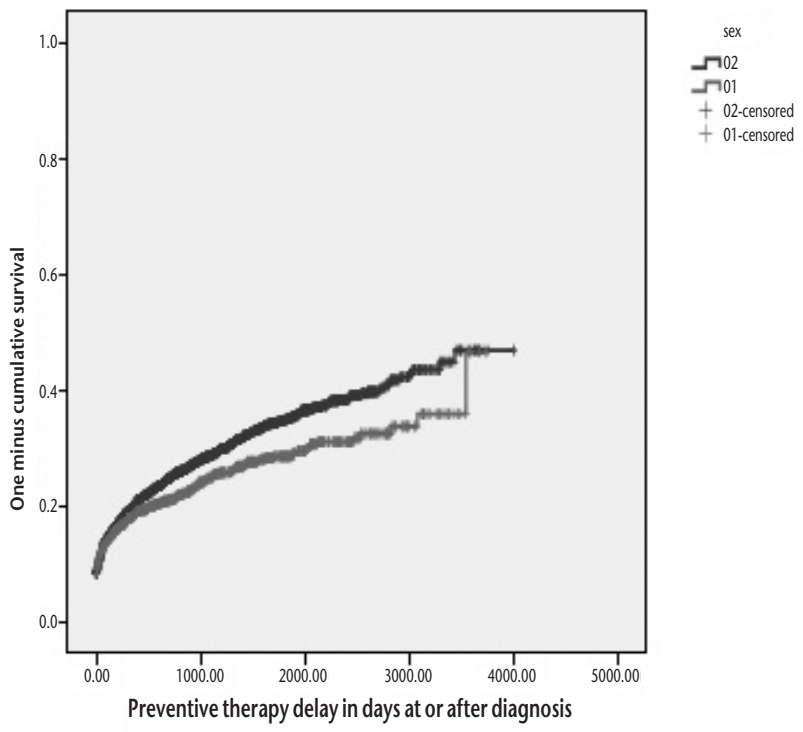
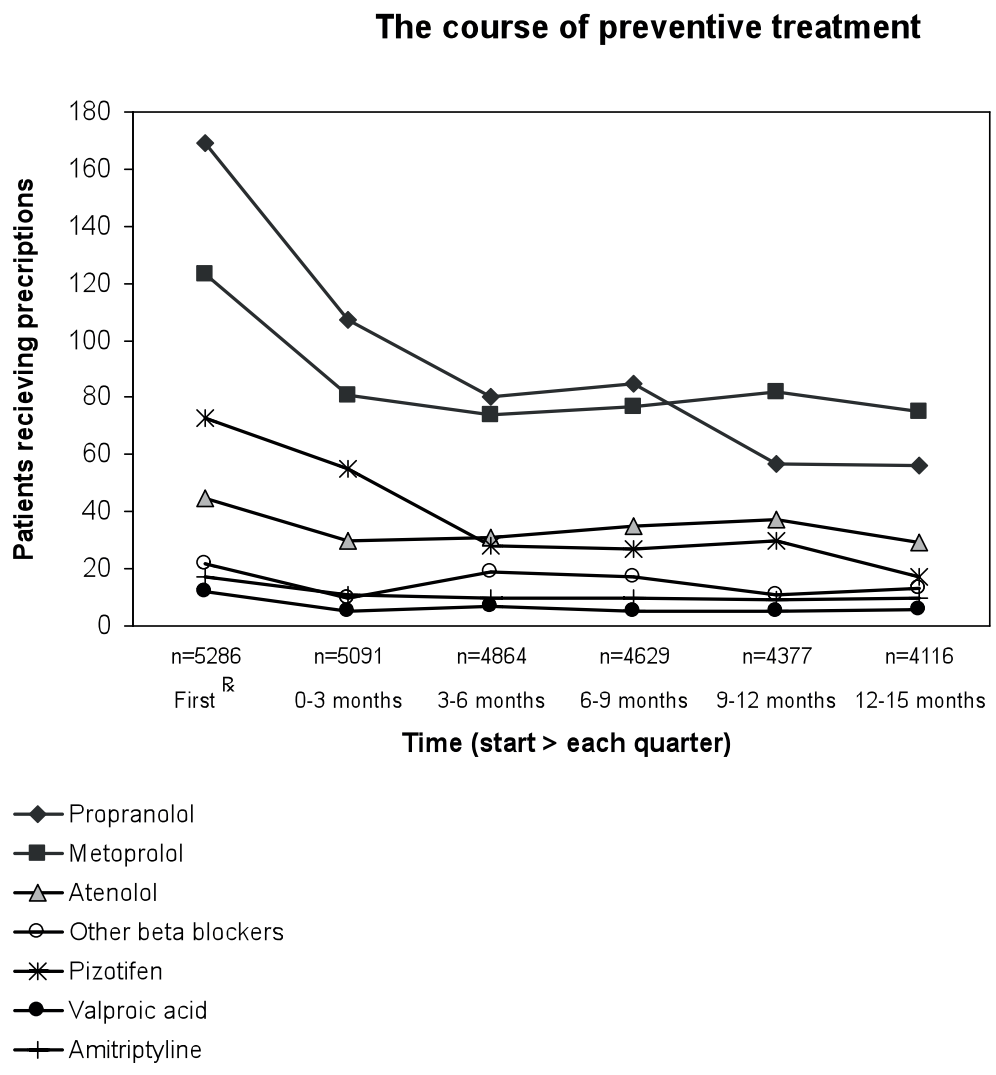


Figure 2. Kaplan-Meier graph of start with preventive treatment related to time after first diagnosis of migraine



One minus cumulative survival curve of the time span between initial migraine diagnosis and the start of preventive treatment, and the difference between males and females. 01 = male 02 = female. Time is shown in days after initial diagnosis of migraine.

Figure 3. Course of preventive treatment



Each line represents a preventive treatment. On the X-axis the total number of patient in follow-up is shown.

CHAPTER

4

Prophylactic treatment of migraine by general practitioners: a qualitative study

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ABSTRACT

Background
Despite the considerable impact of migraine the use of preventive medication in primary care is limited. Only about 5% of migraine patients who qualify for prophylaxis actually receive it and adherence is far from optimal.

Aim
To explore the opinions of general practitioners (GPs) regarding preventive medication for migraine.

Design
A qualitative focus group study.

Setting
Dutch general practice.

Participants
A total of 24 GPs.

Method
Four focus groups (6 GPs each) were formed. GPs were purposively sampled to acquire a range of participants, reflecting the more general GP population.

Results
GPs perceived patients' concerns about the impact of migraine and the potential benefits of prophylaxis. However, some were hesitant to start prescribing prophylaxis due to doubts about effectiveness, potential side-effects, and the risk of developing drug dependency. GPs' decisions were often based on considerations other than those presented in national guidelines, e.g. the patient's need to control their own problem. Many GPs placed responsibility for initiating prophylaxis with the patient.

Conclusion
Various considerations hamper GPs from managing migraine with preventive medication, and various patient-related concerns cause GPs to deviate from national headache guidelines.

INTRODUCTION

Migraine is a common and disabling brain disorder, and many patients with migraine have severe and disabling attacks.[1] Primary care is an important setting for the management of migraine; for example, in the Netherlands, 95% of triptans are prescribed in primary care.[2]
Prophylactic therapy is an option for patients with frequent or long-lasting migraine, where treatment can reduce attack frequency by 50% and also reduce attack severity.[3-5] Suggested thresholds for starting prophylactic therapy range from attacks twice a month to twice a week.[3,4,6] Dutch headache guidelines for general practitioners (GPs) recommend discussing prophylactic therapy in case of (on average) at least 2 attacks each month.[7] In Dutch general practice beta-blockers are the most frequently prescribed preventive migraine medication, together with anti-epileptics and other anti-hypertensive drugs.[8]
Preventive therapy is probably indicated in about a third of patients with migraine, and a broad range of pharmaceutical and non-pharmaceutical options are available[1]. However, despite that prophylaxis is a safe and effective intervention[9-11] only 5-13% of migraine patients who qualify for prophylaxis actually receive it.[8,12] In many countries a substantial proportion of those who might benefit from prevention do not receive it.[12,13] Moreover, the adherence to prophylaxis is modest.[9] In addition, although many patients express a wish for prophylaxis[14] (even for infrequent headache) GPs and patients are often reluctant to exploit its possibilities.[14] Little is known about the opinions of GPs and patients regarding prophylaxis or about the considerations involved in making a decision about prophylaxis.
To reduce the unmet needs of migraine patients, it is important to elucidate why GPs do not prescribe preventive medication and why many patients do not ask for it.[14] Therefore, this study explores GPs' decision-making regarding prophylactic migraine therapy.

METHODS

Recruitment
Because little is known about how GPs deal with preventive treatment of migraine and their underlying motivations, we chose for qualitative research. It was expected that, in a focus group, the GPs would stimulate one another to a more profound discussion on preventive treatment than might occur during an individual interview.
The aim was to recruit a sample of GPs that reflects a mix of urban/rural practitioners with a range of age, experience, gender, and type and size of practice. We used 'theoretical sampling' and expected to reach data saturation with 3-4 focus groups.[15] GPs who appeared to have a special interest in headache were excluded. Four groups of GPs (2 urban and 2 rural) were recruited. The GPs were targeted as existing regional

groups and all the GPs of the four groups received (via e-mail) an invitation and an answer form.
Of the 32 invited GPs, 24 attended the focus group meetings, with (on average) 6 GPs per group. Their mean age was 48 (range 31-59) years and there were 10 females and 14 males. This distribution broadly reflects the Dutch situation.[8,14] Of the 24 GPs, 11 worked in a group practice, 3 in a two-handed practice, and 10 in a single-handed practice. Of the 24 participating GPs, 18 had ≥ 10 years experience and 22 worked full-time in general practice. Of all GPs, 3 suffered from infrequent migraine themselves, and 2 suffered from frequent migraine attacks.

Data generation

Each focus group meeting was chaired by an independent health scientist experienced in moderating headache focus groups (Muller JAG, see Acknowledgements). The moderator conducted the group meetings using an interview guide (compiled by AKN and FD). To facilitate discussion we used the themes 'general attitudes towards migraine' (such as feeling comfortable in consultations with migraine patients),[16] and 'scenarios for treatment goals and prophylactic treatment', supported by a range of questions and statements. Each session lasted about 2 hours and was digitally recorded. The audio-recordings were transcribed.

Analysis

The recordings were analysed independently by three researchers (FD, AKN and BA). Because the DVD recordings provided the most detailed information on both verbal and non-verbal communication, these served as the primary data source.[17-19] The researchers used regular DVD-reading software with good on-screen forward/backward and other search possibilities. The DVDs allowed both verbal and non-verbal indications to support an opinion given by others in the group.
The three investigators independently identified 'themes' on preventive treatment, emerging from the data. These themes were written in text form and then organised into categories and (sub-) themes according to the rules of thematic analysis (by FD).[19-21] The subsequent draft analytical framework was discussed and decided upon with the other members of the team. In case of disagreement between the researchers, the theme was analysed again by those involved; in case of a persisting discrepancy consensus was sought and reached between the researchers. Using this framework, an interpretative analysis of the data enabled to identify several related, but separate, topics of experience and reasoning regarding prophylactic treatment for migraine, and a tentative model to elucidate GPs' considerations regarding preventive migraine treatment.

RESULTS

Analysis of the data revealed six main themes.

1) GPs' general views on migraine

In the present study many GPs believed that even when acute treatment was optimal, migraine patients with frequent attacks still had a 'serious' health problem. Of the 24 GPs, 17 stated that migraine patients need as much attention as patients with, e.g. COPD or diabetes, but migraine patients did not receive any form of chronic disease monitoring.

> *'Why is so little attention paid to migraine? We're expected to go along with the hype that diabetes is a really nasty disease, asthma is a really nasty disease, but with migraine we just have to accept the lack of attention for it.'* (Group 3, GP 2)

However, a minority of GPs believed that the patient is to blame for the high attack frequency, or that the decision to consult the GP should be left to the patient without actively offering follow-up appointments.
GPs felt positive about migraine patients and their search for help, valued migraine consultations because they challenged their knowledge, believed that migraine is a treatable disease, and regarded their own treatment as sufficiently patient-centred. Those GPs with migraine themselves (at least one in each focus group) claimed a greater understanding of the significance of the impact of migraine. Almost all GPs were able to describe the patients' (or recall exceptional) stories about the severity of migraine attacks.

2) Reluctance to start prescribing prophylaxis

GPs frequently mentioned that patients were reluctant to take medication for preventive purposes, even when they understood its benefit. Many GPs found that the disadvantages often outweigh the benefits of preventive therapy. For example, four GPs were concerned about the 'medicalising' effects of preventing migraine or thought that the patient's concerns about this hampered the initiation of prevention.

> *'With migraine there's a price to pay every single day for effective prevention, it's the same with epilepsy.'* (Group 2, GP 4)

> *'In my estimation, about half of the patients who qualify for prophylaxis don't really want it.'* (Group 1, GP 6)

GPs believed that patients did take any downside of preventive treatment into account, such as adverse reactions and drug dependency. GPs told that they often heard from patients about their fear of drug dependency. These downsides of medication

could make patients less positive toward preventive therapy. GPs understood and accepted this reluctance; this sometimes made them unwilling to initiate treatment and/or convince the patient about the benefits of prophylaxis.

'Whenever I offer prophylaxis for migraine I feel as though I'm adding another problem to the patient's already existing health problems.' (Group 4, GP 1)

'Patients see prophylaxis as a heavy form of therapy – that's the way they experience it. And that's an important reason to decline prophylactic treatment.' (Group 4, GP 4)

'In the case of prophylaxis, patients receive a huge leaflet full of instructions and warnings - this means that the medication prescribed by GPs is a serious matter.' (Group 4, GP 4)

Secondly, GPs felt that when patients used a lot of medication to treat acute attacks, the patients would sometimes be more reluctant to consider further/more medication, even when it was for prevention purposes. Thirdly, GPs thought that patients had many concerns about the side-effects of prophylaxis; on this topic GPs thought they shared the concerns with their patients.

'In the case of migraine, the side-effects of beta-blockers weigh much more heavily (compared with hypertension).' (Group 2, GP 5)

Although some GPs were pessimistic about changing the health behaviour of migraine patients, the majority believed that when the goals and benefits of preventive therapy were adequately explained, it should be possible to reduce the burden of migraine.

'The unpredictability of the attacks makes migraine a serious problem; you can't ignore that … and as a doctor you have to do something about it.' (Group 2, GP 4)

3) Initiating prophylactic medication

A recurring theme was that the trigger to initiate prophylaxis was not a simple sum of migraine frequency plus duration. If acute attacks were treated successfully, patients are less likely to ask for other types of migraine treatment. However, in the GPs opinion, many patients experienced insufficient relief from acute medication, whether or not prescribed by a specialist. GPs believed that patients often did not realise that their care was less than optimal.

'You often hear: I'm satisfied, I don't need daily treatment myself.' (Group 2, GP 3)

'Migraine patients come to the GP's office only for that 'stronger' cure that they really hope is available.' (Group 2, GP 2)

GPs found that the threshold to instigate preventive medication in migraine was less clear than in other diseases, such as asthma. However, in migraine two factors were important. First, the patient's feelings of being in control of the headache played an important role in determining whether they were satisfied with their therapy, a goal that was not always achieved with acute treatment only. Second, the functional impact on regular activities (work, school, etc) was also important. About 50% of the GPs reported that if they personally experienced two or more attacks each month, they would accept preventive treatment.

4) Taking the initiative for prophylaxis - patient or physician?

GPs felt reluctant to initiate or explore prophylactic treatment for some patients, even when they noticed a high frequency of migraine attacks. Generally, they responded to questions or cues coming from the patient. An important cue was when the patient expressed that they were unable to cope with their migraine. Some GPs (especially those who monitored attack medication) noticed the need for prophylaxis at an earlier stage, e.g., in case of an excessive use of triptans.
The approachability of the physician was considered to be an important factor in exploring or initiating preventive medication.

'If a general practitioner is open and approachable, then it's also the patient's responsibility whether or not to start taking prophylactic treatment. Patients don't need to be assertive when the doctor is approachable.' (Group 3, GP 2)

GPs acknowledged the impact of medication overuse and its importance as a marker for possible preventive therapy. However, it was felt that this was an area that was not well recognised.

'When practice assistants identify triptan overuse, this is a clear warning that the patient needs preventive treatment.' (Group 1, GP 4)

When patients asked about preventive treatments, the GPs were of the opinion that they had already explored other therapies, including dietary approaches and complementary therapies. GPs considered it important to offer prophylaxis at the most appropriate moment. This was not necessarily the moment of diagnosis, and was influenced by realising the impact of the problem by patients.

'When considering prophylaxis, you have to choose the right moment to present this option to the patient.' (Group 2, GP 1)

5) Start prescribing and managing prophylaxis

GPs felt that their role differed from that of specialists, e.g. they differed in their motives for starting prophylaxis and its management. GPs were of the opinion that spe-

cialists simply carried out their protocols (often personal protocols) whereas GPs also took co-morbidity and other health-related circumstances into account, and GPs thought they gave more notice to the complexity of the context in which prescribing took place.

'If migraine is combined with some other diseases, then you're much more likely to give a beta-blocker (when indicated).' (Group 3, GP 4)

'When you think about the individual tailoring of prophylaxis, GPs handle a lot more co-morbidity than specialists.' (Group 3, GP 5)

'Migraine therapy actually involves quite a lot of creativity.' (Group 4, GP 3)

'Migraine management is more a medical art than just medicine itself.' (Group 2, GP 1)

There was no consensus among GPs as to how to manage prophylaxis. Some scheduled regular appointments whereas others had contact only at the start of prophylaxis and considered the patients to be responsible for their own subsequent treatment.

'If the aim of the prophylaxis is achieved, your patients don't come back again. If you compare migraine to diseases like asthma, the control policy is much more structured in those other diseases.' (Group 2, GP 2)

'Because starting preventive treatment is generally at the patient's wish, then the moment to stop should also be the patient's decision - I can accept that.' (Group 4, GP 4)

For participating GPs, the first choice in preventive treatment were beta-blockers as prophylactic therapy and about 50% of the GPs thought that the use of beta-blockers would result in an additional cardiovascular health benefit. Less than 25% prescribed anti-epileptic medication. GPs reported that they were honest and open-minded with their patients about the claims made for prophylaxis in relation to the frequency and reduction in severity of attacks. Non-compliance was seen as a common problem, but the GPs were not particularly worried about this.

6) Expectations of the benefit of prophylaxis

GPs differed in their expectations regarding benefit. Some suggested that prophylaxis should make migraine disappear, some accepted the evidence-based expectation of a 50% reduction in attack frequency and attack severity, and others had a low expectation because of lack of efficacy or because of patients' reluctance to accept regular medication. This low expectation was reflected in a reluctance to instigate prophylactic treatment.

'The ultimate aim of prophylactic therapy ('to be free of migraine attacks') can never really be reached.' (Group 1, GP 6)
'Sometimes it's very difficult to give prophylaxis, especially when the patients keep coming back without good results.' (Group 4, GP 3)

'If a patient has suffered from migraine for the past 30 years, then he'll also suffer for the next 30 years.' (Group 3, GP 2)

'Even after preventive treatment you don't leave the surgery whistling, you know that you're still in deep water ' (Group 1, GP 4)

GPs felt that patients also differed in their appreciation of the benefits of prophylaxis. In the perception of GPs some patients were satisfied with only small benefits, whilst others expected total resolution of their headache. If patients had a long history of migraine, small benefits were often welcome. GPs emphasised that there is no gold standard or endpoint for measuring the effects of prophylaxis in the individual patient.

DISCUSSION

Summary of main findings

When considering preventive treatment for migraine, GPs related several facilitating and inhibiting factors influencing their actions (Figure 1). GPs perceived the patient's concerns about the impact of migraine. Although the benefits of prophylaxis were appreciated, they were hesitant about advising their patients, not because of lack of knowledge or lack of interest, but because of doubts about its effectiveness and fear of side-effects.

It is not a simple matter to decide whether GPs sufficiently comply with the current guideline on headache. In the Netherlands, most GPs generally tend to comply with their guidelines.[22] However, in the present study the respondents deviate from the guidelines on the above-mentioned points, indicating that for GPs prophylaxis is not simply induced by multiplying duration by frequency. Other guidelines also tend to neglect the above-mentioned factors when discussing the decision whether or not to start preventive treatment.[12,23-29] Some guidelines refer to the patient's wishes or preferences;[12,23,27] however, even when this is mentioned, this is not further specified.

Another difference between the actions of our GPs and the Dutch GP guideline[7] involves taking the initiative for prophylaxis. On this issue some GPs were much more reluctant than advised in the guideline, because they felt that the responsibility for initiating prophylaxis should lie with the patient. Therefore, prophylaxis was not always promoted in an active way; this finding warrants further exploration.

A parallel study on migraine patients shows that some elements in the decision-making process are similar between GPs and patients, whereas differences also occur.[30] For example, GPs more often mention the inability to cope with migraine attacks as a reason to start taking preventive treatment. It would be worthwhile to further quantify these differences between GPs and patients.
GPs indicated that they are more respectful to other patient-related conditions and co-morbidity than specialists. Contextual factors have a large influence on medical care as delivered by GPs. Further exploration of differences between GPs and specialists in the consideration of contextual factors needs further research.[31]
Most GPs show realistic expectations, although in each focus group one or two were pessimistic. This might be due to the discrepancy between the 'ideal' of a total relief of migraine in contrast to a sometimes moderate or absent effect in actual practice. Because GPs and/or patients often have a too positive vision on prevention in advance, it is important discuss this issue in postgraduate training and patient education.
In the present study the GPs expressed a fear regarding drug dependency, but it is unclear whether they refer to fear for actual addiction, such as with benzodiazepines. Also, the GPs seemed to refer to a broader negative association with the daily use of medication, such as when patients use (too) many drugs.

GPs occasionally felt that patients were suggesting that they did not take migraine seriously. The GPs did not agree with this and sincerely believed that they always paid adequate attention to migraine headaches. The patients were told to be aware that, even with optimal attack treatment, migraine patients with frequent attacks had a 'serious' health problem. GPs' approach to migraine as a health problem was not different from other diseases and some GPs regarded headache as an interesting problem because it challenges their own knowledge and skills. The lack of regular follow-up was seen as being unlike other chronic conditions in which preventive medication is used.

Study strengths and limitations

Although the composition of the focus groups broadly reflects the characteristics of GPs in the Netherlands, our GP group may have reflected those with a particular interest in headache. In the fourth focus group no new themes or additional information on those themes were raised, so it is unlikely that we missed any important themes.
A weakness of the study was that all meetings were conducted in the Dutch language and are reported here in English. Qualitative studies aim to capture meaning from the narrative of the respondents and some distortion may have occurred in the translation process. The text was corrected by two native English speakers, with the Dutch text at hand, and verified by a physician-headache expert.

Comparison with other studies

Although migraine has a complex biopsychosocial context, few qualitative studies on this topic are available. Reports have included patients' perceptions of migraine and chronic daily headache,[32,33] the needs of migraine patients [34,35], migraine-related decision-making,[36-38] the burden of migraine and impact on quality-of-life,[39,40] patient's experience and the expectations of management [16,41,42]. One of these latter studies addressed prophylaxis,[42] but the setting was a specialised care clinic and the study aim was different from ours. The latter study focuses on whether the physician involves the patient in choosing a preventive agent when the decision to start this was already made, not on the decision making in starting preventive therapy as in our study. A questionnaire study provided information on the extent to which patients accept the side-effects of preventive treatment, which is consistent with the findings in the present study.[43] Another study addressed how GPs treated themselves and close relatives,[44] one study explored physicians' understanding of patients with migraine,[45] and another study reports clinical determinants of preventive therapy in primary care.[46]

Implications for practice and future research

Appropriate prophylaxis is an important factor in the aim to improve the quality of care of migraine patients by reducing attack frequency and duration, improving functioning and productivity, reducing use of acute medication, and preventing medication over-use. The present study has elucidated some factors that prevent GPs from adequately managing migraine from this perspective, and might inform the development of educational strategies to improve migraine prophylaxis in general practice. The results also highlight the difficulties GPs experience in translating guidelines into practice and the need to develop guidelines that realistically reflect the context in which they are applied.
These factors should be addressed in guideline-setting and post-graduate education. Finally, some aspects of our findings need further exploration, and some deserve quantification.

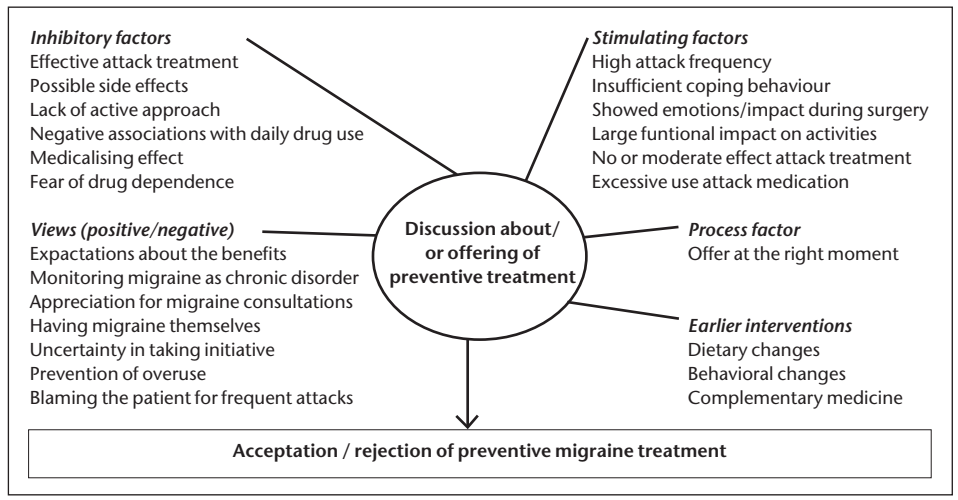

Figure 1. Interactions of elements playing a role in the considerations of GPs, preventive treatment

References

1. Goadsby PJ, Sprenger T. Current practice and future directions in the prevention and acute management of migraine. *Lancet Neurol* 2010;9(3):285-298.
2. Dekker F, Wiendels N, de Valk V, van der Vliet C, Knuistingh Neven A, Assendelft WJJ, Ferrari MD. Triptan overuse in the Dutch general population: A nationwide pharmaco-epidemiology database analysis in 6.7 million people. *Cephalalgia* 2011;31(8):943-952.
3. D'Amico D, Solari A, Usai S, Santoro P, Bernardoni P, Frediani F, De Marco R, Massetto N, Bussone G. Improvement in quality of life and activity limitations in migraine patients after prophylaxis. A prospective longitudinal multicentre study. *Cephalalgia* 2006;26(6):691-696.
4. Ramadan NM, Schultz LL, Gilkey SJ. Migraine prophylactic drugs: proof of efficacy, utilization and cost. *Cephalalgia* 1997;17(2):73-80.
5. Silberstein SD, Winner PK, Chmiel JJ. Migraine preventive medication reduces resource utilization. *Headache* 2003;43(3):171-178.
6. Silberstein SD, Goadsby PJ. Migraine: preventive treatment. *Cephalalgia* 2002;22 (7):491-512.
7. Grol MH, Neven AK, Pijnenborg L, Goudswaard AN. [Summary of the practice guideline 'Headache' from the Dutch College of General Practitioners]. *Ned Tijdschr Geneeskd* 2006;150(6):305-309.
8. Rahimtoola H, Buurma H, Tijssen CC, Leufkens HG, Egberts AC. Incidence and determinants of migraine prophylactic medication in the Netherlands. *Eur J Clin Pharmacol* 2002;58(2):149-155.
9. Linde M, Jonsson P, Hedenrud T. Influence of disease features on adherence to prophylactic migraine medication. *Acta Neurol Scand* 2008;118(6):367-372.
10. Mulleners WM, Chronicle EP. Anticonvulsants in migraine prophylaxis: a Cochrane review. *Cephalalgia* 2008;28(6):585-597.
11. Victor S, Ryan SW. Drugs for preventing migraine headaches in children. *Cochrane Database Syst Rev* 2003;(4):CD002761.
12. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 2007;68 (5):343-349.
13. Cevoli S, D'Amico D, Martelletti P, Valguarnera F, Del BE, De SR, Sarchielli P, Narbone M, Testa L, Genco S, Bussone G, Cortelli P. Underdiagnosis and undertreatment of migraine in Italy: a survey of patients attending for the first time 10 headache centres. *Cephalalgia* 2009;29(12):1285-1293.
14. Kol CM, Dekker F, Neven AK, Assendelft WJ, Blom JW. Acceptance or rejection of prophylactic medicine in patients with migraine: a cross-sectional study. *Br J Gen Pract* 2008;58(547):98-101.
15. Kuper A, Lingard L, Levinson W. Critically appraising qualitative research. *BMJ* 2008;337a1035.
16. Morgan M, Jenkins L, Ridsdale L. Patient pressure for referral for headache: a qualitative study of GPs' referral behaviour. *Br J Gen Pract* 2007;57(534):29-35.

17. Heath C, Hindmarsh J, Luff P. Video in Qualitative Research. SAGE. 2010.
18. Pope C, Mays N. Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. *BMJ* 1995;311 (6996):42-45.
19. Pope C, Ziebland S, Mays N. Qualitative research in health care. Analysing qualitative data. *BMJ* 2000;320(7227):114-116.
20. Joffe H, Yardley L. Content and thematic analysis. In: Marks DF, Yardley L, editors. Research methods for clinical and health psychology. London, Sage publications. 2003. 56-68.
21. Chamberlain K, Camic P, Yardley L. Qualitative analysis of experience: grounded theory and case studies. In: Marks DF, Yardley L, editors. Research methods for clinical and health psychology. London, Sage publications. 2003. 69-89.
22. Lugtenberg M, Burgers JS, Westert GP. Effects of evidence-based clinical practice guidelines on quality of care: a systematic review. *Qual Saf Health Care* 2009;18 (5):385-392.
23. D'Amico D, Tepper SJ. Prophylaxis of migraine: general principles and patient acceptance. *Neuropsychiatr Dis Treat* 2008;4(6):1155-1167.
24. Dowson AJ, Lipscombe S, Sender J, Rees T, Watson D. New guidelines for the management of migraine in primary care. *Curr Med Res Opin* 2002;18(7):414-439.
25. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sandor PS. EFNS guideline on the drug treatment of migraine - report of an EFNS task force. *Eur J Neurol* 2006;13 (6):560-572.
26. Lewis D, Ashwal S, Hershey A, Hirtz D, Yonker M, Silberstein S. Practice parameter: pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. *Neurology* 2004;63 (12):2215-2224.
27. Modi S, Lowder DM. Medications for migraine prophylaxis. *Am Fam Physician* 2006;73(1):72-78.
28. Pryse-Phillips WE, Dodick DW, Edmeads JG, Gawel MJ, Nelson RF, Purdy RA, Robinson G, Stirling D, Worthington I. Guidelines for the diagnosis and management of migraine in clinical practice. Canadian Headache Society. *CMAJ* 1997;156 (9):1273-1287.
29. Tepper SJ, D'Amico D, Baos V, Blakeborough P, Dowson A. Guidelines for Prescribing Prophylactic Medications for Migraine: A Survey Among Headache Specialist Physicians in Different Countries. *Headache Care* 2004;1(4):267-272.
30. Dekker, F., Knuistingh Neven, A., Andriesse, B., Kernick, D., Ferrari, M. D., and Assendelft, W. J. J. Prophylactic treatment of migraine; the patient's view, a qualitative study. *BMC Fam Pract* 2012;13(1):13.
31. Weiner SJ, Schwartz A, Weaver F, Goldberg J, Yudkowsky R, Sharma G, Binns-Calvey A, Preyss B, Schapira MM, Persell SD, Jacobs E, Abrams RI. Contextual errors and failures in individualizing patient care: a multicenter study. *Ann Intern Med* 2010;153(2):69-75.

32. Peters M, Abu-Saad HH, Vydelingum V, Dowson A, Murphy M. Migraine and chronic daily headache management: a qualitative study of patients' perceptions. *Scand J Caring Sci* 2004;18(3):294-303.
33. Peters M, Huijer Abu-Saad H, Vydelingum V, Dowson A, Murphy M. The patients' perceptions of migraine and chronic daily headache: a qualitative study. *J Headache Pain* 2005;6(1):40-47.
34. Belam J, Harris G, Kernick D, Kline F, Lindley K, McWatt J, Mitchell A, Reinhold D. A qualitative study of migraine involving patient researchers. *Br J Gen Pract* 2005; 55(511):87-93.
35. Cottrell CK, Drew JB, Waller SE, Holroyd KA, Brose JA, O'Donnell FJ. Perceptions and needs of patients with migraine: a focus group study. *J Fam Pract* 2002; 51(2): 142-147.
36. Peters M, Abu-Saad HH, Vydelingum V, Dowson A, Murphy M. Patients' decision-making for migraine and chronic daily headache management. A qualitative study. *Cephalalgia* 2003;23(8):833-841.
37. Ivers H, McGrath PJ, Purdy RA, Hennigar AW, Campbell MA. Decision making in migraine patients taking sumatriptan: an exploratory study. *Headache* 2000; 40(2):129-136.
38. Meyer GA. The art of watching out: vigilance in women who have migraine headaches. *Qual Health Res* 2002;12(9):1220-1234.
39. Tenhunen K, Elander J. A qualitative analysis of psychological processes mediating quality of life impairments in chronic daily headache. *J Health Psychol* 2005; 10(3):397-407.
40. Ruiz dV, I, Gonzalez N, Etxeberria Y, Garcia-Monco JC. Quality of life in migraine patients: a qualitative study. *Cephalalgia* 2003;23(9):892-900.
41. Moloney MF, Strickland OL, DeRossett SE, Melby MK, Dietrich AS. The experiences of midlife women with migraines. *J Nurs Scholarsh* 2006;38(3):278-285.
42. Rozen TD. Migraine prevention: what patients want from medication and their physicians (a headache specialty clinic perspective). *Headache* 2006;46(5):750-753.
43. Kowacs PA, Piovesan EJ, Tepper SJ. Rejection and acceptance of possible side effects of migraine prophylactic drugs. *Headache* 2009;49(7):1022-1027.
44. Ducros A, Romatet S, Saint MT, Allaf B. Use of antimigraine treatments by general practitioners. *Headache* 2011;51(7):1122-1131.
45. Lipton RB, Stewart WF. Acute migraine therapy: do doctors understand what patients with migraine want from therapy? *Headache* 1999;39(suppl 2):S20-S26.
46. Valade D, Lanteri-Minet M, Radat F, Mekies C, Lucas C, Vives E, Joubert JM, Geraud G. Clinical determinants of migraine preventive treatment: contribution of SMILE, an observational survey of primary care migraine management in France. *Cephalalgia* 2010;30(10):1207-1213.

CHAPTER 5

Prophylactic treatment of migraine; the patient's view, a qualitative study

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ABSTRACT

Background

Prophylactic treatment is an important but under-utilised option for the management of migraine. Patients and physicians appear to have reservations about initiating this treatment option. This paper explores the opinions, motives and expectations of patients regarding prophylactic migraine therapy.

Methods

A qualitative focus group study in general practice in the Netherlands with twenty patients recruited from urban and rural general practices. Three focus group meetings were held with 6-7 migraine patients per group (2 female and 1 male group). All participants were migraine patients according to the IHS (International Headache Society); 9 had experience with prophylactic medication. The focus group meetings were analysed using a general thematic analysis.

Results

For patients several distinguished factors count when making a decision on prophylactic treatment. The decision of a patient on prophylactic medication is depending on experience and perspectives, grouped into five categories, namely the context of being active or passive in taking the initiative to start prophylaxis; assessing the advantages and disadvantages of prophylaxis; satisfaction with current migraine treatment; the relationship with the physician and the feeling to be heard; and previous steps taken to prevent migraine.

Conclusion

In addition to the functional impact of migraine, the decision to start prophylaxis is based on a complex of considerations from the patient's perspective (e.g. perceived burden of migraine, expected benefits or disadvantages, interaction with relatives, colleagues and physician). Therefore, when advising migraine patients about prophylaxis, their opinions should be taken into account. Patients need to be open to advice and information and intervention have to be offered at an appropriate moment in the course of migraine.

BACKGROUND

Primary care is an important setting for the management of migraine and in many countries most migraine consultations occur in this context[1]. In the Netherlands, migraine is mainly managed in primary care and 95% of prescriptions for triptans are issued in this setting [2].

Prophylactic therapy is an option for patients with frequent or long-lasting migraine headaches[3-8]. The results of 6-12 months of preventive treatment are that in about 50% of patients the attack frequency decreases by 50%. Also, the attacks are often less severe [9]. Drop-out by adverse events is around 5%[10], drop-out due to ineffectiveness is unknown in usual care.

Dutch GP guidelines on headache recommend discussing prophylactic therapy with patients who suffer (on average) 2 or more attacks each month[11]. Despite it being a safe and more or less effective treatment option, only 7-13 % of the migraine patients receive it[7,12] and the benefits are not widely accepted. Little is known about the opinions of GPs and patients regarding prophylaxis, or the determinants behind decisions whether or not to start prophylaxis.

This qualitative study explores the opinions, motives and expectations of migraine patients about prophylactic migraine therapy. A similar study focusing on GPs' opinions is reported separately.

METHODS

Recruitment

Three focus groups of migraine patients were formed, 2 from urban areas and 1 from a rural area. Patient selection was based on pre-specified criteria, aiming to reflect a broad range of experience (from young to old), gender (separate groups for males and females), attack frequency (≥ 2attacks/month) and pain level (≥ 6 on a scale of 10 matching migraine, 1 being almost no headache and 10 being the worst headache ever). Our goal was to achieve a diversity of migraine patients, corresponding to general practice and with a sufficiently high frequency to be eligible for preventive therapy[12,13]. The study was approved by the Ethics Committee of the Leiden University Medical Centre.

One group of 7 females and a second group of 6 males were recruited from 5 urban primary care health centres or group practices. See patient characteristics in Table 2. We selected patients based on the diagnosis migraine and all these patients used prescribed medication for acute treatment. Thirteen patients had consulted their GP or a neurologist for their migraine (2 groups). A third group, comprising 7 females from a rural area, was recruited by a researcher investigating consumer behaviour. In this group each participant was approached by telephone and selected if they had migraine according to the IHS criteria. In this group 2 participants had not received any medical supervision yet.

Table 1. Patient characteristics, 2 female and 1 male groups.

		Total	Female 1	Male	Female 2
		N = 20	n = 7	n = 6	n = 7
Pain score* (1-10)		8.4	8.2	8.4	8.6
Attack freq./month	2 - 5	16	6	5	5
age	≥ 5	4	1	1	2
	< 25	4	2	-	2
	25 – 50	11	3	4	4
	> 50	5	2	2	1
	mean	43 yrs	42 yrs	47 yrs	39 yrs
Education level	low	3	-	1	2
	medium	14	5	5	4
	high	3	2	-	1
Paid work (hrs/wk)	none	5	2	1	2
	< 36	8	4	1	3
	≥ 36	7	1	4	2
	mean (hours/ week)	22	15	29	21

** Pain level during maximum of attack on a 1-10 numeric scale (10 being unbearable pain)*

The application form contained two questions on migraine (severity and frequency), one on the level of education and one about the number of hours in paid work. Based on this application form, the researcher made a comparison with national data on migraine patients in general practice[12]. Regarding the severity and frequency of the migraine, the composition of the three groups corresponded well with the average characteristics of migraine patients in Dutch general practice. The subject mentioned on the invitation was migraine headache in general, without a specific indication of our interest in preventive treatment.

Data generation

The focus group meetings were chaired by an independent moderator experienced in focus group research. The principal investigator (FD) observed all meetings from an adjacent room via a monitor with sound, but had no influence on the discussions. The moderator used a specially prepared interview guide (compiled by AKN and FD) which started with an introduction and familiarization, followed by discussion on the characteristics of the patients' migraine experience (e.g. age at onset, changes in migraine over time, treatment for attacks, and treatment goals, etc.). Prophylaxis was discussed, including the advantages and disadvantages, and the patients' experiences and attitudes towards preventive medication. In all focus groups sessions a topic list was used, which included some provocative statements to stimulate discussion and the exchange of ideas. The quantitative data listed in the results section are based on this topic list. All sessions were digitally recorded on DVD.

Data analysis

The recordings were analysed independently by three researchers (FD, AKN and BA). Because the DVD recordings provided the most detailed information on both verbal and non-verbal communication, these served as the primary data source[14-16]. The researchers used regular DVD-reading software with good on-screen forward/backward and other search possibilities. The DVDs allowed both hearing and seeing of non-verbal indications as to whether or not an opinion was supported by others in the group. The three investigators individually identified 'themes', that is remarks containing information on prophylactic therapy, or relevant or closely related to it. A transcript was made of all the comments by the participants on preventive treatment. Subsequently these comments were grouped independently by three researchers. The identified themes were written out and then organised into categories and (sub-) themes by the principal investigator, according to the rules of 'thematic analysis[16-18], into a draft analytical framework. This framework was consecutively discussed and decided upon with the other members of the team.
When there was disagreement between researchers in the analysis, the theme was analysed again by the disagreeing researchers and in case of a persisting discrepancy consensus was soughed and reached between the researchers. The analysis was coordinated by the principal investigator, who did put the remaining questions each time to both the other researchers. An interpretative analysis of the data with the help of this framework enabled the identification of several related but separate topics of experience and reasoning regarding prophylactic treatment for migraine and a tentative model for understanding patients' decision making regarding such treatment.

RESULTS

Five main categories of themes emerged from the focus group meetings.

1) Previous steps taken to prevent migraine

With regard to preventive measures, many participants were concerned that migraine was not well understood, and some found it hard to rely on prophylactic therapy because the mechanism was still unclear to them.
Almost all patients had experimented with behavioural, lifestyle or dietary actions, mostly without success and later therefore abandoned. However, some patients con-

tinued with these behaviours, even when they believed that they probably provided no benefit. Many participants avoided certain foods and other types of products. Some used specific products in order to promote their health.
'Stabilizing the biological clock', i.e., developing a stable day-night rhythm, was a widely used precaution by more than half of participants. Interventions were often supported by their physicians. For some patients, prophylaxis was the last resort.

> *"I 'did' the whole alternative circuit. I tried everything. Only after all that was I ready for prophylaxis."* (Group 1, PT 1)

Many types of complementary medicines had been or were being used. Most patients believed that although prophylactic treatment is only moderately effective, it is still more effective than complementary therapies. Using a complementary therapy often hampered patients from considering prophylaxis; they were waiting for the effects of the complementary interventions. Once complementary therapies had failed, they were more willing to try regular therapies.

> *"In the beginning, when my migraines were first diagnosed, we tried everything and every therapy to treat the attacks. Later on, I stopped making appointments for my migraines, I was so disappointed … and I tried everything myself, avoided all kinds of food, gulped down vitamins and other supplements, relaxation therapies, etc., etc."* (Group 3, PT 5)

2) Satisfaction with current migraine treatment

Migraine patients differed in how they determined whether or not they were satisfied with their treatment. Some patients were satisfied when they were able to keep on functioning at work or at home, others were only satisfied when the headache disappeared.
A few participants kept a highly structured diary to ascertain whether there were any factors that influenced their migraine. Keeping a diary made patients more accessible to prophylactic medication.

> *"My GP gave a kind of brochure; later on I continued keeping record of my headaches. I think that's very important; noting parallel things, food and so, looking back whether medication works."* (Group 1, PT 1)

According to the patients, preventing the overuse of attack treatment was only occasionally considered by the GP. According to the patients, almost no GP used that argument in the discussion about whether or not to start preventive treatment. Remarkably, some patients who used excessive attack treatment mistakenly called it 'prevention'. In their incorrect but exemplary way of thinking, they considered it to be prophylaxis because they used the attack treatment before a migraine attack occurred. Some patients showed very limited awareness about the risks of overuse of attack treatment.

> *"I already take so many medications, so don't do that preventive thing to me. When I feel a headache coming, I just take a tablet and that's prevention to me."* (Group 2, PT 3)

Most patients agreed that effective migraine treatment consists of effective attack management in addition to effective prophylaxis. More than half of the patients wanted to reduce the use of attack treatment, because they felt they were using too many triptans or painkillers. However, patients still focused on the importance of attack treatment; prophylaxis took second place. This focus on attack treatment hampered their thinking about other strategies to reduce the burden of migraine.

> *"I'm afraid of the side-effects of triptans; that's making me more open to prophylaxis."* (Group 1, PT 5)

The feeling of being in control of the migraine and not being controlled by it was considered a very important factor. Participants accepted a high frequency of migraine and/or long-lasting attacks as arguments for prophylaxis. However, the vast majority believed that if the attack treatment was extremely effective, there would be no need for prophylaxis. This was irrespective of the number of attacks and was in relation to what patients found 'normal' for them.

> *"I'm not stuffing my body with medication when I have an attack 3 times a month, even if it is terribly intense, but when it's good treatable."* (Group 2, PT 7)

3) Taking the initiative for prophylaxis

Although not every patient had personal experience with migraine prophylaxis, almost everyone knew about its existence. Most patients received information from family members, physicians, the Internet, the media or pharmacists. Many participants had searched the Internet for specific information on prophylaxis and encountered both positive and negative information such as stories of patients who have had a lot to benefit from prophylaxis and others who had no good effect and suffered from significant side effects.

> *"I'm using preventive therapy now. I didn't hear anything about it from the doctor … I found out myself that something like that was available. It was in a women's magazine, not via the GP. I'm unhappy about that…"(*Group 3, PT 7)

Testimonies of other patients or information of a patient headache association was not clear enough or too ambiguous to make a first step. It did not have a direct influence on their own health-seeking behaviour.

> *"Anti-epileptics, that sounds dreadful. The sort of thing you associate with lying on the ground with foam around your mouth."* (Group 2, PT 3)

There was no consensus as to who should take the initiative for prophylaxis. About half of the patients expected an active approach from their GP. Others (more urban and/or more highly educated) preferred to take the initiative themselves. All patients expected that their GP should be able to discuss the advantages and disadvantages of prophylaxis.
Patients found it important that discussion about prophylaxis should take place at the appropriate moment. This was not necessarily at the initial diagnosis, but when the patient knew more about the impact of migraine and the effectiveness of attack treatment. The need for prophylaxis could then be considered within a more realistic context.

> *"I never wanted it; I'm not a pill swallower. But I find it terrible to have to call my colleagues that I have another attack again. Then they stare at me with negatively loaden, piercing eyes. And I have started to think differently about daily treatment."* (Group 2, PT 6)

Prophylaxis was often discussed when patients indicated they were no longer able to cope with the headache attacks.

> *"My migraines were so severe that I went to the doctor … I couldn't do anything but cry. He tried to comfort me and offered prophylaxis."* (Group 3, PT 4)

For a few participants, the initiative for prophylaxis was taken by the GP based on the amount of prescribed attack medication; these GPs actively monitored the use of triptans and painkillers. When confronted with such an active approach, the patients were initially cautious but subsequently regarded the GP's intervention as positive. Ultimately, almost all patients desired to have their own control over the final decision.

> *"Sometimes I'm afraid he'll phone again … because I take too much medication. I once phoned for a repeat prescription, but the doctor called back and said: You've used too much this month. Then he mentioned preventive therapy. It feels OK, that he's concerned about me."* (Group 1, PT 5)

4) Assessing the advantages and disadvantages of prophylaxis
From the patient's perspective, the decision to start prophylaxis is complex. There is a wide range of perceived advantages and disadvantages, migraine patterns often vary, and the underlying concerns also differ.

> *"The pattern of attacks of my migraine is too weird to be able to figure out whether prophylaxis will help me or not."* (Group 3, PT 2)

> *"Accepting prophylaxis is difficult, because my attacks sometimes stay away for a long time. It's sometimes months before I have another attack, but once they start they're very frequent."* (Group 3, PT 3)
> *"I'm now using so many triptans … this can't be a good thing."* (Group 3, PT 2)
> *"I just don't want to do it. I'm very anti-drugs."* (Group 3, PT 1)

When considering prophylaxis, all patients experienced negative or obstructive elements, as well as positive factors. Participants had differing views on this subject, some mainly emphasised the positive aspects and others mainly the negative aspects.
The most important negative factors were the fear of side-effects, the assumption that prophylaxis will have little impact, and the feeling of becoming a chronic patient. The issue of 'becoming a chronic patient' was expressed in all sessions, and about 50% of the patients associated the use of prophylactic drugs with 'old age' and 'chronic disease'. Participants emphasised that they did not feel like a 'patient' in between the migraine attacks, so it did not feel appropriate to use medication on a daily basis. Despite a high impact of migraine and although many (daily) preventive measures and behavioural adaptations has been adopted, the use of prophylactic drugs was not easily accepted.
More than half of the patients stated that daily use of tablets for migraine would make them feel emotionally unhealthier. Other negative factors included the fear of drug dependency, a low assessment of their own capacity for compliance, and the negative reactions of persons in their direct surroundings.

> *"If I were to take tablets every day, I'd feel like I'm a patient. Now I just have a headache sometimes … actually it's many times."* (Group 3, PT 3)
> *"I think I'd forget it (medication) so often that it wouldn't be effective."* (Group 3, PT 7)
> *"I'm afraid of becoming dependent on those drugs."* (Group 3, PT 2)
> *"It's something in the head about not wanting to take tablets every day."* (Group 2, PT 4)
> *"When you receive preventive therapy for something, people think you're a pitiful case."* (Group 2, PT 6)
> *"The question is: how does migraine affect your life. I don't want migraine to affect my life, and taking drugs every day would have a major effect on my life."* (Group 1, PT 6)

The factors that contribute to positive decision appear to rest on a more calculated way of thinking or approach; weighing the advantages against the disadvantages and assessment of the degree of effectiveness.
Half of the participants had benefited from prophylaxis. The main positive benefits were a reduction in the burden of migraine with an increase in the range of abilities; this was particularly important when the impact was high. Other positive features were the ease of administration, an overall general gain in health, a reduction in acute

medication, less confrontations with the GP in case acute medication was used excessively, and less pressure from others close to them. When the benefits were clearer, patients were able to accept prophylaxis or were at least willing to try it. Most of the patients stated they would accept daily drug intake if their migraine frequency would be halved.

"I don't care what I have to do; I'd do anything to get rid of my headaches." (GR 2, PT 4)
"If it worked for 100%, I would certainly join the users!" (Group 3, PT 3)
"With prophylactic drugs you're able to participate much more in sport activities - which I enjoy very much." (Group 1, PT 4)
"If somebody said to me: "The migraines will disappear if I cut off your hand", then I'd say: Cut off my whole arm!" (Group 3, PT 3)

Many patients anticipated reimbursement problems with the healthcare insurance companies when receiving prophylactic therapy (in fact, in the Netherlands, all costs of prophylactic therapies are fully covered by healthcare insurance for all patients). Patients who had experience with prophylaxis reported that they had no problems with health insurance or the financial side of treatment costs.
Apart from the duration of the attack another important factor was the situation involved, e.g. being at school, at work, or with friends or family. For similar attack rates the perceived need for prophylaxis differed between patients.
Not being able to take care of others was a strong positive factor for prophylaxis. Apart from the impact of migraine on themselves also the impact on other persons for whom they are responsible (e.g. children, family members, colleagues, etc.) was an important argument for preventive treatment.

"I can't even make it to the meetings of my sports club. I might manage it once, but the second, third and fourth time they wouldn't understand. When you feel that negative impact from migraine, then you really want to start thinking about preventive treatment." (Group 3, PT 4)

5) The relationship with the physician and the feeling to be heard
At the time of diagnosis, being taken seriously about the burden of the migraine and acknowledgement of their suffering was considered most important. But this was not the appropriate time when patients were interested in prevention. Many migraine patients felt there was a limit to the extent to which their physician is able to comprehend the burden they bear. They considered that their GP unable to imagine how difficult it is to experience a migraine attack, whereas others mentioned a sympathetic response from their GP. Patients indicated that at a later stage a good empathetic relationship with the doctor was important for the acceptance of prevention.

"He (GP) was really concerned about me, about the enormous number of attacks I had. That was good and very considerate of him." (Group 1, PT 4)
"I think that he (GP) thinks: what on earth can I do for you anyway…" (Group 2, PT 2)
"I found that now something really has to be done … so I went to the doctor. He said: It sounds like classic migraine; we'll see what we can do. I should have done this much earlier … at last I felt that someone understood." (Group 1, PT 2)
"There's always that fear of the next attack, and my family doctor seemed to understand that fear. First and foremost, you have to be taken seriously by your doctor." (Group 1, PT 1)

An important influence was the way their GPs treated them. Positive factors in promoting prevention were having a positive interaction and the feeling being taken seriously. On the other hand, being dissatisfied about the approach of the physician hampered the willingness to consider prophylaxis.

"Primarily I want to be taken seriously, but I can not complain. He's handled it well, with the start of preventive treatment." (Goup1 PT 5)
"If you have more than two attacks a month, they just give you a prescription for anti-epileptics and - before you know it - you're outside again." (Group 3, PT 6)

DISCUSSION

Summary of main findings
The present study describes patients' subjective opinions about prophylaxis as a treatment option for migraine.
A number of conditions that must be met before preventive therapy is accepted and that these often are related to each other (figure 1). These conditions can be patient related, clinician related or be related to the disease or the disease process. Knowledge on the importance of these issues for the decision making of patients is crucial for physicians dealing with migraine patients in daily practice.
Patients indicate a number of important factors in favour of the use of prophylaxis related to the perceived burden of migraine; a high frequency of attacks, severe attacks, and lack of effectiveness of attack treatment. These are characteristics of the migraine itself, on which physicians do not have much influence (however they have certainly on proper attack treatment). The patient makes a balance of pros and cons. Expectations of the beneficial effects, fear of side effects and drug dependency and negative health feeling in case of daily use of medication, play a considerable role in making this balance.
The willingness to try prophylaxis increased after other interventions had been tried (e.g. dietary changes, changes in lifestyle or previous complementary treatments). Patients prefer strongly to take the decision themselves and want to have responsibil-

ity themselves. The individual history of earlier interventions is pivotal. Several factors increase the resistance to accepting prophylaxis, such as changing the scope from seeing migraine as an intermittent to seeing it as a chronic disease.

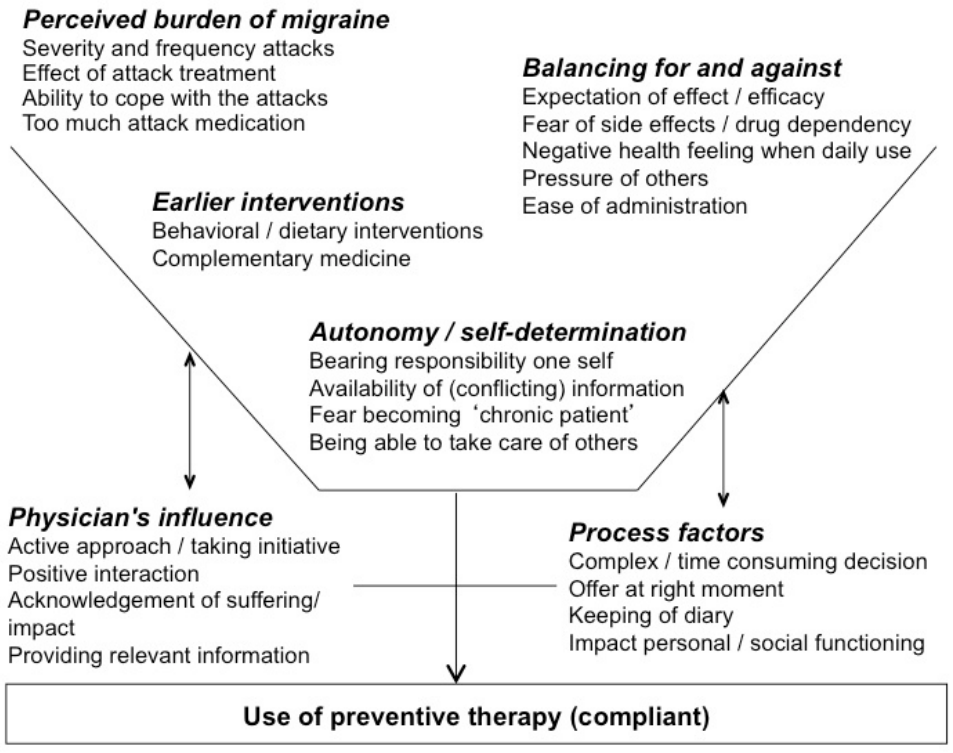

Figure 1. Interactions of elements playing a role in accepting of and compliance with preventive treatment

When weighing the facts and reaching a decision on prophylaxis, the physician has a major influence, especially by providing relevant information. In the process of getting more insight on their migraine, patients feel that the physician can be helpful. Patients attach great importance to a good and trusted relationship with the physician and often prefer an active approach.
It is important to acknowledge that a patient is going through a process, and in time tend more and more towards a decision. It takes time to realize that one has a severe problem with migraine and that the migraine has a large impact. Keeping a diary can provide such an insight in an earlier stage [19]. From the management perspective, patients need to be receptive to the idea of prophylaxis at the right moment in their migraine history.

Study strengths and limitations

This focus group research aimed to explore opinions through a purposeful sample covering a range of subjects and doesn't provide numbers and clear conclusions such as quantitative research.
We decided to have separate male and female groups based on the assumption that their approaches to migraine differ, and that a mixed group may inhibit the exploration of some key elements of migraine for woman, such as a relation with menstruation.
Saturation of themes occurred within the three groups, when no new themes arose that had not been included in our topic guide. Within the groups, a diversity of approaches was found. For example, the urban group was more highly educated and displayed more resistance to prophylaxis, and needed a more rational and evidence-based requirement for its introduction. The rural group had a more passive attitude and indicated more acceptance to the propositions from their physician.
A weakness of the present study is that it was conducted in the Dutch language and is reported in English. Qualitative studies aim to capture meaning from the narratives of respondents and some loss and/or distortion may have occurred in the translation process. However, we had the Dutch texts translated by two experienced translators and from the perspective of migraine a native English speaking expert physician on migraine looked into the patient remarks.

Comparison with other studies

Parallel to this study another qualitative study from the same research group, also on prophylaxis for migraine, explored the attitude of GPs[20]. That study confirmed the complexity of the decision-making process, which from the perspective of the GP was also not based on the impact of migraine alone. Patients and GPs showed a similar degree of hesitance, not because of lack of knowledge or lack of interest, but because of doubts about effectiveness, side-effects, and the risk of developing drug dependence.
Of the qualitative studies on migraine, only one has addressed preventive therapy[21]. In that study by Rozen, the method (questionnaire) and setting (third-line centre) were different to ours and all patients had prior exposure to migraine prophylaxis. The decision whether or not to start preventive therapy had already been made, and the questionnaire mainly addressed side-effects and the choice of drugs. That study provided no information on its aims or how the decision concerning prophylaxis was made.
Two qualitative studies show agreement with our study in relation to prevention. One study shows remarkable similarities on the patient communication with the GP and on the search for complementary therapies by patients. Because this study is not about prevention, is does cover the influence of these two issues on prevention[22]. The other study reports that self-efficacy scores were positively associated with the use of positive psychological coping strategies to prevent headaches[23].

Other studies which address patient factors in migraine do not address prophylaxis and focus on the needs of migraine patients[24,25], decision-making in migraine[26-28], the burden of migraine and quality of life[29,30], perimenopausal headache[31], migraine in midlife women [32], and pressure on patients related to referral[33], and therefore have almost no overlap to our study. The questionnaire study by Kowacs et al. on the patients' view on side effects of preventive treatment revealed that side effects are better accepted by patients with high use or actual overuse of attack treatment, which is consistent with our findings[34]. The questionnaire study of Kol et al. found that 55 % of patients with two or more attacks per month wanted to use prophylaxis, while only 8% actually used this treatment. This paradox is one of the underlying themes in our study[12].

Similar studies have also been conducted with other chronic diseases. For example, the study of Adams et al. on acceptance of the preventive treatment for asthma[35]. Specific for prophylactic asthma treatment is that it is given even in asymptomatic periods, the inhalation therapy is visible to others and there is fear for side effects on the longer term ('steroid fear'). In contrast, in migraine only patients with frequent and severe attacks are treated, mainly the side effects on the short term are feared, and in general patients have no trouble with the acceptance of the migraine as such. This comparison shows that migraine has similarities, but also differences with other chronic diseases. Most likely the opinions of patients differ per indication.

CONCLUSIONS

The benefits of prophylactic medication for migraine are under-exploited. Future research should focus on the various aspects involved in decisions about preventive treatment, as reflected in the present study. An understanding by physicians of the patient's feelings and concerns towards prevention are important for more effective use of these agents. When advising migraine patients on prophylaxis it is important to explicitly address their underlying thoughts and emotions, and to consider the intervention at an appropriate moment in the course of the patient's migraine experience.

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References

1. Freitag FG. The cycle of migraine: patients' quality of life during and between migraine attacks. *Clin Ther* 2007;29(5):939-949.
2. Dekker F, Wiendels N, de Valk V, van der Vliet C, Knuistingh Neven A, Assendelft WJJ, Ferrari MD. Triptan overuse in the Dutch general population: A nationwide pharmaco-epidemiology database analysis in 6.7 million people. *Cephalalgia* 2011;31(8):943-952.
3. D'Amico D, Solari A, Usai S, Santoro P, Bernardoni P, Frediani F, De Marco R, Massetto N, Bussone G. Improvement in quality of life and activity limitations in migraine patients after prophylaxis. A prospective longitudinal multicentre study. *Cephalalgia* 2006;26(6):691-696.
4. Silberstein SD, Winner PK, Chmiel JJ. Migraine preventive medication reduces resource utilization. *Headache* 2003;43(3):171-178.
5. Goadsby PJ. Recent advances in the diagnosis and management of migraine. *BMJ* 2006;332(7532):25-29.
6. Peres MF, Silberstein S, Moreira F, Corchs F, Vieira DS, Abraham N, Gebeline-Myers C. Patients' preference for migraine preventive therapy. *Headache* 2007;47(4):540-545.
7. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 2007;68(5):343-349.
8. Goadsby PJ, Sprenger T. Current practice and future directions in the prevention and acute management of migraine. *Lancet Neurol* 2010;9(3):285-298.
9. Mulleners WM, Haan J, Dekker F, Ferrari MD. [Preventive treatment for migraine.]. *Ned Tijdschr Geneeskd* 2010;154(29):A1512.
10. Linde K, Rossnagel K. Propranolol for migraine prophylaxis. *Cochrane Database Syst Rev* 2004;(2):CD003225.
11. Grol MH, Neven AK, Pijnenborg L, Goudswaard AN. [Summary of the practice guideline 'Headache' from the Dutch College of General Practitioners]. *Ned Tijdschr Geneeskd* 2006;150(6):305-309.
12. Kol CM, Dekker F, Neven AK, Assendelft WJ, Blom JW. Acceptance or rejection of prophylactic medicine in patients with migraine: a cross-sectional study. *Br J Gen Pract* 2008;58(547):98-101.
13. Wiendels NJ, Knuistingh Neven A, Rosendaal FR, Spinhoven P, Zitman FG, Assendelft WJJ, Ferrari MD. Chronic frequent headache in the general population: prevalence and associated factors. *Cephalalgia* 2006;26(12):1434-1442.
14. Heath C, Hindmarsh J, Luff P. Video in Qualitative Research. SAGE. 2010.
15. Pope C, Mays N. Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. *BMJ* 1995;311 (6996):42-45.
16. Pope C, Ziebland S, Mays N. Qualitative research in health care. Analysing qualitative data. *BMJ* 2000;320(7227):114-116.

17. Chamberlain K, Camic P, Yardley L. Qualitative analysis of experience: grounded theory and case studies. In: Marks DF, Yardley L, editors. Research methods for clinical and health psychology. London, Sage publications. 2003. 69-89.
18. Joffe H, Yardley L. Content and thematic analysis. In: Marks DF, Yardley L, editors. Research methods for clinical and health psychology. London, Sage publications. 2003. 56-68.
19. Nappi G, Jensen R, Nappi RE, Sances G, Torelli P, Olesen J. Diaries and calendars for migraine. A review. *Cephalalgia* 2006;26(8):905-916.
20. Dekker, F., Knuistingh Neven, A, Andriesse, B, Kernick, D., Ferrari, MD, and Assendelft, W. J. J. Prophylactic treatment of migraine by general practitioners: a qualitative study. *Br J Gen Pract* 2012;62(597):268-274.
21. Rozen TD. Migraine prevention: what patients want from medication and their physicians (a headache specialty clinic perspective). *Headache* 2006;46(5):750-753.
22. Peters M, Abu-Saad HH, Vydelingum V, Dowson A, Murphy M. Migraine and chronic daily headache management: a qualitative study of patients' perceptions. *Scand J Caring Sci* 2004;18(3):294-303.
23. Peters M, Huijer Abu-Saad H, Vydelingum V, Dowson A, Murphy M. The patients' perceptions of migraine and chronic daily headache: a qualitative study. *J Headache Pain* 2005;6(1):40-47.
24. Belam J, Harris G, Kernick D, Kline F, Lindley K, McWatt J, Mitchell A, Reinhold D. A qualitative study of migraine involving patient researchers. *Br J Gen Pract* 2005;55(511):87-93.
25. Cottrell CK, Drew JB, Waller SE, Holroyd KA, Brose JA, O'Donnell FJ. Perceptions and needs of patients with migraine: a focus group study. *J Fam Pract* 2002; 51(2):142-147.
26. Peters M, Abu-Saad HH, Vydelingum V, Dowson A, Murphy M. Patients' decision-making for migraine and chronic daily headache management. A qualitative study. *Cephalalgia* 2003;23(8):833-841.
27. Ivers H, McGrath PJ, Purdy RA, Hennigar AW, Campbell MA. Decision making in migraine patients taking sumatriptan: an exploratory study. *Headache* 2000; 40(2):129-136.
28. Meyer GA. The art of watching out: vigilance in women who have migraine headaches. *Qual Health Res* 2002;12(9):1220-1234.
29. Tenhunen K, Elander J. A qualitative analysis of psychological processes mediating quality of life impairments in chronic daily headache. *J Health Psychol* 2005; 10(3):397-407.
30. Ruiz dV, I, Gonzalez N, Etxeberria Y, Garcia-Monco JC. Quality of life in migraine patients: a qualitative study. *Cephalalgia* 2003;23(9):892-900.
31. Moloney MF, Dietrich AS, Strickland O, Myerburg S. Using Internet discussion boards as virtual focus groups. *ANS Adv Nurs Sci* 2003;26(4):274-286.

32. Moloney MF, Strickland OL, DeRossett SE, Melby MK, Dietrich AS. The experiences of midlife women with migraines. *J Nurs Scholarsh* 2006;38(3):278-285.
33. Morgan M, Jenkins L, Ridsdale L. Patient pressure for referral for headache: a qualitative study of GPs' referral behaviour. *Br J Gen Pract* 2007;57(534):29-35.
34. Kowacs PA, Piovesan EJ, Tepper SJ. Rejection and acceptance of possible side effects of migraine prophylactic drugs. *Headache* 2009;49(7):1022-1027.
35. Adams S, Pill R, Jones A. Medication, chronic illness and identity: the perspective of people with asthma. *Soc Sci Med* 1997;45(2):189-201.

CHAPTER

6

Acceptance or rejection of prophylactic medicine in patients with migraine: a cross-sectional study

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ABSTRACT

Most patients with two or more migraine attacks per month do not use prophylactic medication. The aim of this study is to investigate how many patients use prophylaxis or would like to use them, and which aspects of migraine contribute to the choice to use prophylactic treatment. In a cross sectional survey in three general practices, patients were selected who were diagnosed with migraine or had prescriptions for migraine medication. A questionnaire was sent to 283 patients and completed by 166 patients, of whom 15 were excluded. A total of 129 females and 22 males were included (median age 41 years). Most patients had two or more attacks per month (66.2%). Fifty-five per cent of patients with two or more attacks per month wanted to use prophylaxis; only 8% actually used this treatment. To get more insight into the ideas for or against prophylactic use, qualitative research is indicated.

INTRODUCTION

Migraine is a common episodic headache disorder affecting about 6% of men and 15–18% of women in the general population,[1,2] and is often associated with significant disability and reduced quality of life.[3]
Guidelines on migraine prophylaxis differ internationally, with prophylactic treatment recommended for patients with two attacks per month up to twice a week. According to guidance from the Dutch College of General Practitioners, patients with migraine attack frequency of more than two times per month should be offered prophylaxis.[4] In the US, 50% of patients with migraine meet the criteria for use of prophylactic treatment, but only 5–12% actually use it.[3] In the Netherlands, 12% of all patients with migraine use prophylactic treatment.[5]
The first study aim was to investigate how many and which patients use prophylaxis, and how many patients would like to use this form of treatment. The second aim was to investigate how frequency, duration, severity, and impact of migraine attacks relate to the wish to use prophylactic treatment.

METHOD

Study design and setting

This was a crosssectional survey conducted in three general practices with five GPs (approximately 10 000 registered patients).

Patient recruitment

Patients aged 18 to 65 years diagnosed with migraine who were treated by their GP and recorded in the electronic patient register, were selected using the International Classification of Primary Care (ICPC).[6] To identify patients with migraine who were not given a diagnosis according to the ICPC code, the database was searched for patients who had been prescribed migraine medication. Diagnostic codes were applied by the GP at any time from patient registration and after establishing the diagnosis.

Data collection

Data on patients' age, sex, number of visits, and the medication prescribed were collected from the electronic patient register. Data regarding frequency and duration of migraine attacks, migraine medication, and additional symptoms were selfreported using a mailed questionnaire.
The diseasespecific quality of life of patients was measured with the Headache Impact Test (HIT6), which is used to determine personal disease burden.[7] The scores are categorised into four grades: representing 'minimal' (score of 49 or less), 'mild' (50–55 points), 'moderate' (56–59 points), or 'severe' (60 points or more).[8]

The questionnaire explored reasons for and against using prophylaxis, and whether patients preferred to ask their GP for information about prophylaxis, or preferred the GP to raise the issue. Explanations were presented in a simplified manner to make the information understandable to patients. The questionnaire asked the following:

'Consider a medicine which reduces your migraine symptoms by 50%. This medicine would need to be taken every day. Ten per cent of patients have mild sideeffects, such as dizziness, feeling cold, and fatigue. Would you be prepared to take this medicine?'

A reduction of more than 50% in disease burden is estimated to occur in over 50% of patients taking prophylactic therapy.[9] For the remaining 50% of patients, the efficacy of prophylactic therapy is slightly less: for ßblockers an average reduction of 44% in migraine activity was shown.[10]

Statistical analysis

Associations between accepting prophylaxis and frequency, duration, and severity of migraine attacks, HIT6 score, and consulting the GP were calculated using odds ratios with 95% confidence intervals. A logistic regression model was used to analyse associations between these variables and the willingness to consider prophylaxis independently from each other.

RESULTS

Population description

The questionnaire was sent to 283 patients, and completed by 166 patients (response rate 58.7%). Thirteen patients stated in the questionnaire that they did not have migraine or had not experienced an attack for more than a year, and two patients did not answer the questions on prophylactic treatment. The study population consisted of 129 females (85.4%) and 22 males (14.6%). Median age was 41 years (interquartile range = 32–48 years). Median HIT6 score was 64 points (interquartile range = 60–68 points). Ten patients were already using prophylactic treatment.

Response analysis

Patients who completed the questionnaire visited their GP slightly more often in the previous year (56.6% versus 46.2%, $P = 0.082$), and received medication for migraine more often than those who did not complete the questionnaire (69.3% versus 55.6%, $P = 0.003$).

Preference for prophylaxis

Of the patients with two or more attacks per month, 7.9% already used prophylaxis. Most patients with migraine (78.0%) with a low attack frequency (less than two times per month) did not want to consider using prophylaxis. However, the remaining 22.0% of patients with migraine with a low attack frequency also reported that they would be interested in trying prophylaxis. In the group of patients with two or more attacks each month, 55.4% reported that they would like to consider prophylactic treatment, whereas 80.0% of the patients with more than five attacks each month were interested.

Apart from the duration of migraine attack, the HIT6 score, GP consultation during the year prior to this study, and use of migraine medication were associated with the willingness to consider using prophylaxis (Table 1, page 108). Most patients (60.9%) felt sufficiently confident to ask their GPs about prophylaxis, rather than expecting the physician to initiate discussions. However, a substantial group of patients with migraine with an indication for prophylaxis expressed a wish to be informed by their GP about preventive treatment for migraine (39.1%).

A logistic regression model showed that only frequency of migraine attacks was a strong independent determinant of desire for prophylaxis.

Patients who were against use of prophylaxis (n = 84) gave the following reasons (more than one answer was possible): fear of side effects (38.1%), experiencing minimal attacks (44.0%), feeling as if by using daily medication they had a chronic disease (23.8%), and 'other' (31.0%).

DISCUSSION

Summary of main findings

In this study, most patients with migraine attacks of five or more per month, and about half of patients with two or more attacks per month, would like to consider prophylaxis. Even in the group of patients with fewer than two attacks per month, one in five w ould like to consider prophylactic treatment. Most patients felt sufficiently confident to approach their GP themselves for prophylaxis. However, a substantial subgroup preferred an active approach by their physician. This finding is confirmed in a British study which reports that patients often do not consult their GP for their headache symptoms but still would like more help.[11]

Strengths and limitations of the study

A weakness of this study is that the question used to inquire about the wish for prophylaxis is rather theoretical and does not adequately address individual patient motivations and situations influencing their needs. However, the findings indicate that further qualitative research into the different motivations of patients and doctors is required.

Patients in this study visited their GPs slightly more often and were prescribed triptans more than those who did not fill in the questionnaire. It is likely that those completed the questionnaire had a higher disease burden than those who did not fill it in. This might have caused a slight overestimation of the percentage of patients with migraine in general practice who wish to use prophylaxis.

Table 1. Participant characteristics and preference for prophylactic treatment.

Total	Total (n = 151)	Yes to prophylaxis	No to prophylaxis	Odds ratio (95% CI)
Migraine frequency				
<2x per month	50 (33,1)	11 (22,0)	35 (31,5)	
≥2x per month	101 (66,2)	56 (55,4)	35 (31,5)	4,4 (2,0 to 9,6)
<5x per month	111 (73,5)	35 (31,5)	35 (31,5)	
≥5x per month	40 (26,5)	32 (80,0)	35 (31,5)	8,7 (3,6 to 20,8)
Migraine durationa				
<2x per month	58 (38,9)	23 (39,7)	35 (60,3)	
<2x per month	91 (61,1)	43 (47,3)	48 (52,7)	1,4 (0,7 to 2,7)
<2x per month	111 (74,5)	45 (40,5)	66 (59,5)	
<2x per month	38 (25,5)	21 (55,3)	17 (44,7)	1,8 (0,9 to 3,8)
Additional symptoms				
Not sensitive to light/sound	32 (21,2)	11 (34,4)	21 (65,6)	
Sensitive to light/sound	119 (78,8)	56 (47,1)	63 (52,9)	1,7 (0,8 to 3,8)
Nausea/vomiting absent	41 (27,2)	16 (39,0)	25 (61,0)	
Nausea/vomiting	110 (72,8)	51 (46,4)	59 (53,6)	1,4 (0,7 to 2,8)
Other	49 (32,5)	28 (57,1)	21 (42,9)	
HIT-6 scoreb				
<60	31 (20,7)	9 (29,0)	22 (71,0)	
≥60	119 (79,3)	58 (48,7)	61 (51,3)	2,3 (1,0 to 5,5)
Electronic patient register				
Medication				
No triptan use	72 (47,7)	21 (29,2)	51 (70,8)	
Triptan use	79 (52,3)	46 (58,2)	33 (41,8)	3,4 (1,7 to 6,7)
No medication	41 (27,2)	11 (26,8)	30 (73,2)	
Analgesic use (excluding triptan use)	31 (20,5)	10 (32,3)	21 (67,7)	1,3 (0,5 to 3,6)
Consultation frequency				
Never	86 (57,0)	29 (33,7)	57 (66,3)	
≥1 in the previous year	165 (43,0)	38 (58,5)	27 (41,5)	2,8 (1,4 to 5,4)

[a]Two participants did not fill in this question. [b]One participant did not fill in this question.

Comparison with existing literature

In a recent study in the UK it was found that patients who were referred to neurologists more often consulted their GP and had more concerns about their headache symptoms.[12] The current study's finding that patients who had seen their GP in the previous year were more likely to report an interest in prophylactic therapy, could also be explained by an increased concern about their symptoms.

Implications for clinical practice

The present findings suggest that physicians can play a more active role in optimising migraine therapy for their patients. Many patients with migraine experience disability and absence from work.[13] Better management by GPs could reduce individual suffering and have considerable gains for society.

References

1. Lipton RB, Scher AI, Kolodner K, Liberman J, Steiner TJ, Stewart WF. Migraine in the United States: epidemiology and patterns of health care use. *Neurology* 2002; 58(6):885-894.
2. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 2007;68 (5):343-349.
3. Diamond M, Dahlof C, Papadopoulos G, Neto W, Wu SC. Topiramate improves health-related quality of life when used to prevent migraine. *Headache* 2005;45 (8):1023-1030.
4. Knuistingh Neven A, Bartelink MEL, De Jongh TOH, Ongering JEP, Oosterhuis WW, Van der Weerd PCM, Pijnenborg L, Grol MH. NHG-Standaard Hoofdpijn. *Huisarts en Wetenschap* 2004;46411-422.
5. Rahimtoola H, Buurma H, Tijssen CC, Leufkens HG, Egberts AC. Incidence and determinants of migraine prophylactic medication in the Netherlands. *Eur J Clin Pharmacol* 2002;58(2):149-155.
6. International Classification Committee of WONCA. ICPC-2 International Classification of Primary care, second ed. Oxford, Oxford University Press. 1998.
7. QualityMetric, Inc. and GlaxoSmithKline. Headache Impact Test (HIT-6). 2012. Interpretation The Netherlands (Dutch) Version 1.1. 10-1-2008. http://www.headachetest.com/HIT6/PDFS/Dutch.pdf
8. Kosinski M, Bayliss MS, Bjorner JB, Ware JE, Jr., Garber WH, Batenhorst A, Cady R, Dahlof CG, Dowson A, Tepper S. A six-item short-form survey for measuring headache impact: the HIT-6. *Qual Life Res* 2003;12(8):963-974.
9. Bigal ME, Lipton RB. The preventive treatment of migraine. *Neurologist* 2006;12 (4):204-213.
10. Holroyd KA, Penzien DB, Cordingley GE. Propranolol in the management of recurrent migraine: a meta-analytic review. *Headache* 1991;31(5):333-340.
11. Belam J, Harris G, Kernick D, Kline F, Lindley K, McWatt J, Mitchell A, Reinhold D. A qualitative study of migraine involving patient researchers. *Br J Gen Pract* 2005; 55(511):87-93.
12. Ridsdale L, Clark LV, Dowson AJ, Goldstein LH, Jenkins L, McCrone P, Morgan M, Seed PT. How do patients referred to neurologists for headache differ from those managed in primary care? *Br J Gen Pract* 2007;57(538):388-395.
13. Rasmussen BK. Epidemiology of headache. *Cephalalgia* 2001;21(7):774-777.

Part 2

Attack treatment of migraine

CHAPTER

7

Patient preference in a randomized double-blind rizatriptan- ibuprofen multi-migraine attack trial

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ABSTRACT (SUBMITTED)

Background

The 2hr pain-free rate after treating a single migraine attack in a parallel-group study design is the recommended primary endpoint to establish acute antimigraine efficacy versus placebo. However, when comparing established treatments, the clinical validity of this approach seems limited. Cross-over trials, in which patients express a preference after exposure to both treatments, may better detect differences that are clinically meaningful for individual patients.

Methods

In a randomized, double-blind, cross-over, clinical trial, 29 triptan-naive patients expressed a quantified preference (0-5) after treating three attacks with rizatriptan 10 mg (R) and three with ibuprofen 400 mg (I).

Results

Ten (35%) patients expressed strong preference for R and six (21%) for I ($p = 0.15$). Thirteen (45%) had no or only a moderate preference. Mean ($\pm$ SD) overall preference (on a 10 point scale) was 0.62 ± 2.61 in favour of R ($p = 0.219$). Patients with high MIDAS baseline disability had stronger preference for R (73% vs. 9% for I; $p = 0.039$).

Conclusions

Most patients had a clear preference for one of both treatments, which was correlated only moderately to 2hr pain-free responses. Multi-attack, cross-over, patient-preference trials, may better detect clinically meaningful differences between established treatments.

INTRODUCTION (SUBMITTED)

Migraine is characterized by disabling attacks of headache and associated symptoms which may be treated with simple analgesics, NSAIDs, or triptans (1;2). For cost constraints, triptans are usually only prescribed if first line treatments have failed (1;3). Many patients are undertreated as little is known of who might benefit most from switching to triptans (1;3).

Traditionally, antimigraine efficacy is established by assessing "2hr pain-free rates after treating a single, moderate/severe attack in parallel-group studies" (4). While useful against placebo, the validity of this design to detecting clinically relevant differences between established agents seems limited (5). Although responder rates versus placebo usually are higher for triptans than for analgesics/NSAIDs (6) and triptans generally are considered more effective than painkillers (1), only small differences were found in traditional comparator trials (5;7;8). A possible explanation for this discrepancy may be that migraineurs asses drug performance on a range of attributes in multiple attacks rather than on just a single attribute in only one attack (6;9-12). Moreover, patients cannot truly compare treatments in a parallel-group design.

Post-treatment patient-preference (PTPP) trials, in which patients express preference after exposure to both treatments, are a promising, relatively new and potentially more valid approach to detecting clinically meaningful differences between established treatments (9;13-25). Such trials perfectly fit recent strong recommendations for a greater involvement of patients in treatment decisions: "… it [therefore] is increasingly the clinician's responsibility to find out what patients want" (26;27). PTPP studies must not to be confused with designs in which, to avoid bias, the allocation to a treatment group is based on the patients' pre-study preference (24;25).

Here, we present the results of the first randomized, double-blind, PTPP migraine trial. Migraineurs expressed a quantified preference after treating three attacks with rizatriptan and three with ibuprofen. This novel trial design allows for a better real-life, yet controlled evaluation of treatments and may also be used to compare other medications.

METHODS

Triptan and ergot-naive migraineurs(28) of 18 years or older with an average frequency of 1 to 7 migraine days per month during the last 6 months were invited to participate and screened for eligibility. Exclusion criteria were aimed at avoiding contraindications for study medication and included: history of atherosclerotic cardio- and cerebrovascular disease, blood pressure above 160/95, impaired hepatic or renal function,

gastrointestinal disorders, asthma, use of propranolol or MAO-inhibitors, and abuse of alcohol or recreational or analgesic drugs. Females had to use a medically accepted form of contraception and were not pregnant or breastfeeding. The study was approved by the Medical Ethics Committee of LUMC and all patients gave written consent. Trial registry id: NTR33 (www.trialregister.nl).

In a single-centre, randomized, double-blind, cross-over study, participants treated three migraine attacks with rizatriptan 10 mg and three attacks with ibuprofen 400 mg. Each treatment period could maximally last three months. Participants who were extremely dissatisfied after treating at least one attack with study medication, or who had suffered intolerable adverse events, could make an early (though still blinded) cross-over to the other treatment. They were instructed to treat as soon as possible after onset of a migraine headache and recorded time of onset of the attack, timing of dosing, and headache severity (none, mild, moderate, severe)(4) immediately prior to and two hours post dose. Participants could take a second blinded dose of study medication at two hours after the initial dose and rescue medication at three hours (but not rizatriptan or ibuprofen).

Ibuprofen 400 mg was chosen as it is globally the most widely recommended NSAID and dose for migraine (29-31). Some physicians might argue that a higher dose could have a better analgesic effect. However, as preference not only assesses efficacy but also tolerability and higher doses may increase the risk of adverse events and thus potentially could bias against ibuprofen, we decided to use an initial dose of 400 mg, but allowed for a second dose at 2hrs in case of inefficacy. Rizatriptan was chosen because it is one of the triptans with the highest responder rates in traditional trials (1;6) and the manufacturer could provide both the active medication and fully matching placebos. All triptans are fully reimbursed in the Netherlands, so readiness to pay could not be assessed.
For this study, triptan naivety was required because the easily recognizable qualities of triptans would disrupt the blinding. Triptan naivety in the Netherlands is rare; it was difficult to find suitable candidates for this study. Most patients used ibuprofen before the study. However, this does not imply that patients had a preference for ibuprofen, resulting in bias pro ibuprofen. When they had been satisfied with ibuprofen, there was little scope to engage in this study. Most participants used only OTCs, never consulted a physician for the attack treatment of migraine and all per definition never used a triptan as alternative.
Randomization was done by computer in blocks of four to ensure equal numbers in both groups. For blinding purposes, a double-dummy technique was used with fully matching placebos without encapsulation. Randomization and medication preparation were independently done by the hospital pharmacist who also kept the code until the study was completed.

There were three pre-planned study visits: (i) at baseline, when patients were fully explained about the study design and purpose, gave oral and written informed consent, underwent a baseline assessment including the validated Migraine Disability Assessment Scale (MIDAS) (32), and received the study treatment for the first three attacks; (ii) after the first treatment period, when the diary results and remaining study medication were checked and the study medication for the second treatment period was distributed; and (iii) after the second treatment period when the diary results and remaining study medication were checked, and the treatment preference and reasons therefore, were recorded.

Preference was recorded on a Visual Analogue Scale ranging from -5 (extremely strong preference for first treatment) to +5 (extremely strong preference for second treatment), and where 0 indicated no preference (Figure 1). Reasons for preference were noted firstly in the patient's own words and then by ticking off a list of predefined drug-attributes. The proportion of attacks with 2hr pain-free was the secondary endpoint. To minimize the burden to the patients and to mimic a real life situation as closely as possible, the study diary was kept as simple as possible and thus no other assessments were done.

Data analysis and sample size

We tested whether the overall mean preference score significantly differed from 0 (no preference), using the single t-test. We compared the study medications for the number of (i) participants with a clinically relevant preference score (strong to extremely strong: 2.6-5); and (ii) first and total attacks resolved within 2 hours post dose, using Chi-square analysis. We used the GEE-model (generalized estimating equations, repeated measures) to correct for different numbers of attacks per patient treated in the two study arms. Correlations were tested by calculating the correlation coefficient (r). Post hoc analyses were done for differences in outcome for attacks treated at mild and moderate or severe headache, and for MIDAS disability grades I – IV. Success of blinding was tested by guessing which medication was received in the second period and analysis for period effects by comparing the results for each sequence.
It was estimated that a total of 22 randomized subjects was needed to demonstrate a clinically relevant and statistically significant difference of 1.5 cm between the "mean preference score" and "no preference", with 80% power at $p<0.05$. To allow for drop-outs we included 30 subjects.

RESULTS

Flow diagram and study population

We assessed 283 subjects for eligibility and excluded 253, mainly because they had ever used at least one dose of triptans or ergots (Figure 2). Thirty patients, who never

had used triptans or ergots, were randomized. Twenty-nine completed the study and treated in total 153 attacks: 79 with rizatriptan and 74 with ibuprofen. Twelve participants experienced and treated less than three attacks in one or both treatment periods. One participant was withdrawn in the second treatment period because of starting daily doses of ibuprofen for fibromyalgia.

Baseline characteristics of the 30 study participants are summarized in Table 1. The majority (67%) had mild or moderate (grade I - II) MIDAS disability and 33% had high (grade III-IV) MIDAS disability. Twenty-one (70%) were using ibuprofen for their attacks, either alone (n=17), or in combination with acetaminophen (n=4). Prior to the study, none spontaneously expressed major dissatisfaction with their current medication.

The majority of study attacks (130/153; 85%) were treated while the headache was moderate or severe, 70 with rizatriptan and 60 with ibuprofen. Only 23/153 (15%) attacks were treated while the headache was mild, 9 with rizatriptan and 14 with ibuprofen. Treatment delay ranged from 0-11 hrs (median = 1hr).

Preference

The individual and summed preference scores are depicted in Figure 3. Ten participants (34.5%) had a strong to very strong preference (scores: 2.6 – 4) for rizatriptan and six (20.7%) for ibuprofen, while 13 (44.8%) had either no preference (n = 4) or only a slight to moderate preference (scores 1 - 2.5) for rizatriptan (n = 5) or ibuprofen (n = 4) (p = 0.15). The overall mean preference score was 0.62 $\pm$ 2.61 (SD) in favour of rizatriptan (p = 0.219). The results were very similar for the subgroups of 17 participants who had treated, per protocol, three attacks in each treatment arm, and for 21 participants who treated their pre-study attacks with ibuprofen (data not shown).

The spontaneously reported reasons for preference are given in Table 2. No main reason stood particularly out. Several aspects of "a rapid and complete reduction of pain severity" were listed as a reason by 9/16 (56%) of the patients who expressed (very) strong preference and by 19/25 (76%) of those with at least some preference. When asked to tick off from a list of predefined reasons for preference, 5/16 (31%) of the participants with (very) strong preference indicated "restoration of the ability to function normally" as their main reason, 6/16 (37%) "rapid onset of relief", and 2/16 (12%) "complete freedom of pain" (Table 3 and 4).

Predictive factors for preference

Of the 11 subjects with high (grades III-IV) baseline MIDAS disability, 8/11 (73%) expressed very strong preference for rizatriptan and 1/11 (9%) for ibuprofen (p = 0.039); the remaining two had no, or only some preference. In contrast, of the 18 subjects with low (grade I-II) MIDAS disability, 3/18 (17%) very strongly preferred rizatriptan, 5/18 (28%) ibuprofen, and 10/18 (55%) had no, or only some preference. As severity of the study attacks intra-individually varied, this could not be analyzed as a predictive factor.

Pain-free responses and relation with preference

An analysis of all 153 treated attacks on the endpoint 2 hr pain-free showed a difference between rizatriptan and ibuprofen in favour of rizatriptan. 28.8% off all patients were pain free at 2 hours. Patient using rizatriptan were 2 hr pain-free in 35.4% and patients using ibuprofen in 21.6%. The odds ratio (OR), calculated with correction for headache severity at the time of treatment, was 2.611 (1.145 – 5.956, p = 0.084).
When performing a subgroup analysis on severity on the 130 severe and moderate attacks, we found 24.6% 2 hr pain-free for the total, 32.4% for rizatriptan and 15.3% for ibuprofen. The OR was 2.755 (1.103 - 6.883, p = 0.030). For the remaining attacks, obvious all mild, we found 2 hr pain-free for all 23 patients 52.2%, for rizatriptan 62.% and for ibuprofen 46.7%. The OR was 2.038 (0.242 – 17.195, p = 0.513).
Thus the 2hr pain-free rates were numerically higher for rizatriptan, reaching statistical significance for attacks treated while moderate or severe. Similar results were found for the 17 patients, who had treated, per protocol, three attacks in each treatment arm (data not shown). There was no clear benefit of attacks that were treated early, within an hour from onset, compared to attacks treated later (data not shown).

Figure 4 shows, for each study participant, the individual correlation between direction and strength of their preference (y-axis) and number of attacks with 2hr pain-free with rizatriptan or ibuprofen (x-axis). Data are presented as number of 2hr pain-free attacks with the preferred treatment minus those with the non-preferred treatment. The overall correlation was modest (r = 0.56; p = 0.001; slope = 0.346). For instance, six participants without any attack with 2hr pain-free with either study drug still expressed very strong preference for one, three participants (n=3) with equal numbers of attacks with 2hr pain-free with both study drugs still expressed a very strong preference for one, and seven participants who experienced 2hr pain-free more frequently with the one study drug, either expressed preference for the other, or could not decide between the two.

However, when studied at the group level, of the 16 subjects with a very strong preference, the 2hr pain-free attack rate with the preferred drug was 22/48 (46%) and 7/39 (18%) with the not-preferred drug. This difference was particularly large for participants very strongly preferring rizatriptan: 15/30 (50%) versus 3/24 (12.5%).

Un-blinding and period effects

We asked participants to guess their treatment in the second period: 15/29 (52%) guessed correctly (of these 6 strongly preferred rizatriptan and 4 ibuprofen), 8/29 (27%) made a wrong guess and 6/29 (21%) could not decide (r = 0.31; p = 0.146). The

observers guessed correctly in 15/29 (52%) of the cases (r = 0.19; p = 0.341). The mutual agreement r was 0.66 (p = 0.001). There were no period effects for any of the endpoints (data not shown; p = 0.996).

DISCUSSION

We used a novel, real life, yet controlled, multi-attack study design to assess which patients on pain killers might benefit most from switching to triptans. After double-blind multi-attack exposure to a triptan for the first time in their life, one third of the participants expressed very strong preference for the triptan and could thus be considered undertreated (33). The clinical challenge now is to identifying such patients.

Our study suggests that high baseline disability and attack severity may be useful indicators for a successful switch to triptans. Among the 11 subjects with a grade III or IV MIDAS baseline disability, two-thirds very strongly preferred rizatriptan and only one ibuprofen. In contrast, among patients with low baseline disability, preference was equally distributed between both treatments. Similarly, rizatriptan showed higher 2hr pain-free rates than ibuprofen in moderate or severe, but not in mild attacks. Both findings are in accordance with a previous report that high MIDAS disability predicts higher pain-free response to triptans than to non-triptans (3). Although the results were already statistically significant, despite the small number of participants, they need to be confirmed in larger trials using a similar design.

A major advantage of the present PTPP design is that patients can truly compare the effects of both treatments over a number of attacks and for a wide range of treatment attributes. It allows for a real personal judgment of what is clinically meaningful. This sharply contrasts to traditional comparator trials where, for methodological reasons, patients only treat a single attack with only one of the study drugs. Moreover, superiority is claimed for a single treatment-attribute that is defined by investigators, but may not necessarily be relevant to all patients (34;35). For example, “restoration of the ability to function normally” (and not “fast headache relief”) was the most frequently reported reason for preference in our trial. The only modest correlation of 2hr pain-free with preference underscores that patients evaluate treatments on the basis of overall performance rather than on speed of headache relief alone.

Potential limitations of cross-over studies are increased risk of un-blinding, pre-study bias, and patients dropping out prematurely. In our study, blinding appeared to have been well preserved and only one participant was withdrawn because of reasons unrelated to the study. To minimize the risk of pre-study bias in favour or against either study medication, we only included patients who were not overtly dissatisfied with their current treatment and who never had used a triptan. The downside of this “bias

prevention approach” was that many subjects had to be excluded from participation, limiting the generalizability of the results to “triptan-naïve migraineurs not overtly dissatisfied with their current treatment”.

Bias in comparing 2hr pain-free rates may also be introduced if the average number of attacks per patient significantly differs between the treatment arms (34;35). However, only slightly more attacks were treated with rizatriptan and there was no difference in outcome when only including, for each patient, the first attack treated with each study drug.
In summary, traditional trials estimate the average response in a group of patients and attempt to identifying “the overall winning drug” for all patients on the basis of the success rate for a single attribute. In contrast, in PTPP trials the individual patient will be the winner as the PTPP design seeks to identify the best match between individual needs and specific drug profiles. PTPP trials may therefore prove superior in assessing clinically meaningful differences between established agents and identifying patient-profiles predictive of success. Patients with high migraine-related MIDAS disability and moderate to severe attacks are likely to benefit most from switching from first-line acute antimigraine medication to triptan therapy. This study provides evidence for the assertion that different drugs work for different patients.

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References

(1) Goadsby PJ, Lipton RB, Ferrari MD. Migraine--current understanding and treatment. N Engl J Med 2002 Jan 24;346(4):257-70.

(2) Terwindt GM, Ferrari MD, Tijhuis M, Groenen SM, Picavet HS, Launer LJ. The impact of migraine on quality of life in the general population: the GEM study. *Neurology* 2000 Sep 12;55(5):624-9.

(3) Lipton RB, Stewart WF, Stone AM, Lainez MJ, Sawyer JP. Stratified care vs step care strategies for migraine: the Disability in Strategies of Care (DISC) Study: A randomized trial. *JAMA* 2 000 Nov 22;284(20):2599-605.

(4) Tfelt-Hansen P, Block G, Dahlof C, Diener HC, Ferrari MD, Goadsby PJ, et al. Guidelines for controlled trials of drugs in migraine: second edition. *Cephalalgia* 2000 Nov;20(9):765-86.

(5) Tfelt-Hansen P. Triptans vs other drugs for acute migraine. Are there differences in efficacy? A comment. *Headache* 2008 Apr;48(4):601-5.

(6) Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 2001 Nov 17;358(9294):1668-75.

(7) Lipton RB, Bigal ME, Goadsby PJ. Double-blind clinical trials of oral triptans vs other classes of acute migraine medication - a review. *Cephalalgia* 2004 May;24 (5):321-32.

(8) Steiner T. Triptans vs other drugs for acute migraine. *Headache* 2008 Oct;48(9):1378-9.

(9) Bigal M, Rapoport A, Aurora S, Sheftell F, Tepper S, Dahlof C. Satisfaction with current migraine therapy: experience from 3 centers in US and Sweden. *Headache* 2007 Apr;47(4):475-9.

(10) Cutrer FM, Goadsby PJ, Ferrari MD, Lipton RB, Dodick DW, McCrory D, et al. Priorities for triptan treatment attributes and the implications for selecting an oral triptan for acute migraine: a study of US primary care physicians (the TRIPSTAR Project). *Clin Ther* 2004 Sep;26(9):1533-45.

(11) Lipton RB, Cutrer FM, Goadsby PJ, Ferrari MD, Dodick DW, McCrory D, et al. How treatment priorities influence triptan preferences in clinical practice: perspectives of migraine sufferers, neurologists, and primary care physicians. *Curr Med Res Opin* 2005 Mar;21(3):413-24.

(12) Lanteri-Minet M. What do patients want from their acute migraine therapy? *Eur Neurol* 2005;53 Suppl 1:3-9.

(13) Pascual J, Garcia-Monco C, Roig C, Yusta IA, Lopez-Gil A. Rizatriptan 10-mg wafer versus usual nontriptan therapy for migraine: analysis of return to function and patient preference. *Headache* 2005 Oct;45(9):1140-50.

(14) Diez FI, Straube A, Zanchin G. Patient preference in migraine therapy. A randomized, open-label, crossover clinical trial of acute treatment of migraine with oral almotriptan and rizatriptan. *J Neurol* 2007 Feb;254(2):242-9.

(15) Lainez MJ, Evers S, Kinge E, Allais G, Allen C, Rao NA, et al. Preference for rizatriptan 10-mg wafer vs. eletriptan 40-mg tablet for acute treatment of migraine. *Cephalalgia* 2006 Mar;26(3):246-56.

(16) Schoenen J, Pascual J, Rasmussen S, Sun W, Sikes C, Hettiarachchi J. Patient preference for eletriptan 80 mg versus subcutaneous sumatriptan 6 mg: results of a crossover study in patients who have recently used subcutaneous sumatriptan. *Eur J Neurol* 2005 Feb;12(2):108-17.

(17) Evans RW, Dahlof CG. Determining triptan preference for the individual patient. *Headache* 2004 Jul;44(7):723-5.

(18) Dahlof C. Assessing patient preference in migraine treatment. *Cephalalgia* 2001 Oct;21(8):791-5.

(19) Loder E, Brandes JL, Silberstein S, Skobieranda F, Bohidar N, Wang L, et al. Preference comparison of rizatriptan ODT 10-mg and sumatriptan 50-mg tablet in migraine. *Headache* 2001 Sep;41(8):745-53.

(20) Pascual J, Munoz R, Leira R. An open preference study with sumatriptan 50 mg and zolmitriptan 2.5 mg in 100 migraine patients. *Cephalalgia* 2001 Jul;21(6):680-4.

(21) Pascual J, Bussone G, Hernandez JF, Allen C, Vrijens F, Patel K. Comparison of preference for rizatriptan 10-mg wafer versus sumatriptan 50-mg tablet in migraine. *Eur Neurol* 2001;45(4):275-83.

(22) Powers C, Szeto S, Pangtay D, Bort T, Cervi M, Cady R. Evaluation of migraineurs' preferences for naratriptan over conventional first-line agents. *Arch Fam Med* 2000 Aug;9(8):753-8.

(23) Adelman JU, Mannix LK, Von Seggern RL. Rizatriptan tablet versus wafer: patient preference. *Headache* 2000 May;40(5):371-2.

(24) Silverman WA, Altman DG. Patients' preferences and randomised trials. *Lancet* 1996 Jan 20;347(8995):171-4.

(25) Torgerson DJ, Sibbald B. Understanding controlled trials. What is a patient preference trial? *BMJ* 1998 Jan 31;316(7128):360.

(26) Krahn M, Naglie G. The next step in guideline development: incorporating patient preferences. *JAMA* 2008 Jul 23;300(4):436-8.

(27) Methodological standards and patient-centeredness in comparative effectiveness research: the PCORI perspective. *JAMA* 2012 Apr 18;307(15):1636-40.

(28) Headache classification subcommittee of the International Headache Society. The International Classification of Headache Disorders. *Cephalalgia* 2004;24(supplement 1):8-160.

(29) Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, et al. EFNS guideline on the drug treatment of migraine - report of an EFNS task force. *Eur J Neurol* 2006 Jun;13(6):560-72.

(30) Pryse-Phillips WE, Dodick DW, Edmeads JG, Gawel MJ, Nelson RF, Purdy RA, et al. Guidelines for the diagnosis and management of migraine in clinical practice. Canadian Headache Society. *CMAJ* 1997 May 1;156(9):1273-87.

(31) Silberstein SD. Practice parameter: evidence-based guidelines for migraineheadache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2000 Sep 26;55(6):754-62.
(32) Stewart WF, Lipton RB, Kolodner K, Liberman J, Sawyer J. Reliability of the migraine disability assessment score in a population- based sample of headache sufferers. *Cephalalgia* 1999 Mar;19(2):107-14.
(33) Stovner L, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia* 2007 Mar;27(3):193-210.
(34) Savi L, Omboni S, Lisotto C, Zanchin G, Ferrari MD, Zava D, et al. A double-blind, randomized, multicenter, Italian study of frovatriptan versus rizatriptan for the acute treatment of migraine. *J Headache Pain* 2010 Aug 5.
(35) Tullo V, Allais G, Ferrari MD, Curone M, Mea E, Omboni S, et al. Frovatriptan versus zolmitriptan for the acute treatment of migraine: a double-blind, randomized, multicenter, Italian study. *Neurol Sci* 2010 Jun;31 Suppl 1:S51-S54.

Table 1. Baseline characteristics of study population

	Total N = 30	**Rizatriptan first n = 14**	**Ibuprofen first n = 16**
Age, mean (SD), y	44 (9.6)	43 (12.0)	46 (6.8)
Sex, n (%)			
Female	25 (83)	11 (79)	14 (88)(*)
Male	5 (17)	3 (21)	2 (13)
Diagnosis, n (%)			
Migraine without aura	19 (63)	8 (57)	11 (69)(*)
Migraine without aura	11 (37)	6 (43)	5 (31)
Age at onset, y (SD)	22 (11)	19 (10)	25 (12)
Attack frequency / month (SD)	2.1 (1.5)	2.3 (1.9)	2.0 (1.2)
Disability grade, n (%)			
Grade I (0-5)	11 (37)	8 (57)	3 (19)
Grade II (6-10)	8 (27)	1 (7)	7 (44)(*)
Grade III (11-20)	10 (33)	4 (29)	6 (38)
Grade IV (≥ 21)	1 (3)	1 (7)	-
Average MIDAS-score (SD)	8.3 (7.0)	7.4(8.3)	9.2(5.5)
Usual acute migraine treatment, n (%)			
Only Ibuprofen	17 (57)	8 (57)	9 (56)
Both ibuprofen and acetaminophen	4 (13)	2 (14)	2 (13)(*)
Only acetaminophen	2 (7)	1 (7)	1 (6)
Combination tablets	2 (7)	1 (7)	1 (6)
Other (acetylsalicylic acid, naproxen)	4 (13)	1 (7)	3 (19)
No medication for attacks	1 (3)	1 (7)	-
Prophylaxis, n (%)	1 (3)	1 (6)	-

Numbers are patients (%), unless otherwise mentioned. (*)Including one drop out.

Table 2. Main spontaneously reported reasons for preference (determined by open question)

	Total	**All preference**		**Preference for rizatriptan**		**Preference for ibuprofen**		**No preference**
		Any	(Very) Strong	Any	(Very) Strong	Any	(Very) Strong	-
	(n = 25)	**(n = 25)**	**(n = 16)**	**(n = 15)**	**(n = 10)**	**(n = 10)**	**(n = 6)**	**(n = 4)**
Decrease severity of attack	10 (34.5)	8 (32.0)	4 (25.0)	5 (33.3)	2 (20.0)	3 (30.0)	2 (33.3)	2 (50.0)
Rapid onset of relief	5 (17.2)	5 (20.0)	2 (12.5)	3 (20.0)	1 (30.0)	2 (20.0)	1 (16.7)	-
Complete pain free	3 (10.3)	3 (12.0)	3 (18.8)	3 (20.0)	3 (30.0)	-	-	-
Return to normal function	3 (10.3)	3 (12.0)	3 (18.8)	3 (20.0)	3 (30.0)	-	-	-
No adverse events	4 (13.8)	4 (16.0)	3 (18.8)	1 (6.7)	1 (10.0)	3 (30.0)	2 (33.3)	-
One dose sufficient	1 (3.4)	1 (4.0)	1 (6.3)	-	-	1 (10.0)	1 (16.7)	-
None	3 (10.3)	1 (4.0)	-	-	-	1 (10.0)	-	2 (50.0)

Values are numbers of patients (%).

Table 3. Main reasons for preference from a predefined list

	Total	**All preference**		**Preference for rizatriptan**		**Preference for ibuprofen**		**No preference**
		Any	(Very) Strong	Any	(Very) Strong	Any	(Very) Strong	-
	(N = 29)	**(n = 25)**	**(n = 16)**	**(n = 15)**	**(n = 10)**	**(n = 10)**	**(n = 6)**	**(n = 4)**
Return to normal function	6 (20.7)	6 (24.0)	5 (31.3)	5 (33.3)	4 (40.0)	1 (10.0)	1 (16.7)	-
Rapid onset of relief	11 (37.9)	10 (40.0)	6 (37.5)	5 (33.3)	3 (30.0)	5 (50.0)	3 (50.0)	1 (25.0)
Complete pain free	2 (6.9)	2 (8.0)	2 (12.5)	2 (13.3)	2 (20.0)	-	-	-
No adverse events	2 (6.9)	2 (8.0)	1 (6.3)	-	-	2 (20.0)	1 (16.7)	-
Prevent worsening of pain	1 (3.4)	1 (4.0)	1 (6.3)	-	-	1 (10.0)	1 (16.7)	-
Decrease of photo- and phonophobia	2 (6.9)	1 (8.0)	-	1 (6.7)	-	-	-	1 (25.0)
Decrease of nausea	2 (6.9)	1 (4.0)	1 (6.3)	1 (6.7)	1 (10.0)	-	-	1 (25.0)
Reliable effect, consistency	1 (3.4)	1 (4.0)	-	1 (6,7)	-	-	-	-
One dose sufficient	1 (3.4)	-	-	-	-	-	-	1 (25.0)
No reason	1 (3.4)	1 (4.0)	-	-	-	1 (10.0)	-	-

Values are numbers of patients (%). Patients could tick off only one main reason.

Table 4. All reasons for preference from a predefined list

	Total	**All preference**		**Preference for rizatriptan**		**Preference for ibuprofen**		**No preference**
		Any	(Very) Strong	Any	(Very) Strong	Any	(Very) Strong	-
	(N = 29)	**(n = 25)**	**(n = 16)**	**(n = 15)**	**(n = 10)**	**(n = 10)**	**(n = 6)**	**(n = 4)**
Return to normal function	18 (62.1)	17 (68.0)	11 (68.8)	10 (66.7)	7 (70.0)	7 (70.0)	4 (66.7)	1 (25.0)
Rapid onset of relief	22 (75.9)	18 (72.0)	10 (62.5)	9 (60.0)	6 (60.0)	9 (90.0)	4 (66.7)	4 (100)
Complete pain free	14 (48.3)	12 (48.0)	10 (62.5)	9 (60.0)	8 (80.0)	3 (30.0)	2 (33.3)	2 (50.0)
No adverse events	12 (41.4)	12 (48.0)	7 (43.8)	9 (60.0)	6 (60.0)	3 (30.0)	1 (16.7)	-
Prevent worsening of pain	12 (41.4)	10 (40.0)	8 (37.5)	5 (33.3)	4 (40.0)	5 (50.0)	4 (66.7)	2 (50.0)
Decrease of photo- and phonophobia	11 (37.9)	8 (32.0)	6 (25.0)	6 40.0)	5 (50.0)	2 (20.0)	1 (16.7)	3 (75.0)
No recurrence after initial relief	7 (24.1)	7 (28.0)	4 (25.0)	4 (26.7)	2 (20.0)	3 (30.0)	2 (33.3)	-
Reliable effect, consistency	9 (31.0)	7 (28.0)	5 (31.3)	6 (40.0)	4 (40.0)	1 (10.0)	1 (16.7)	2 (50.0)
Decrease severity of attack	7 (24.1)	5 (20.0)	4 (25.0)	3 (20.0)	3 (30.0)	2 (20.0)	1 (16.7)	2 (50.0)
Decrease of nausea	4 (13.8)	4 (16.0)	4 (25.0)	4 (26.7)	4 (40.0)	-	-	-
One dose sufficient	5 (17.2)	4 (16.0)	4 (25.0)	3 (20.0)	3 (30.0)	1 (10.0)	1 (16.7)	1 (25.0)
Taste	2 (6.9)	2 (8.0)	1 (6.3)	2 (13.3)	1 (10.0)	-	-	-

Values are numbers of patients (%). Patients could tick off several reasons

Figure 1. Preference scale

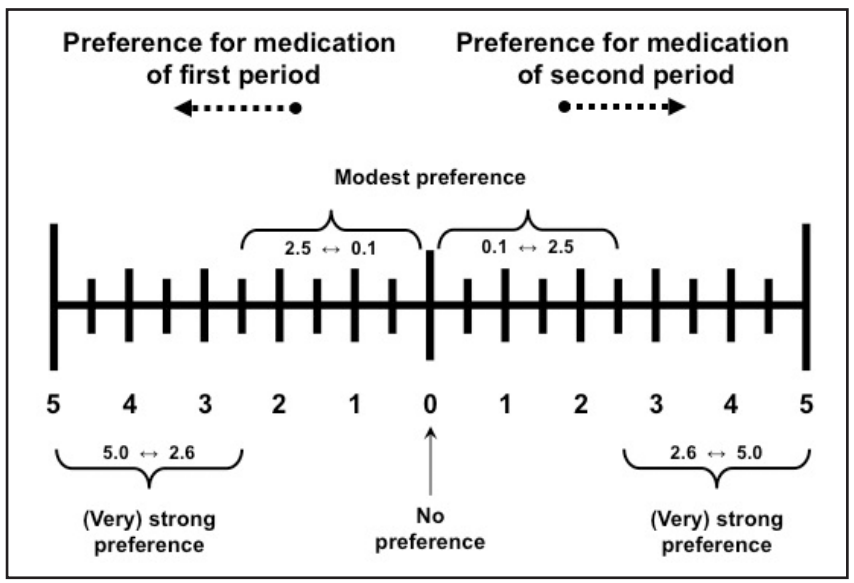


Figure 2. Flow diagram of the study participants

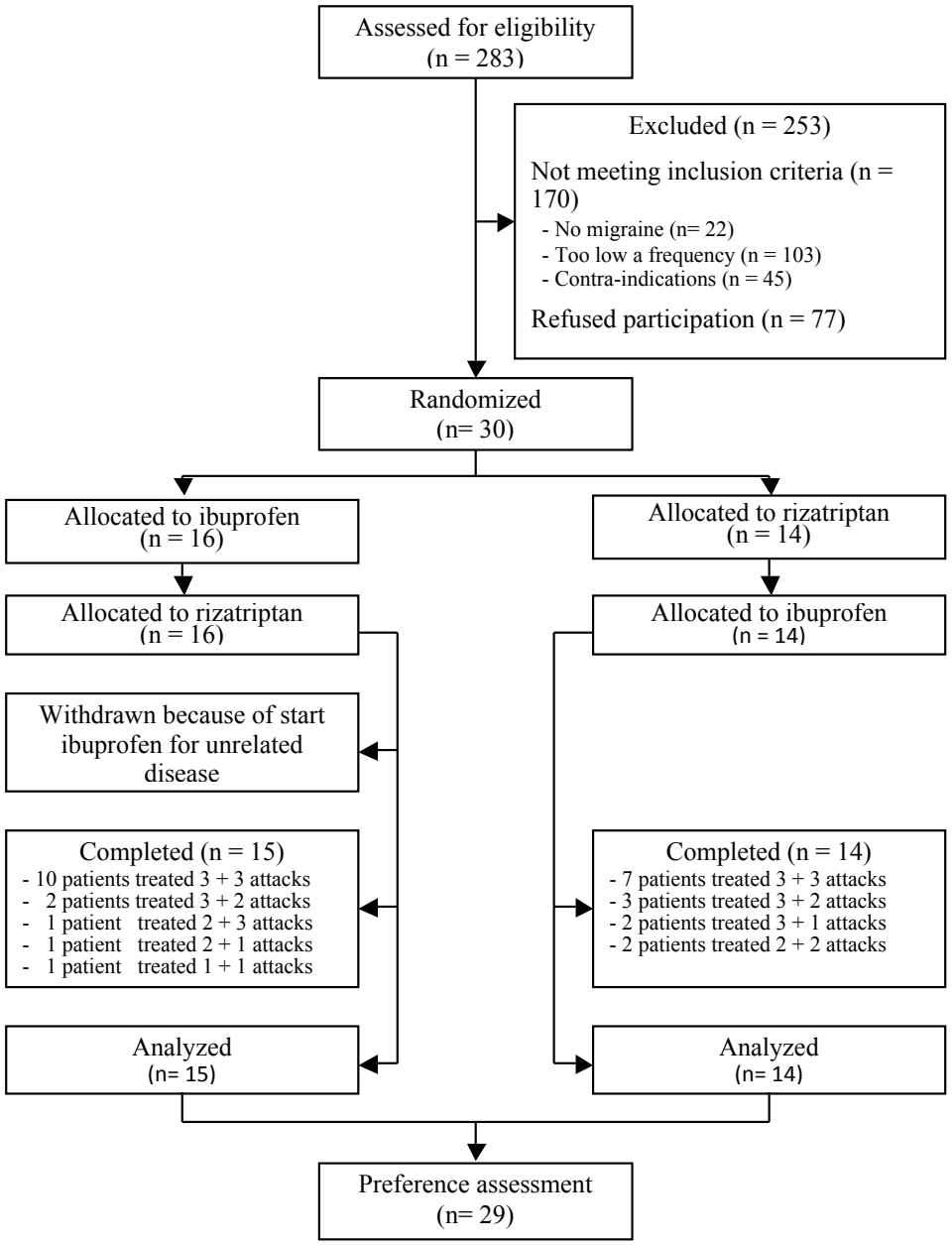


Figure 3. Distribution of preference scores

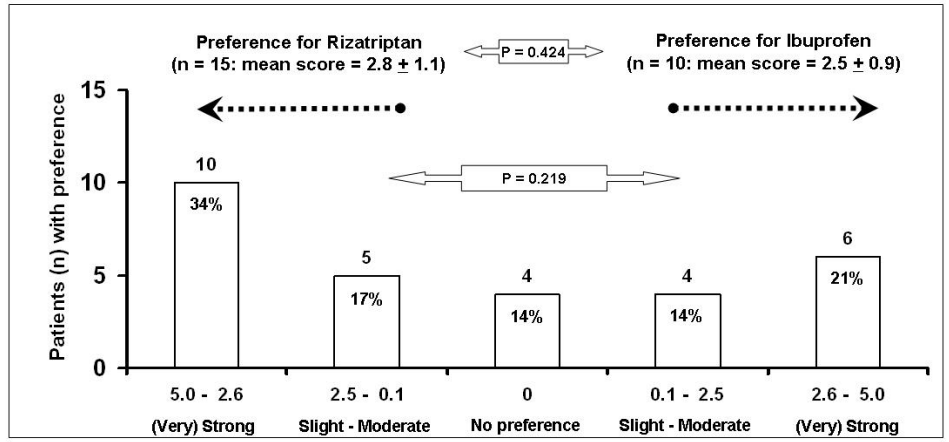
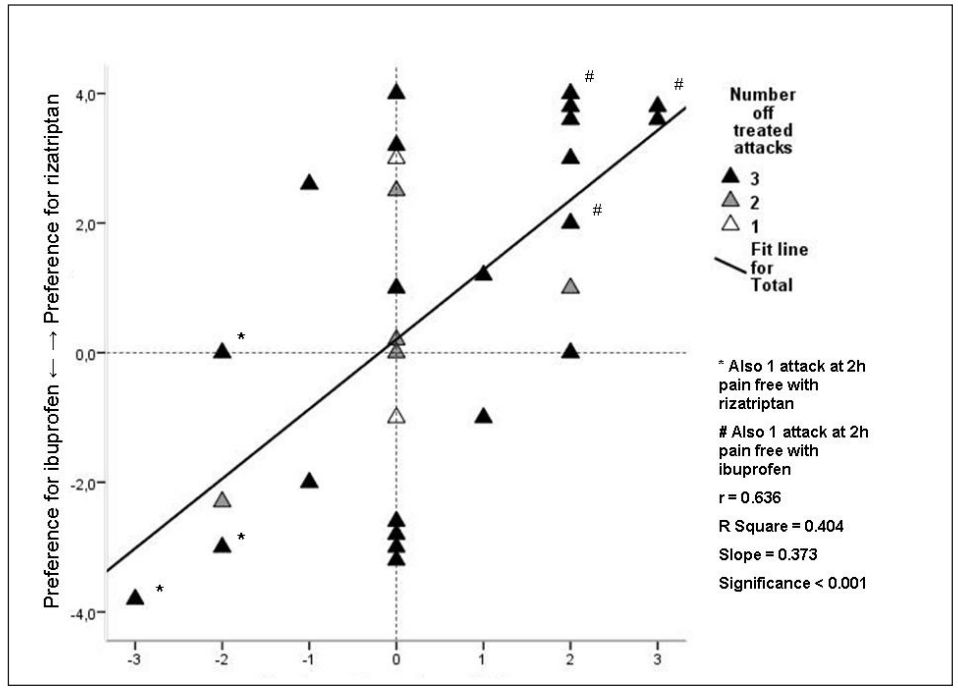


Figure 4. Correlation between direction and strength of preference and 2hr pain-free



*Each triangle represents one patient. Per patient the number of attacks with 2h pain free and the preference for rizatriptan (right) or ibuprofen (left) is shown. Patients with a preference for rizatriptan are shown in the upper half; patients with a preference for ibuprofen are shown in the bottom half. The patients of the black triangles all have three attacks treated. Six patients had an attack with 2h pain free in the opposite arm, which is indicated by * (for rizatriptan) or # (for ibuprofen). The overall correlation was modest (r = 0.56; p = 0.001; slope = 0.346).*

References

1. Goadsby PJ, Lipton RB, Ferrari MD. Migraine--current understanding and treatment. *N Engl J Med* 2002;346(4):257-270.
2. Terwindt GM, Ferrari MD, Tijhuis M, Groenen SM, Picavet HS, Launer LJ. The impact of migraine on quality of life in the general population: the GEM study. *Neurology* 2000;55(5):624-629.
3. Lipton RB, Stewart WF, Stone AM, Lainez MJ, Sawyer JP. Stratified care vs step care strategies for migraine: the Disability in Strategies of Care (DISC) Study: A randomized trial. *JAMA* 2000;284(20):2599-2605.
4. Ferrari MD. Migraine. *Lancet* 1998;351(9108):1043-1051.
5. Tfelt-Hansen P, Block G, Dahlof C, Diener HC, Ferrari MD, Goadsby PJ, Guidetti V, Jones B, Lipton RB, Massiou H, Meinert C, Sandrini G, Steiner T, Winter PB. Guidelines for controlled trials of drugs in migraine: second edition. *Cephalalgia* 2000;20(9):765-786.
6. Tfelt-Hansen P. Triptans vs other drugs for acute migraine. Are there differences in efficacy? A comment. *Headache* 2008;48(4):601-605.
7. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 2001;358(9294):1668-1675.
8. Lipton RB, Bigal ME, Goadsby PJ. Double-blind clinical trials of oral triptans vs other classes of acute migraine medication - a review. *Cephalalgia* 2004;24(5):321-332.
9. Steiner T. Triptans vs other drugs for acute migraine. *Headache* 2008;48(9):1378-1379.
10. Bigal M, Rapoport A, Aurora S, Sheftell F, Tepper S, Dahlof C. Satisfaction with current migraine therapy: experience from 3 centers in US and Sweden. *Headache* 2007;47(4):475-479.
11. Cutrer FM, Goadsby PJ, Ferrari MD, Lipton RB, Dodick DW, McCrory D, Williams P. Priorities for triptan treatment attributes and the implications for selecting an oral triptan for acute migraine: a study of US primary care physicians (the TRIPSTAR Project). *Clin Ther* 2004;26(9):1533-1545.12. Lipton RB, Cutrer FM, Goadsby PJ, Ferrari MD, Dodick DW, McCrory D, Liberman JN, Williams P. How treatment priorities influence triptan preferences in clinical practice: perspectives of migraine sufferers, neurologists, and primary care physicians. *Curr Med Res Opin* 2005;21(3):413-424.
13. Lanteri-Minet M. What do patients want from their acute migraine therapy? *Eur Neurol* 2005;53 Suppl 13-9.
14. Pascual J, Garcia-Monco C, Roig C, Yusta IA, Lopez-Gil A. Rizatriptan 10-mg wafer versus usual nontriptan therapy for migraine: analysis of return to function and patient preference. *Headache* 2005;45(9):1140-1150.

15. Diez FI, Straube A, Zanchin G. Patient preference in migraine therapy. A randomized, open-label, crossover clinical trial of acute treatment of migraine with oral almotriptan and rizatriptan. *J Neurol* 2007;254(2):242-249.
16. Lainez MJ, Evers S, Kinge E, Allais G, Allen C, Rao NA, Massaad R, Lis K. Preference for rizatriptan 10-mg wafer vs. eletriptan 40-mg tablet for acute treatment of migraine. *Cephalalgia* 2006;26(3):246-256.
17. Dowson AJ, Tepper SJ, Dahlof C. Patients' preference for triptans and other medications as a tool for assessing the efficacy of acute treatments for migraine. *J Headache Pain* 2005;6(3):112-120.
18. Schoenen J, Pascual J, Rasmussen S, Sun W, Sikes C, Hettiarachchi J. Patient preference for eletriptan 80 mg versus subcutaneous sumatriptan 6 mg: results of a crossover study in patients who have recently used subcutaneous sumatriptan. *Eur J Neurol* 2005;12(2):108-117.
19. Evans RW, Dahlof CG. Determining triptan preference for the individual patient. *Headache* 2004;44(7):723-725.
20. Dahlof C. Assessing patient preference in migraine treatment. *Cephalalgia* 2001;21 (8):791-795.
21. Loder E, Brandes JL, Silberstein S, Skobieranda F, Bohidar N, Wang L, Boyle D, Kolodny A, Guerra F, Santanello N, Johnson-Pratt L. Preference comparison of rizatriptan ODT 10-mg and sumatriptan 50-mg tablet in migraine. *Headache* 2001;41(8):745-753.
22. Pascual J, Munoz R, Leira R. An open preference study with sumatriptan 50 mg and zolmitriptan 2.5 mg in 100 migraine patients. *Cephalalgia* 2001;21(6):680-684.
23. Pascual J, Bussone G, Hernandez JF, Allen C, Vrijens F, Patel K. Comparison of preference for rizatriptan 10-mg wafer versus sumatriptan 50-mg tablet in migraine. *Eur Neurol* 2001;45(4):275-283.
24. Powers C, Szeto S, Pangtay D, Bort T, Cervi M, Cady R. Evaluation of migraineurs' preferences for naratriptan over conventional first-line agents. *Arch Fam Med* 2000;9(8):753-758.
25. Adelman JU, Mannix LK, Von Seggern RL. Rizatriptan tablet versus wafer: patient preference. *Headache* 2000;40(5):371-372.
26. Christie S, Gobel H, Mateos V, Allen C, Vrijens F, Shivaprakash M. Crossover comparison of efficacy and preference for rizatriptan 10 mg versus ergotamine/caffeine in migraine. *Eur Neurol* 2003;49(1):20-29.
27. Dahlof C. How to assess patient preference of migraine treatments. *Cephalalgia* 1999;19 Suppl 242-5.
28. Silverman WA, Altman DG. Patients' preferences and randomised trials. *Lancet* 1996;347(8995):171-174.
29. Torgerson DJ, Sibbald B. Understanding controlled trials. What is a patient preference trial? *BMJ* 1998;316(7128):360.

30. Krahn M, Naglie G. The next step in guideline development: incorporating patient preferences. *JAMA* 2008;300(4):436-438.
31. Methodological standards and patient-centeredness in comparative effectiveness research: the PCORI perspective. *JAMA* 2012;307(15):1636-1640.
32. Headache classification subcommittee of the International Headache Society. The International Classification of Headache Disorders. *Cephalalgia* 2004;24(supplement 1):8-160.
33. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sandor PS. EFNS guideline on the drug treatment of migraine - report of an EFNS task force. *Eur J Neurol* 2006; 13(6):560-572.
34. Pryse-Phillips WE, Dodick DW, Edmeads JG, Gawel MJ, Nelson RF, Purdy RA, Robinson G, Stirling D, Worthington I. Guidelines for the diagnosis and management of migraine in clinical practice. Canadian Headache Society. *CMAJ* 1997;156(9):1273-1287.
35. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2000;55(6):754-762.
36. Stewart WF, Lipton RB, Kolodner K, Liberman J, Sawyer J. Reliability of the migraine disability assessment score in a population- based sample of headache sufferers. *Cephalalgia* 1999;19(2):107-114.
37. Stovner L, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, Steiner T, Zwart JA. The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia* 2007;27(3):193-210.
38. Savi L, Omboni S, Lisotto C, Zanchin G, Ferrari MD, Zava D, Pinessi L. A double-blind, randomized, multicenter, Italian study of frovatriptan versus rizatriptan for the acute treatment of migraine. *J Headache Pain* 2010.
39. Tullo V, Allais G, Ferrari MD, Curone M, Mea E, Omboni S, Benedetto C, Zava D, Bussone G. Frovatriptan versus zolmitriptan for the acute treatment of migraine: a double-blind, randomized, multicenter, Italian study. *Neurol Sci* 2010;31 Suppl 1S51-S54.

CHAPTER 8

Naratriptan 2.5 mg versus paracetamol (acetaminophen) 1000 mg for the acute treatment of migraine in General Practice: patients preference as primary outcome.

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To bee submitted

ABSTRACT

Background
In clinical trials comparing triptans with analgesics, no clear difference for on the 2hr pain free rate endpoint has been observed. The validity of testing efficacy using single attack treatment, with the endpoint pain free rates, seems limited. We evaluated whether patients preference after exposure to both treatments is better suited to detect clinical meaningful and relevant differences.

Design
Randomised, double blind, double dummy, crossover clinical trial.

Method
31 triptan-naive participants were randomised to naratriptan 2.5 mg or paracetamol 1000 mg with a crossover after three attacks. 28 participants were able to make a preference assessment. Primary outcome measure was direction and strength of patient preference (10 point scale).

Results
Preference score was 0.17 in favour of naratriptan. Nine (32%) participants strongly preferred naratriptan, and also nine (32%) paracetamol. When looking at all the preferences 16 (57%) participants preferred naratriptan and 11 (42.1%) preferred paracetamol. The 2hr pain-free attack rates were 15/76 (20%; naratriptan) and 9/74 (12%; paracetamol) for all attacks ($p = 0.25$). When treating the first attack naratriptan has a higher pain-free rate ($p = 0.05$). Correlation of 2hr pain-free response with preference was poor ($r = 0.27$).

Conclusion
The preference from patients as a group for either naratriptan or paracetamol in the acute attack treatment of migraine is similar, but individual patients have a strong preference for one or the other, with no relation to attack severity or migraine impact. Multi-attack, cross-over, patient-preference trials may better detect clinically meaningful differences between established treatments.

INTRODUCTION

Migraine is a common, often highly disabling brain disorder, characterised by recurrent attacks of severe headaches, autonomic dysfunction and, in one-third of patients, neurological aura symptoms.[1,2] There is a remarkable inter- and intraindividual variability in attack frequency, duration, symptomatology, severity, and response to treatment.[3] Treatment guidelines often recommend a stepped care approach, starting with paracetamol or others 'simple analgesics'. If these prove ineffective, Non-Steroidal Anti-inflammatory Drugs (NSAIDs) are recommended. The third step usually consists of triptans (selective 5-$HT_{1B/1D}$ receptor agonists).[4,5] In most countries only 10-40% of migraine patients receive prescription medications, mostly due to unjustified safety concerns, cost restraints, and limited awareness that potentially better treatments are available.[1,2,6,7]

Acute antimigraine efficacy is traditionally assessed using "the 2hr pain-free rate" in randomised, parallel-group trials, in which patients treat a single attack.[8] There is evidence that this is a justified approach to establish efficacy versus placebo, but the clinical validity for comparing established treatments seems limited. In trials versus placebo, triptans generally show higher "2hr responder rates and therapeutic gains" than analgesics or NSAIDs.[4] In clinical experience, in particular for severe attacks, many physicians and patients consider triptans to be more effective than analgesics or NSAIDs.[5,7,9] However, in traditional, single-attack, parallel-group, comparator trials, evaluating the 2hr responder rates of a triptan versus an analgesic or NSAID, no or only a few statistically significant differences were found.[7,9-13] The remarkable discrepancy between clinical trials and experience in clinical practice complicates rational treatment recommendations and suggests that the traditional trial design and choice of endpoints may miss clinically relevant differences between established treatments.

Migraine patients treat multiple attacks, not just one, and assess treatments on the basis of the overall performance on a range of both positive and negative treatment-attributes. Some patients prioritize rapid onset of relief, while others may prioritize absence of adverse events, longer duration of action, consistent effect over multiple attacks, or good tolerability.[14-20] Moreover, in parallel-group trials patients cannot truly compare the treatments.

Post-treatment patient-preference (PTPP) cross-over trials, in which patients express a preference after exposure to both treatments, are a promising, relatively new and potentially more valid approach to detecting clinically meaningful differences between established treatments.[21-37]
There is an increased emphasis on the experience of the patient and the patient plays an increased role in decision making, which makes it appropriate to give serious consideration to the preferences of the patient[35] and the matching design to ensure pa-

tients' influence (PTPP studies).[24,34] PTPP studies should not to be confused with pre-treatment patient-preference trials in which, to avoid pre-study bias, the allocation to a certain treatment group in a standard parallel-group randomised trial is based on the patients' pre-study preference (or lack of preference) for a certain treatment.[36,37]
Here, we present the results of a single-centre, double-blind, double-dummy, cross-over PTPP trial, in which triptan-naïve participants were randomised to treat three attacks with naratriptan 2.5 mg and three attacks with paracetamol 500 mg. The primary outcome measure was the direction and strength of patient preference after having completed both treatment options. This allows a real life, controlled evaluation of acute treatments in a number of attacks. Many patients consider consistency of effectiveness over multiple attacks an important attribute of acute antimigraine treatments,[4,14-18,20] yet this is not assessed in traditional single attack studies.
Naratriptan 2.5 mg was selected for the following reasons: (i) efficacy is well established and (ii) tolerability has proven to be good: the overall incidence of adverse events during treatment with naratriptan 2.5 mg was similar to that observed for placebo and (iii) is in some countries available as over-the-counter medication.[4,38-40]
We selected paracetamol because paracetamol is an effective drug for the attack treatment and it is the most frequently used as over-the-counter analgesic for migraine.[13,41-46] It is often recommended to combine paracetamol with anti-emetics such as domperidone or metoclopramide to increase absorption.[47,48] However, it has never been shown that such regime is also associated with an increase in clinical efficacy.[49] Therefore, we decided not to combine paracetamol treatment with an anti-emetic.
There are no randomised direct head-to-head comparisons of naratriptan with paracetamol.[13,31,50] Yet there are RCTs comparing paracetamol with other triptans, showing equal efficacy[13,46,51,52] or even more efficacious when used in combination with aspirin and caffeine.[53] Recently the results of a non-published trial looking at preference for naratriptan or naproxen became available from manufacturers data.[54,55]

The aim of this study is (i) to determine the preference of patients for either naratriptan or paracetamol in the attack treatment of migraine, and (ii) to evaluate whether a patients preference design is more sensitive to detect clinical relevant differences between a triptan and an analgesic compared to the traditional study design, using only the effect on pain as the primary outcome measure.

METHODS

Triptan and ergot-naïve migraine patients of 18 years or older, with an average frequency of 1 to 7 migraine days per month during the last 6 months were invited to participate and screened for eligibility. Exclusion criteria related to avoiding contraindications for study medication and included: history of atherosclerotic disease, ischemic heart disease, transient ischemic attack or cerebrovascular accident, current

blood pressure above 160/95, impaired hepatic or renal function, current abuse of alcohol or any other drug, including analgesics, a history of basilar, hemiplegic or ophtalmoplegic migraine, any other severe concurrent medical condition, which might effect the interpretation in a clinical trial, or known or suspected hypersensitivity to, intolerance of, or contraindications to any component of the study medication. Females had to use a medically accepted form of contraception and were not pregnant or breastfeeding.
This study was approved by the medical ethics committee of LUMC and all patients gave written consent.

In a randomised single centre, double blind, double dummy, crossover study, participants were randomised to either naratriptan 2.5 mg or paracetamol 1000 mg with a crossover after three attacks or three months with at least one treated attack. Participants who were extremely dissatisfied with treatment or suffer from intolerable adverse events were allowed to make an early (still blinded) crossover to the other treatment. They were instructed to treat as soon as possible after onset of a migraine headache and recorded time and onset of the attack, timing and dosing and headache severity during start of treatment and two hour post-dose. Participants could take a second dose of study medication after four hours and if that did not work, they could take their own rescue medication, as long as it was not paracetamol or naratriptan.
Randomization was done by computer in blocks of four to ensure equal numbers in both groups. For blinding, a double-dummy technique was used. Both were independently done by the hospital pharmacist who also kept the code until the study was completed.
There were three pre-planned study visits: (i) at baseline, when patients were fully explained about the study design and purpose, gave oral and written informed consent, underwent a baseline assessment including the validated "Migraine Disability Assessment Scale" (MIDAS)[56] and Migraine Specific Quality of Life Questionnaire' (MSQ) version 2.1[56-60] and received the study treatment for the first three attacks; (ii) after the first treatment period, when the diary results and remaining study medication were checked and the study medication for the second treatment period was distributed; and (iii) after the second treatment period when the diary results and remaining study medication were checked, and the treatment preference and reasons therefore, were recorded. The MSQ was also completed during each next visit. Participants were also asked to give a treatment appreciation on a scale of 1-10 (pre-treatment, first and second treatment period).
The patient's preference was recorded on a visual analogue scale ranging from +5 (very strong preference for first treatment) to -5 (very strong preference for second treatment), where 0 indicates no preference (Figure 1). 'Appreciation' is listed here in the meaning of a separate appreciation for both treatments, and 'preference' is the preference for one of these treatments.

Reasons for preference were noted firstly in own words and then by ticking off items on a list of pre-defined drug attributes. Secondary outcome measure was percentage of attacks that was pain free (no headache) at 2hr post-dose.

We tested whether the overall mean preference score significantly differed from 0 cm (no preference) by using the single t-test. We compared the study medications for the number of (i) participants with a a priori determined clinically relevant preference score (strong to very strong: 2.6-5); and (ii) first and total attacks resolved within 2 hours post dose, using Chi-square analysis. Correlations were tested by calculating the correlation coefficient (r). Posthoc analyses were done for differences in outcome for attacks treated at mild and moderate or severe headache, for MIDAS disability grades I – IV at baseline and for MSQ Quality of Life score. Success of blinding was tested by guessing which medication was received in the in the second period and by analysis of period effects.

Sample size

It was estimated that a total of 22 randomised participants were needed to demonstrate a clinically relevant and statistically significant difference of 1.5 cm between the 'mean preference score' and 'no preference', with 80% power at $p<0.05$.[61] To accommodate for possible dropouts we included 31 participants.

RESULTS

Flow diagram and study population

We assessed 287 subjects for eligibility and excluded 256 (Figure 2). Thirty-one patients, who never used triptans or ergots, were randomised. Twenty-eight completed the study and treated in total 154 attacks; 79 with naratriptan and 75 with paracetamol. Two participants had no attacks during the second period and therefore we could not record their preference. One participant was withdrawn due to the development of angina (second period, participant used paracetamol, which was found after unblinding).

Baseline characteristics of 31 participants are presented in table 1. The majority had disability grade I (23%) or II (45%), indicating little to mild disability. Participants were triptan naive by definition, 7 (23%) participants used paracetamol as first choice, 15 (48%) used an NSAID, 5 (16%) used combination tablets and one used acetylsalicylic acid. One subject used prophylactic therapy (propranolol) and one subject used metoprolol for moderate hypertension, without being aware of its preventive effect on migraine.

Preference

Preference scores are presented in Figure 3. Nine participants (32%) had a strong to very strong preference (scores: 2.6 – 4) for naratriptan and also nine (32%) had strong to very strong preference for paracetamol. Two third of the patients (n = 18) expressed a very strong or strong preference for either one of the treatments. Seven (25%) had a slight to moderate preference (scores 1 - 2.5) for naratriptan and three for paracetamol. Of all patients 16/28 (57%) preferred naratriptan and 12/28 (43%) preferred paracetamol (p = 0.42). The mean preference score for naratriptan was 2.8 cm (SD=1.2) and for paracetamol 3.4 cm (SD=1.6). The overall mean preference score, was 0.17 ± 3.4 cm (SD) in favour of naratriptan (p= 0.17).
The main reasons for preference are given in Table 2. Rapid onset of relief was the most given reason for preference (n=13/28, 46%) and was also the most frequently indicated reason when patients could indicate multiple reasons (n=20/28, 17%) (Table not shown). Return to normal function and complete pain free came in second and third place as a reason for preference. When only the main reason for preference could be given, then just three reasons played a decisive role; rapid onset of relief, return to normal function and complete pain free. Participants with high preference scores did not differ significant in their choice of reason for preference from participants with a low preference score.

Predictive factors for preference

The height of the MIDAS-disability did not match with the patient preference for one of both treatments. In this there was also no difference in preference by MIDAS grade. The ten participants with the highest MIDAS disability grade (Class III-IV) had an equal preference for naratriptan as for paracetamol.

The MSQ score did not show a significant correlation with the reported preference. There was no influence of the MSQ on the preference of patients in this study.

Participants rated their appreciation for the study medication before and after each treatment (each cross-over phase) on a visual analogue scale ranging from 1-10. The satisfaction with used medications in advance and during the study ranged from 5.0 - 5.9 on a scale of 10. The appreciation (mean score) was 5.9 for naratriptan and 5.1 for paracetamol (Mean difference 0.842 [95% CI (-2.12203) – (-0.43631)], P= 0.1880. There were no significant differences in appreciation between the by the participants in advance used medication compared with the both studied treatments.
Overall there was no correlation between the results of the medication appreciation scale and the measured value of the preference. In many patients there was agreement, but in some patients there was no matching. These patients proved to be mainly patients with side effects and had a major negative influence on the correlation.

Pain-free response at 2 hours post dose

Fourteen participants had at least one attack with 2hr pain free with naratriptan (of which four with strong preference for naratriptan and three with a strong preference for paracetamol) and eight had at least one attack pain free at 2 hr with paracetamol (of which four with strong preference for naratriptan and two with a strong preference for paracetamol). Fourteen patients had no attacks with 2h pain free. Yet, three of these preferred naratriptan and five of these preferred paracetamol. The remaining six had only moderate preference, four for naratriptan and two for paracetamol. There was no overall correlation between the individual pain free rates and the strength and direction of the preference($r = 0.27$; $p = 0.187$; slope = 0.066).

When studied at the group level, of the 18 subjects who expressed a strong to very strong preference for either naratriptan or paracetamol, the overall 2hr pain free rate was 4/51 (8%) with the preferred drug, compared to 7/51 (14%) with the not-preferred drug. Unexpectedly, participants who strongly to very strongly preferred naratriptan showed a smaller 2hr pain free rate for attacks treated with naratriptan (3/26 = 12%) compared to 6/26 (23%) for attacks treated with paracetamol. For patients strongly to very strongly preferring paracetamol, the 2hr pain free rates were 1/25 (4%) for paracetamol-treated attacks versus 1/25 (4%) for naratriptan-treated attacks.

Unblinding and period effects

We asked patients to guess their treatment in the second period. 15/28 (54%) guessed the sequence correctly, 11 (39%) guessed wrongly, and 2 (7%) were not able to make a choice ($R = 0.31$; $p = 0.146$). The researchers, who provided the medication, took back the completed diaries and heard the experiences of the patients, also made a (blinded) guess and guessed correctly in 19/28 (68%) of the cases. As the researchers' guesses differed in 3 cases from the patient's guesses, the mutual agreement was good ($k = 0.746$, $r = 0.749$; $p < 0.001$). There was no period effect for the preference scores or 2hr pain free rates (data not shown).

DISCUSSION

We used a relatively new real life, randomized, controlled, cross-over, and multi-attack study design to asses whether patients using painkillers or NSAIDs would prefer naratriptan or paracetamol. After double-blind multi-attack exposure to a triptan for the first time in their life, one third of the study participants expressed a strong to very strong preference for naratriptan rather than paracetamol. However, also one-third preferred strong to very strong preferring paracetamol.

Remarkably, the endpoint 'preference' and the endpoint '2hr pain-free' showed almost no correlation. They probably measure different aspects.

The individual appreciation for each treatment of three attacks in each arm did not correlate with the patient preference; a hypothesis for this is that when patients were asked for the appreciation of the treatment effect in the last three attacks, they mainly look at the effect on the headache itself. When they determined their preference for one of the two treatments, also the side effects matter and in some patients this counts heavily.

The 2hr pain free rate in attacks treated while moderate or severe is the usual recommended endpoint to determine and compare efficacy in traditional acute antimigraine trials[8]. Our study was not powered to detect a difference between naratriptan and paracetamol in moderate or severe attacks, and naratriptan proved to have equal efficacy as paracetamol.

This study does not support the often-heard opinion that a high migraine-related MIDAS disability is an indicator for benefit from a triptan.

Because both in mild and severe attacks the 2hr pain free rate between naratriptan and paracetamol was nearly equal, the attack severity is not a good indicator for choice of therapy.

The PTPP design offers some major advantages, but also a few potential limitations. The most important advantage is that patients can truly compare the effects of both treatments over a number of attacks and for a wide range of both positive and negative treatment attributes. The preference endpoint allows for a truly personal judgment of what is clinically meaningful. This contrasts sharply to traditional head-to-head comparator trials where generally patients treat only a single attack with only one of the study drugs. Moreover, superiority in these trials is claimed on the basis of success for a single treatment-attribute that is selected by the investigators but may not necessarily be important to the majority of patients.[62-64] As an example, "restoration of the ability to function normally" (and not "fast headache relief") was the most frequently reported reason for preference in this trial.

In our study, blinding appeared to have been well preserved throughout the study as is shown by the guessing of the treatment in the second period and the MSQ-score and satisfaction per attack.

In summary, whilst traditional trials estimate the average response in a group of patients and attempt to identify "the overall winning drug" for all patients on the basis of the success rate for a single attribute, in PTPP trials the individual patient will be the winner. The PTPP design seeks to identify the best match between individual needs of a patient and specific drug profile. PTPP trials may therefore prove useful to assessing clinically meaningful differences between established agents and identifying patient-profiles predictive of success. At present it is still a major challenge for the clinician to identify patients who most benefit from therapy change. Trying out as well paracetamol as triptans (or NSAIDs) in the individual patient, for at least three successive attacks, will eventually create the greatest patient satisfaction.

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Table 1. Baseline characteristics

		Randomisation	
	Total N = 31	**Naratriptan first N = 13**	**Paracetamol first N = 18**
Age, mean (SD), y	**44 (10.3)**	**46 (12.7)**	**41 (8.8)**
Sex, n (%)			
Female	28 (90)	12 (39)	16 (51)
Male	3 (10)	1 (3)	2 (6)
Diagnosis, n (%)			
Migraine without aura	24 (77)	10 (32)	14 (45)
Migraine with aura	7 (23)	3 (10)	4 (13)
Age at onset, y (SD)	20 (9.6)	26 (9.4)	16 (8.0)
Attack frequency per month (SD)	1.4 (0.7)	1.3 (0.4)	1.6 (0.9)
Disability grade, n (%)			
Grade I	7 (23)	5 (16)	2 (6)
Grade II	14 (45)	5 (16)	9 (29)
Grade III	5 (16)	2 (6)	3 (10)
Grade IV	5 (6)	1 (3)	4 (13)
Average MIDAS-score (SD)	12.1 (13)	9.7 (15)	13.9(11)
Quality of Life score			
Average MSQ 2.1 score (SD)	39.5 (13)	37.2 (12)	41.1 (14)
First choice of acute treatment before intervention, n (%)			
Ibuprofen	10 (32)	4 (13)	6 (19)
Paracetamol	10 (32)	5 (16)	5 (16)
Combination tablets	5 (16)	2 (6)	3 (10)
Other (acetylsalicylic acid, other NSAIDs)	6 (19)	2 (6)	4 (13)
Prophylaxis, n (%)	2 (6)	0	2 (6)†

†One patient used metoprolol for moderate hypertension.

Table 2. Main reasons for preference

	All preference		**Preference for naratriptan**		**Preference for paracetamol**	
	Any	**Very Strong**	**Any**	**Very Strong**	**Any**	**Very Strong**
	(n = 28)	**(n = 28)**	**(n = 28)**	**(n = 28)**	**(n = 28)**	**(n = 28)**
Rapid onset of relief	13 (46.7)	9 (50.0)	8 (50.0)	5 (55.6)	5 (41.7)	4 (44.4)
Return to normal function	6 (21.4)	3 (16.7)	3 (18.8)	1 (11.1)	3 (25.0)	2 (22.2)
Complete pain free	5 (17.9)	3 (16.7)	3 (18.8)	2 (22.2)	2 (16.7)	1 (11.1)
Decrease of photo- and phonophobia	1 (3.6)	1 (5.6)	1 (6.3)	1 (11.1)	-	-
Decrease of nausea	-	-	-	-		-
No adverse events	1 (3.6)		1 (6.3)		-	-
Reliable effect, consistency	-	-	-	-	-	-
One dose sufficient		-	-	-	-	-
Long lasting effect	2 (7.1)	2 (11.1)	-	-	2 (16.7)	2 (22.2)
Taste	-	-	-	-	-	-
No reason	-	-	-	-	-	-

Values are numbers of patients (%). Participants selected one reason from predefined list.

Table 3. Pain free rates at 2hrs post-dose

	All Treated		Naratriptan		Paracetamol		Paracetamol	
	All	**Pain free (%)**	**All**	**Pain free (%)**	**All**	**Pain free (%)**	**OR (95%CI)**	**P value**
All treated attacks (all severities)	150	24 (16.0)	76	15 (19.7)	74	9 (12.2)	1.777 (0.660 - 4.478)	0.255
First treated attack (all severities)	56	13 (23.2)	28	9 (32.1)	29	4 (14.3)	2.842 (0.986 - 8.191)	0.053
For each drug first treated moderate or severe attack	37	7 (18.9)	17	4 (23.5)	20	3 (15.0)	1.621 (0.373 - 7.055)	0.520
All treated moderate or severe attacks	109	13 (11.9)	53	7 (13.2)	56	6 (10.7)	1.057 (0.366 – 3.051)	0.919
All treated mild attacks	44	11 (25.0)	25	8 (32.0)	19	3 (15.8)	2.560 (0.788 - 8.318)	0.118

Estimates obtained by generalized estimated equations.

Figure 1. Preference scale

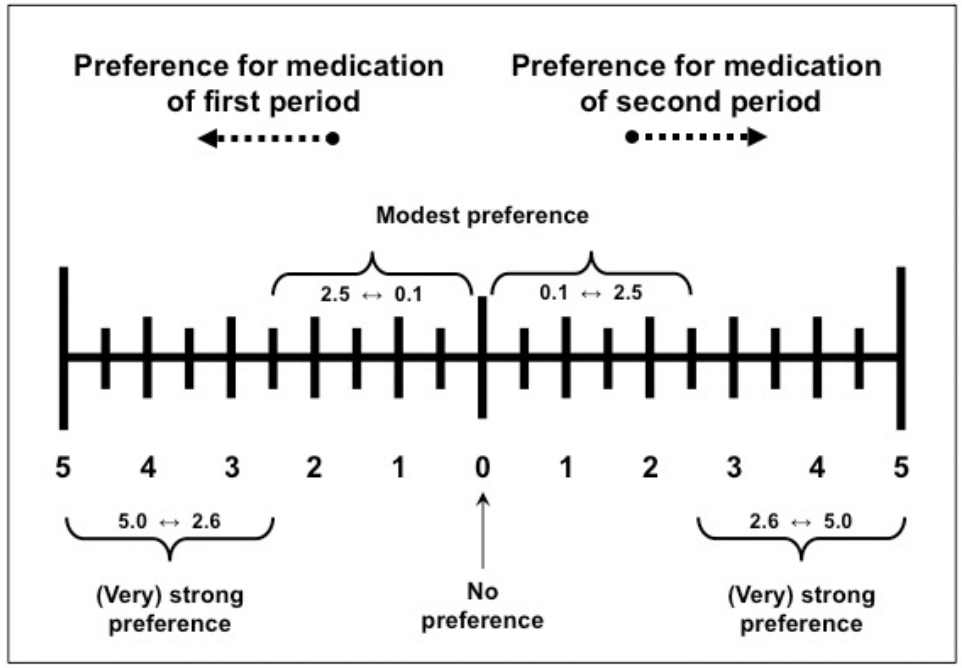


Figure 2. Flow diagram of study participants

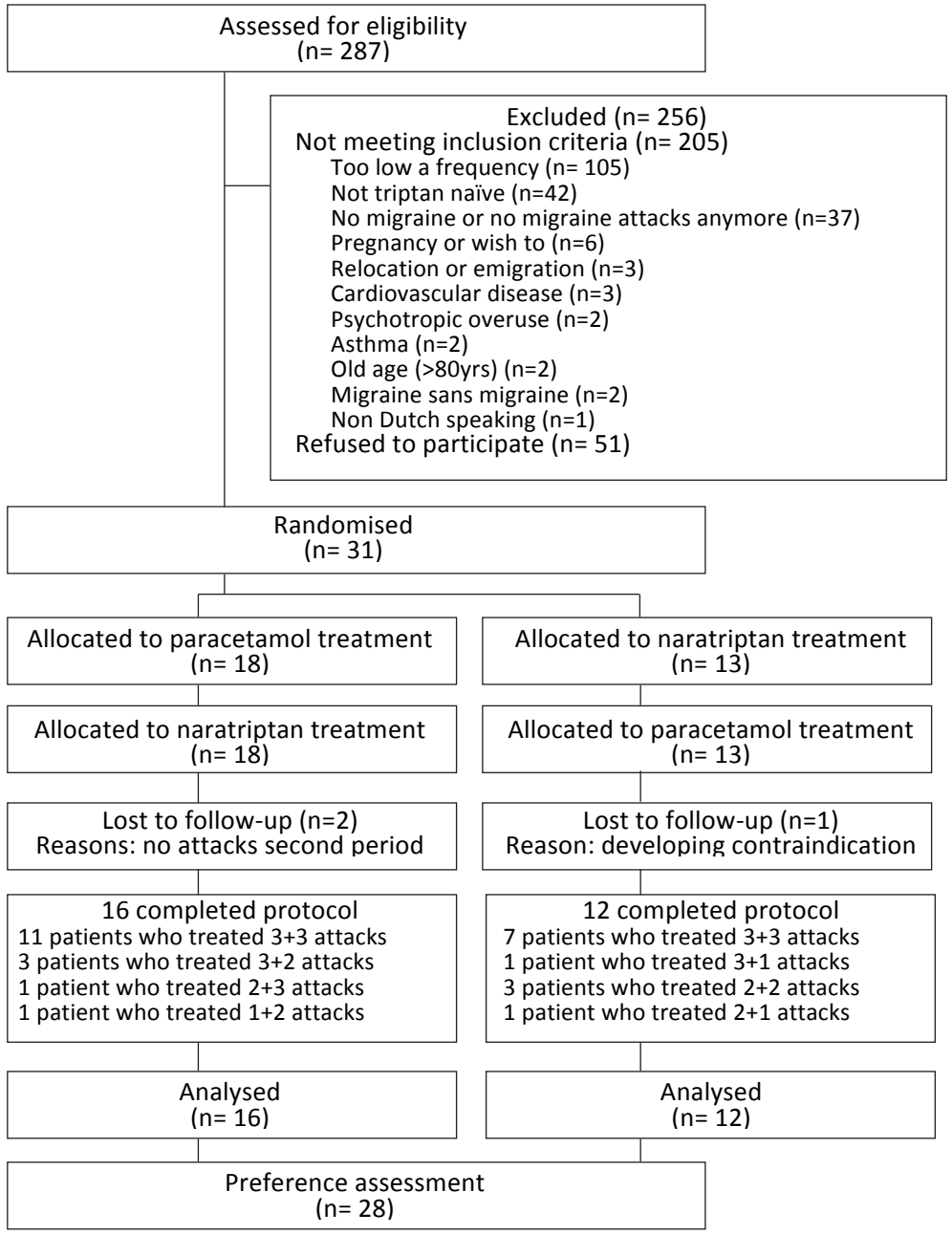
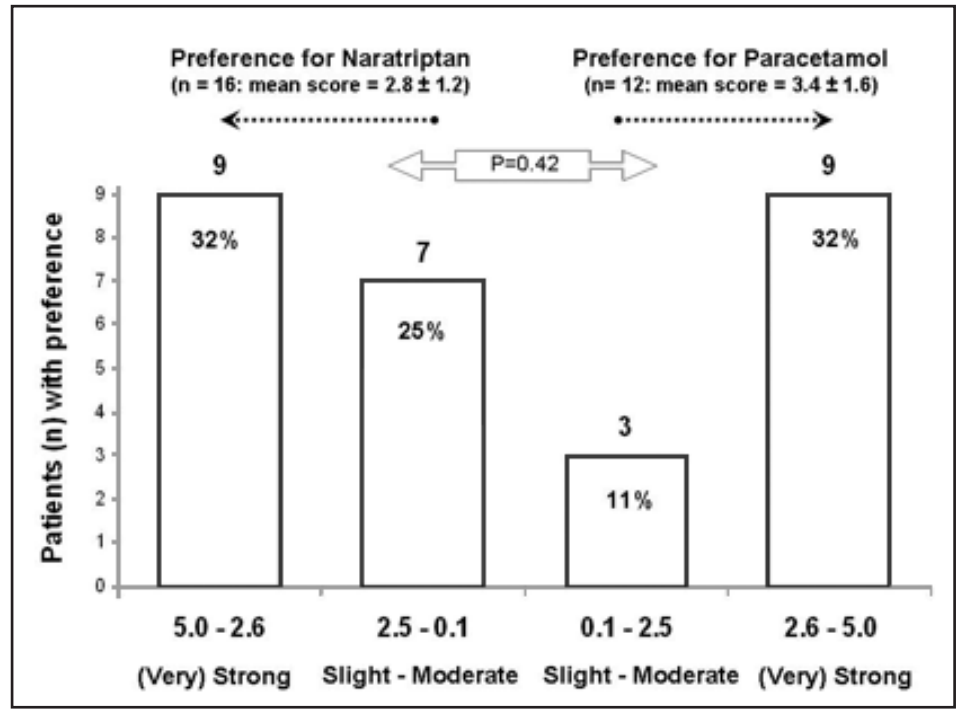


Figure 3. Preference for naratriptan or for paracetamol



Strong of very strong preference >2.5 is shown in outer columns. Preference for naratriptan is presented on the left side and for paracetamol on the right side, in a scale from +5 to -5 (5 represents strong preference and 0 is no preference).

References

1. Ferrari MD. Migraine. *Lancet* 1998;351(9108):1043-1051.
2. Goadsby PJ, Lipton RB, Ferrari MD. Migraine--current understanding and treatment. *N Engl J Med* 2002;346(4):257-270.
3. Terwindt GM, Ferrari MD, Tijhuis M, Groenen SM, Picavet HS, Launer LJ. The impact of migraine on quality of life in the general population: *the GEM study*. *Neurology* 2000;55(5):624-629.
4. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 2001;358(9294):1668-1675.
5. Steiner T. Triptans vs other drugs for acute migraine. *Headache* 2008;48(9):1378-1379.
6. Lipton RB, Stewart WF, Stone AM, Lainez MJ, Sawyer JP. Stratified care vs step care strategies for migraine: the Disability in Strategies of Care (DISC) Study: A randomized trial. *JAMA* 2000;284(20):2599-2605.
7. Lipton RB, Bigal ME, Goadsby PJ. Double-blind clinical trials of oral triptans vs other classes of acute migraine medication - a review. *Cephalalgia* 2004;24(5):321-332.
8. Tfelt-Hansen P, Block G, Dahlof C et al. Guidelines for controlled trials of drugs in migraine: second edition. *Cephalalgia* 2000;20(9):765-786.
9. Tfelt-Hansen P. Triptans vs other drugs for acute migraine. Are there differences in efficacy? A comment. *Headache* 2008;48(4):601-605.
10. Brandes JL, Kudrow D, Stark SR et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. *JAMA* 2007;297(13):1443-1454.
11. Smith TR, Sunshine A, Stark SR, Littlefield DE, Spruill SE, Alexander WJ. Sumatriptan and naproxen sodium for the acute treatment of migraine. *Headache* 2005;45(8):983-991.
12. Silberstein SD, Mannix LK, Goldstein J et al. Multimechanistic (sumatriptan-naproxen) early intervention for the acute treatment of migraine. *Neurology* 2008;71(2):114-121.
13. Derry S, Moore RA, Mcquay HJ. Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev* 2010;11:CD008040.
14. Bigal M, Rapoport A, Aurora S, Sheftell F, Tepper S, Dahlof C. Satisfaction with current migraine therapy: experience from 3 centers in US and Sweden. *Headache* 2007;47(4):475-479.
15. Cutrer FM, Goadsby PJ, Ferrari MD et al. Priorities for triptan treatment attributes and the implications for selecting an oral triptan for acute migraine: a study of US primary care physicians (the TRIPSTAR Project). *Clin Ther* 2004;26(9):1533-1545.
16. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. *Cephalalgia* 2002;22(8):633-658.
17. Lipton RB, Stewart WF. Acute migraine therapy: do doctors understand what patients with migraine want from therapy? *Headache* 1999;39(suppl 2):S20-S26.

18. Lipton RB, Cutrer FM, Goadsby PJ et al. How treatment priorities influence triptan preferences in clinical practice: perspectives of migraine sufferers, neurologists, and primary care physicians. *Curr Med Res Opin* 2005;21(3):413-424.
19. Lanteri-Minet M. What do patients want from their acute migraine therapy? *Eur Neurol* 2005;53 Suppl 1:3-9.
20. Lipton RB, Hamelsky SW, Dayno JM. What do patients with migraine want from acute migraine treatment? *Headache* 2002;42 Suppl 1:3-9.
21. Pascual J, Garcia-Monco C, Roig C, Yusta IA, Lopez-Gil A. Rizatriptan 10-mg wafer versus usual nontriptan therapy for migraine: analysis of return to function and patient preference. *Headache* 2005;45(9):1140-1150.
22. Diez FI, Straube A, Zanchin G. Patient preference in migraine therapy. A randomized, open-label, crossover clinical trial of acute treatment of migraine with oral almotriptan and rizatriptan. *J Neurol* 2007;254(2):242-249.
23. Lainez MJ, Evers S, Kinge E et al. Preference for rizatriptan 10-mg wafer vs. eletriptan 40-mg tablet for acute treatment of migraine. *Cephalalgia* 2006;26(3):246-256.
24. Dowson AJ, Tepper SJ, Dahlof C. Patients' preference for triptans and other medications as a tool for assessing the efficacy of acute treatments for migraine. *J Headache Pain* 2005;6(3):112-120.
25. Schoenen J, Pascual J, Rasmussen S, Sun W, Sikes C, Hettiarachchi J. Patient preference for eletriptan 80 mg versus subcutaneous sumatriptan 6 mg: results of a crossover study in patients who have recently used subcutaneous sumatriptan. *Eur J Neurol* 2005;12(2):108-117.
26. Evans RW, Dahlof CG. Determining triptan preference for the individual patient. *Headache* 2004;44(7):723-725.
27. Dahlof C. Assessing patient preference in migraine treatment. *Cephalalgia* 2001;21(8):791-795.
28. Loder E, Brandes JL, Silberstein S et al. Preference comparison of rizatriptan ODT 10-mg and sumatriptan 50-mg tablet in migraine. *Headache* 2001;41(8):745-753.
29. Pascual J, Munoz R, Leira R. An open preference study with sumatriptan 50 mg and zolmitriptan 2.5 mg in 100 migraine patients. *Cephalalgia* 2001;21(6):680-684.
30. Pascual J, Bussone G, Hernandez JF, Allen C, Vrijens F, Patel K. Comparison of preference for rizatriptan 10-mg wafer versus sumatriptan 50-mg tablet in migraine. *Eur Neurol* 2001;45(4):275-283.
31. Powers C, Szeto S, Pangtay D, Bort T, Cervi M, Cady R. Evaluation of migraineurs' preferences for naratriptan over conventional first-line agents. *Arch Fam Med* 2000;9(8):753-758.
32. Adelman JU, Mannix LK, Von Seggern RL. Rizatriptan tablet versus wafer: patient preference. *Headache* 2000;40(5):371-372.
33. Christie S, Gobel H, Mateos V, Allen C, Vrijens F, Shivaprakash M. Crossover comparison of efficacy and preference for rizatriptan 10 mg versus ergotamine/caffeine in migraine. *Eur Neurol* 2003;49(1):20-29.
34. Dahlof C. How to assess patient preference of migraine treatments. *Cephalalgia* 1999;19 Suppl 24:2-5.

35. Krahn M, Naglie G. The next step in guideline development: incorporating patient preferences. *JAMA* 2008;300(4):436-438.
36. Silverman WA, Altman DG. Patients' preferences and randomised trials. *Lancet* 1996;347(8995):171-174.
37. Torgerson DJ, Sibbald B. Understanding controlled trials. What is a patient preference trial? *BMJ* 1998;316(7128):360.
38. Dulli DA. Naratriptan: an alternative for migraine. *Ann Pharmacother* 1999;33(6):704-711.
39. Gunasekara NS, Wiseman LR. Naratriptan. *CNS Drugs* 1997;8(5):402-408.
40. Tfelt-Hansen P, Steiner TJ. Over-the-counter triptans for migraine : what are the implications? *CNS Drugs* 2007;21(11):877-883.
41. Prior MJ, Codispoti JR, Fu M. A randomized, placebo-controlled trial of acetaminophen for treatment of migraine headache. *Headache* 2010;50(5):819-833.
42. Lipton RB, Stewart WF, Ryan RE, Jr., Saper J, Silberstein S, Sheftell F. Efficacy and safety of acetaminophen, aspirin, and caffeine in alleviating migraine headache pain: three double-blind, randomized, placebo-controlled trials. *Arch Neurol* 1998;55(2):210-217.
43. Lipton RB, Stewart WF, Ryan RE, Jr., Saper J, Silberstein S, Sheftell F. Efficacy and safety of acetaminophen, aspirin, and caffeine in alleviating migraine headache pain: three double-blind, randomized, placebo-controlled trials. *Arch Neurol* 1998;55(2):210-217.
44. Lipton RB, Baggish JS, Stewart WF, Codispoti JR, Fu M. Efficacy and safety of acetaminophen in the treatment of migraine: results of a randomized, double-blind, placebo-controlled, population-based study. *Arch Intern Med* 2000;160(22):3486-3492.
45. Boureau F, Joubert JM, Lasserre V, Prum B, Delecoeuillerie G. Double-blind comparison of an acetaminophen 400 mg-codeine 25 mg combination versus aspirin 1000 mg and placebo in acute migraine attack. Cephalalgia 1994;14(2):156-161.
46. Tfelt-Hansen PC. Unpublished clinical trials with sumatriptan. *Lancet* 2009;374(9700):1501-1502.
47. Grol MH, Neven AK, Pijnenborg L, Goudswaard AN. [Summary of the practice guideline 'Headache' from the Dutch College of General Practitioners]. *Ned Tijdschr Geneeskd* 2006;150(6):305-309.
48. Ross-Lee LM, Eadie MJ, Heazlewood V. Aspirin pharmacokinetics in migraine. The effect of metoclopramide. *Eur J Clin Pharmacol* 1983;24:777-785.
49. MacGregor EA, Wilkinson M, Bancroft K. Domperidone plus paracetamol in the treatment of migraine. Cephalalgia 1993;13(2):124-127.
50. Ashcroft DM, Millson D. Naratriptan for the treatment of acute migraine: meta-analysis of randomised controlled trials. *Pharmacoepidemiol Drug Saf* 2004;13(2):73-82.
51. Freitag F, Diamond M, Diamond S, Janssen I, Rodgers A, Skobieranda F. Efficacy and tolerability of coadministration of rizatriptan and acetaminophen vs rizatriptan or acetaminophen alone for acute migraine treatment. *Headache* 2008;48(6):921-930.
52. Dowson A, Ball K, Haworth D. Comparison of a fixed combination of domperidone and paracetamol (Domperamol) with sumatriptan 50 mg in moderate to severe migraine: a randomised UK primary care study. *Curr Med Res Opin* 2000;16(3):190-197.
53. Goldstein J, Silberstein SD, Saper JR et al. Acetaminophen, aspirin, and caffeine versus sumatriptan succinate in the early treatment of migraine: results from the ASSET trial. *Headache* 2005;45(8):973-982.
54. Tfelt-Hansen PC. Published and not fully published double-blind, randomised, controlled trials with oral naratriptan in the treatment of migraine: a review based on the GSK Trial Register. *J Headache Pain* 2011;12(4):399-403.
55. A randomised, double-blind, cross-over study to compare the patient preference of oral naratriptan (NaramigTM) 2.5 mg with naproxen 500 mg in patients dissatisfied with simple analgesics in the treatment of acute migraine. *Study no.: S2W40010*. 2011. 20-7-2011.
56. Stewart WF, Lipton RB, Kolodner K, Liberman J, Sawyer J. Reliability of the migraine disability assessment score in a population-based sample of headache sufferers. *Cephalalgia* 1999;19(2):107-114.
57. Martin BC, Pathak DS, Sharfman MI et al. Validity and reliability of the migraine-specific quality of life questionnaire (MSQ Version 2.1). *Headache* 2000;40(3):204-215.
58. Wagner TH, Patrick DL, Galer BS, Berzon RA. A new instrument to assess the long-term quality of life effects from migraine: development and psychometric testing of the MSQOL. *Headache* 1996;36(8):484-492.
59. Cole JC, Lin P, Rupnow MF. Validation of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v. 2.1) for patients undergoing prophylactic migraine treatment. *Qual Life Res* 2007;16(7):1231-1237.
60. Jhingran P, Osterhaus JT, Miller DW, Lee JT, Kirchdoerfer L. Development and validation of the Migraine-Specific Quality of Life Questionnaire. *Headache* 1998;38(4):295-302.
61. Senn S. Crossover trials in clinical research. 2nd ed. Chichester: *John Whiley & Sons*; 2002.
62. Pilgrim AJ. Methodology of clinical trials of sumatriptan in migraine and cluster headache. *Eur Neurol* 1991;31(5):295-299.
63. Savi L, Omboni S, Lisotto C et al. A double-blind, randomized, multicenter, Italian study of frovatriptan versus rizatriptan for the acute treatment of migraine. *J Headache Pain* 2010.
64. Tullo V, Allais G, Ferrari MD et al. Frovatriptan versus zolmitriptan for the acute treatment of migraine: a double-blind, randomized, multicenter, Italian study. *Neurol Sci* 2010;31 Suppl 1:S51-S54.

Part 3

Medication overuse

CHAPTER

9

Triptan overuse in the Dutch general population: A nationwide pharmaco-epidemiology database analysis in 6.7 million people

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ABSTRACT

Introduction
Population-based observational study to assess the prevalence, demographics, risk factors, and costs of triptan-overuse, defined as more than 30 (IHS Criteria) or 54 (Stringent Criteria) "defined daily doses" (DDD) per 3 months.

Methods
Analysis of the Dutch Health Care Insurance Board Database for 2005, which included prescriptions for 6.7 million people (46% of the total Dutch population).

Results
Triptans were used by 85,172 (1.3%) people; 8,844 (10.4%; 95% CI 10.2 - 10.6) were IHS-overusers and 2,787 (3.3%; 95% CI 3.2 - 3.4) were stringent-overusers. The triptan-specific odds ratios for the rate of IHS-overuse, compared to sumatriptan were: 0.26 (95% CI 0.19-0.36) for frovatriptan; 0.34 (95% CI 0.32-0.37) for rizatriptan; (0.76; 95% CI 0.68-0.85) for naratriptan; 0.86 (95% CI 0.72-1.02) for eletriptan; 0.97 (95% CI 0.88-1.06) for zolmitriptan; and 1.49 (95% CI 1.31-1.72) for almotriptan. Costs for overuse were 29.7 million Euros; for the IHS criteria it was 46% and for stringent 23%.

Discussion
In the Dutch general population, 1.3% used a triptan in 2005, of which 10.3% were overusers and accounted for half of the total costs of triptans. Users of frovatriptan, rizatriptan and naratriptan had a lower level of overuse.

INTRODUCTION

Migraine is a common [1,2], highly disabling [3,4], and costly [5] episodic brain disorder [6]. Attacks typically last 1-2 days and strike with a median frequency of 1.5 per month; ten percent of patients have two or more attacks per week[6]. A high attack frequency is associated with a substantial increase of disability [4,7,8], costs [5,9], and risk of ischemic brain lesions [10,11]. Overuse of acute headache agents is increasingly recognised as a paradoxical but major reason for sometimes dramatic increases of the attack frequency (medication-overuse headache; MOH) [7,12-15]. MOH is increasingly recognized as a problem worldwide, with an estimated prevalence in the general population of 1-4% [12,14].

Triptans, selective 5-$HT_{1B/1D}$ (serotonin) receptor agonists, are specific, effective, and well tolerated agents to treat migraine attacks [16-18]. Regular use of a triptan on ten or more days a month for more than three consecutive months, may cause triptan-overuse headache (TOH) [13]. Studies in headache clinics and open populations suggest an average critical dosage of 18 single doses per month [19,20] With the increasing availability of triptans over-the-counter and the currently often advocated [21], but still unproven instruction to treat attacks as early as possible while the headache is still mild, the prevalence of TOH is likely to increase. This might have a major impact on the quality of life of migraine patients [22,23] and will cause a considerable increase in costs [9].

Overuse of triptans does not suddenly emerge; it starts with increasing use, develops in to more use, even more use and than sometimes results in overuse. To describe this phenomenon these different levels of triptan use are relevant, starting from a lower threshold of triptan overuse (overuse or serious at risk, which may give an overestimation) up to a strict threshold (which may result in underestimation). To this end, we had access to an unique database of the national Dutch Health Care Insurance Board, which monitors, at the individual level, the dispense of prescribed drugs at pharmacies for all inhabitants of the Netherlands.

In the present study, we sought to assess: (i) the prevalence and associated costs of triptan-overuse in the Dutch general population; (ii) the demographic characteristics of triptan-overusers to identify possible risk factors; and (iii) whether the level of overuse differs among the seven available triptans.

METHODS

Study Setting
Data were obtained from the Drug Information Project (GIP database) of the Health Care Insurance Board (CVZ). The CVZ is a public authority in the domain of drugs. As an independent non-profit governing body, it monitors conditions of the health insurance scheme in the Netherlands. In 2005, more than 10 million persons (65% of all inhabitants of the Netherlands) were mandatory insured on the grounds of the

Sickness Fund Act. People were eligible for sickness fund insurance if they had a yearly income of less than € 33.000. The GIP registered prescribed drugs dispensed at pharmacies for patients that are insured by sickness funds. All prescription drugs are coded according to the Anatomical, Therapeutic and Chemical (ATC) classification [24]. Each registered patient has an anonymous unique identification number, which allows complete observation of medication use over time per patient. Each prescription also includes information on what insurance companies pay to the pharmacist, allowing an exact calculation of the costs. For migraine patients in the Netherlands, there were no financial restrictions in using acute or prophylactic headache therapy in the study year 2005 as long as a physician prescribed the medication. In the Netherlands over-the-counter sales of triptans is prohibited.

Definitions

A triptan-user was defined as a patient for whom minimally one prescribed triptan was dispensed in 2005. We used two definitions for triptan-overuse. One based on the criteria of The International Headache Society (IHS), i.e. use of a triptan on more than 10 days a month for ≥ 3 months [13], and a second more stringent definition, based on studies in headache clinics, i.e. use of 18 single doses or more per month for ≥ 3 consecutive months [19]. When patients use 18 DDDs or more over a long period, chronic daily headache based on medication overuse is evident [19].

We converted these criteria into Defined Daily Dose (DDD) per year, which is, according to the World Health Organization (WHO), the standardised dosage per day of a drug when prescribed for the registered indication (Table 1) [24]. The DDD system has been used in previous triptan database studies and is the system of choice when comparing drugs (http://www.whocc.no/)[25]. Accordingly, "IHS triptan-overuse" was defined as use of 120 DDDs or more per year and "stringent triptan-overuse" as use of 216 DDDs or more per year. As use and overuse of triptans may fluctuate considerably [12] (and see the result section of the present study), and because our aim was to identify consistent rather than incidental overuse, we calculated the 3 month use using the average triptan consumption over a 12 month period rather than over a 3 month period only. For calculating the DDDs we had the real number of tablets (and other formulations) at our disposal.

Table 1 Defined daily dose per triptan according to the World Health Organisation. [24]

Triptan	Year of introduction	Formulation	Defined daily dose (DDD)
Sumatriptan	1991(1996*)	50 mg tablet	1 tablet
		100 mg tablet	½ tablet
		25 mg suppository	1 supp
		20 mg nasal spray	1 spray
		6 mg subcutaneous injection	1 injection
Naratriptan	1997	2.5 mg tablet	1 tablet
Zolmitriptan	1997	2.5 mg tablet	1 tablet
Rizatriptan	1998	5 mg tablet	2 tablets
		10 mg tablet	1 tablet
Eletriptan	2000	20 mg tablet	2 tablets
		40 mg tablet	1 tablet
Almotriptan	2000	12.5 mg tablet	1 tablet
Frovatriptan	2001	2.5 mg tablet	1 tablet

** First year of full availability of tablets without any surcharge..*

Use of migraine prophylactic medication was defined as the dispense of minimally one prescription in 2005 of any medication that is registered in the Netherlands for migraine prophylaxis. Most migraine prophylactic agents have, however, multiple disease indications. As the indication for a prescription is not recorded in the database, we could not establish whether the medication was prescribed for migraine or another disorder.

Statistical analysis

Data are summarised as means with 95% confidence intervals (95% CIs) for continuous variables and as numbers and percentages of subjects for categorical variables. Differences between groups are presented with 95% CIs. For differences among the triptans for the rate of overuse, we calculated the odds ratios (OR) with 95% CIs using sumatriptan as the reference. As sumatriptan is the longest available and most widely prescribed triptan, we adjusted the OR for duration of availability, by the method of indirect standardisation. For this duration we took the number of years the drug was on the market without any surcharge (corresponding to the start of substantial use in the Netherlands). For statistical analyses we used SAS Enterprise Guide version 4.1.

RESULTS

We did find that 10% of all triptan-users, which is 0.1 % of the total Dutch general population, were overusing triptans. They were responsible for nearly half of the total costs for triptans.
We could assess the medication use of 6.7 million persons, covering approximately 46% of the total Dutch population and 67% of all persons that were insured with the sickness fund. The remaining part of the population could not be included in this study because of reasons unlikely to have introduced bias, such as non-connectable databases and other ways of health insurance.
In 2005, 85.172 persons (1.3% of the total sample) had received at least one prescription for a triptan. Of these 31,841 (37.4%) had received only one prescription and 5,536 (6.5%) had received prescriptions for more than one triptan. The vast majority of prescriptions (95%) was from general practitioners; only 5% were from neurologists or other specialists. Table 2 compares the characteristics of triptan-users to those of the total population. The majority of triptan-users were female and over thirty years of age. Nineteen percent of triptan-users also took medication indicated for migraine prophylaxis.

Numbers and characteristics of overusers versus non-overusers are presented in table 3. Among the 85,172 triptan-users, 8,844 persons were overusers according to the IHS criteria (10.4%; 95%CI: 10.2-10.6), and 2,787 persons according to the stringent criteria (3.3%; 3.2-3.4). IHS triptan-overusers accounted for 47.3% (47.2-47.3) and stringent overusers for 23.0% (20.0-24.1) of the total use of triptans. Overusers were equally distributed among females and males and across the whole life span, although on average they were older than non-overusers: 60% of overusers were in the fifth and sixth decade of life. Prophylactic medication was more frequently dispensed in overusers, 30.4% of IHS and 32.1 % of stringent overusers, than in non-overusers (17.9%).

Sumatriptan is available in four different formulations and two oral doses. The vast majority used just one formulation, although overusers (IHS: 17.2%; stringent: 24%) more often used multiple formulations than did non-overusers (5.8%). The majority exclusively used tablets: 64.2% of the total sample; 62.4% of the non-overusers; 75.4% of the IHS-overusers; and 74.1% of the stringent-overusers. Subcutaneous injections were used by 10.3% of the non-overusers, 6.6% of the IHS-overusers and 4.6% of the stringent-overusers.

Table 2. Clinical characteristics and demographics of triptan users compared to the total population.

		Total population		**Triptan users**	
		N = 6,704,627		**N = 85,172**	
		n (%)		**n (%)**	
Females		3,665,773	(55)	71,047	(83)
Age	*< 20*	685,352	(19)	1,916	(3)
	20 – 29	459,630	(13)	9,616	(14)
	30 – 39	586,641	(16)	16,620	(23)
	40 – 49	588,504	(16)	21,628	(30)
	50 – 59	503,518	(14)	14,615	(21)
	60 – 69	365,634	(10)	4,926	(7)
	> 70	476,494	(13)	1,726	(2)
Males		3,038,854	(45)	14,125	(6)
Age	*< 20*	719,131	(24)	871	(13)
	20 – 29	447,465	(15)	1,782	(25)
	30 – 39	486,320	(16)	3,499	(26)
	40 – 49	433,975	(14)	3,644	(19)
	50 – 59	371,537	(12)	2,725	(9)
	60 – 69	297,714	(10)	1,194	(3)
	> 70	282,712	(9)	410	(3)
*Prophylactic medication**		437.354	(6.5)	16.327	19.2
Propranolol		54,254	(0.8)	6,267	(7.4)
Metoprolol		339,244	(5.1)	6,985	(8.2)
Pizotiphen		4,028	(0.1)	1,400	(1.6)
Flunarizine		2,803	(0.0)	218	(0.3)
Valproic acid		30,228	(0.5)	1,713	(2.0)
Clonidine		13,363	(0.2)	747	(0.9)
Topiramate		3,325	(0.0)	1,084	(1.3)

*Source: GIP database/Health Care Insurance Board. *Medication which can be prescribed as prophylactic therapy for migraine. Amitriptyline is not registered and not prescribed as migraine prophylaxis in the Netherlands. Methysergide can only be prescribed for a short period to prevent adverse events and was therefore excluded.*

Table 3. Clinical characteristics and demographics of triptan overusers compared to non-overusers

		Total		**Non-overusers**		**Overusers**							
				< 30 DDDs/qtr		**IHS criteria: ≥30 DDD/qtr**		**Difference 'IHS overusers' non-overusers**		**Stringent criteria* ≥54 DDD/qtr**		**Difference 'stringent overusers' non-overusers**	
		N = 85,172		**N = 76,328**		**N = 8,844**		**(95% CI)**		**N = 2,787**		**(95% CI)**	
Female, n (%)		71,047	(83)	63,622	(83)	7,425	(84)	1%	(-0.2 to 1.4)	2,294	(82)	-1%	(-2.5 to 0.4)
Mean age, y (SD)		43	(13)	42	(13)	47	(11)	5 yrs	(4.7 to 5.3)	48	(11)	6 yrs	(5.2 to 6.2)
Age, n (%)	*< 20*	2,787	(3)	2,765	(4)	22	(0)	-3%	(-3.5 to -3.2)	6	(0)	-3%	(-3.6 to -3.1)
	20 – 29	11,398	(13)	10,913	(14)	485	(6)	-9%	(-9.3 to -8.3)	113	(4)	-10%	(-11.0 to -9.4)
	30 – 39	20,119	(24)	18,439	(24)	1,680	(19)	-5%	(-6.0 to -4.3)	515	(19)	-6%	(-7.1 to 4.2)
	40 – 49	25,272	(30)	22,275	(29)	2,997	(34)	5%	(3.7 to 5.7)	964	(35)	5%	(3.6 to 7.2)
	50 – 59	17,340	(20)	14,861	(20)	2,479	(28)	9%	(7.6 to 9.5)	789	(28)	9%	(7.2 to 10.6)
	60 – 69	6,120	(7)	5,210	(7)	910	(10)	4%	(2.8 to 4.1)	298	(11)	4%	(2.8 to 5.1)
	> 70	2,136	(2)	1,865	(2)	271	(3)	1%	(0.3 to 1.0)	102	(4)	1%	(0.6 to 2.0)
Prophylaxis, n (%)													
Propranolol		6,267	(7.4)	5,287	(6.9)	980	(11.1)	4%	(3.5 to 4.8)	326	(11.7)	5%	(3.6 to 6.0)
Metoprolol		6,985	(8.2)	5,868	(7.7)	1,117	(12.6)	5%	(4.2 to 5.7)	352	(12.6)	5%	(3.7 to 6.2)
Pizotiphen		1,400	(1.6)	1,133	(1.5)	267	(3.0)	2%	(1.2 to 1.9)	106	(3.8)	2%	(1.7 to 3.1)
Flunarizine		218	(0.3)	165	(0.2)	53	(0.6)	0%	(0.2 to 0.6)	17	(0.6)	0%	(0.2 to 0.8)
Valproic acid		1,713	(2.0)	1,352	(1.8)	361	(4.1)	2%	(1.9 to 2.8)	123	(4.4)	3%	(1.9 to 3.5)
Clonidine		747	(0.9)	628	(0.8)	119	(1.3)	1%	(0.3 to 0.8)	38	(1.4)	1%	(0.2 to 1.0)
Topiramate		1,084	(1.3)	757	(1.0)	327	(3.7)	3%	(2.3 to 3.1)	130	(4.7)	4%	(2.9 to 4.5)
Any of the above		16,327	(19.2)	13,635	(17.9)	2,692	(30.4)	13%	(11.6 to 13.6)	895	(32.1)	14%	(12.5 to 16.0)

*Source: GIP database/Health Care Insurance Board. *Medication which can be prescribed as prophylactic therapy for migraine. Amitriptyline is not registered and not prescribed as migraine prophylaxis in the Netherlands. Methysergide can only be prescribed for a short period to prevent adverse events and was therefore excluded.*

Table 4. Use of the various triptans in non-overusers versus overusers

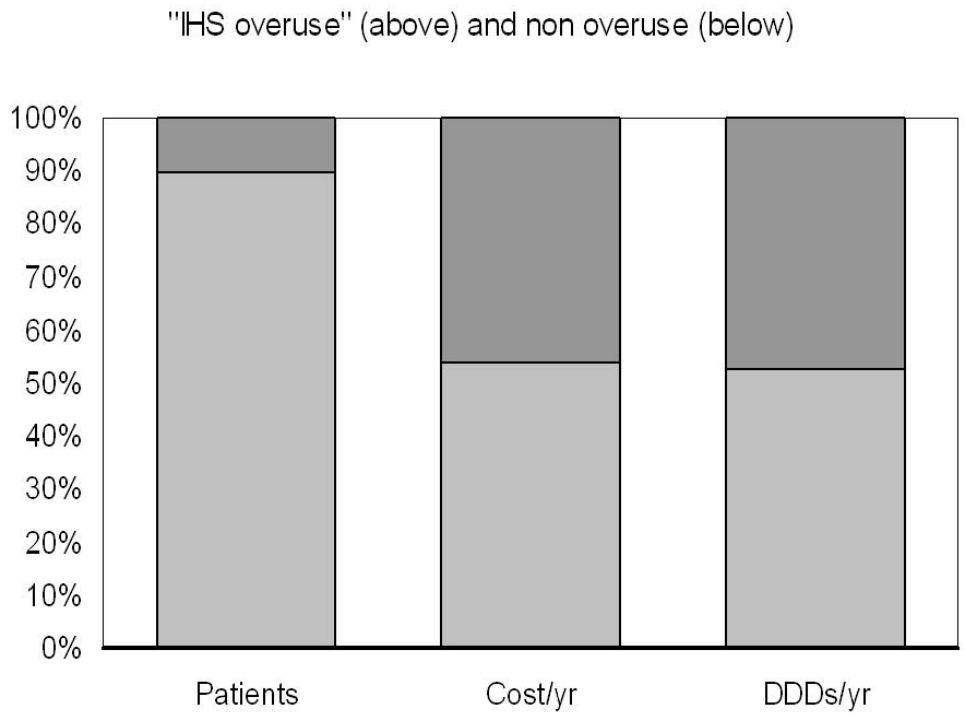
	Total		Non-overusers		Overusers			
			< 30 DDDs/qtr		IHS criteria: ≥30 DDDs/qtr		Stringent criteria* ≥54 DDDs/qtr	
	N = 85,172		N = 76,328		N = 8,844		N = 2,787	
	n	(%)	n	(%)	n	(%)	n	(%)
Single triptan use	79,636	(94)	71,837	(94)	7,799	(88)	2,416	(87)
Sumatriptan	41,352	(52)	35,798	(50)	5,554	(71)	1,952	(81)
Naratriptan	3,798	(5)	3,437	(5)	361	(5)	86	(4)
Zolmitriptan	4,983	(6)	4,397	(6)	586	(8)	134	(6)
Rizatriptan	25,796	(32)	24,770	(35)	1,026	(13)	182	(8)
Eletriptan	1,455	(2)	1,289	(2)	166	(2)	37	(2)
Almotriptan	1,295	(2)	1,206	(2)	89	(1)	23	(1)
Frovatriptan	957	(1)	940	(1)	17	(0.2)	2	(0.1)
Multiple triptans	5,536	(6)	4,491	(6)	1,045	(12)	371	(13)

*Values are numbers (%) of subjects. * 'Stringent overusers' are a subgroup of 'IHS overusers'. Source: GIP Database/ Health Care Insurance Board.*

Table 4 shows the numbers and proportions of patients in each of the three categories: all users of a triptan, triptan non-overusers and triptan-overusers. The majority of patients used only one triptan. Sumatriptan was by far the most frequently prescribed triptan in all three categories. Overuse was observed for all triptans, but the level of overuse differed significantly per triptan as presented in table 5. Compared to sumatriptan, the odds ratio (OR) for the rate of IHS-overuse was 0.11 (95% CI 0.08-017) for frovatriptan, 0.27 (95% CI 0.25-0.28) for rizatriptan, 0.48 (95% CI 0.40-0.57) for almotriptan, 0.68 (95% CI 0.62-0.74) for naratriptan, 0.83 (95% CI 0.72-0.95) for eletriptan and 0.86 (95% CI 0.80-0.93) for zolmitriptan. When adjusted for the different durations of availability, the level of overuse remained significantly reduced for frovatriptan (0.26; 95% CI 0.19-0.36), rizatriptan (0.34; 95% CI 0.32-0.37) and naratriptan (0.76; 95% CI 0.68-0.85), but not for eletriptan (0.86; 95% CI 0.72-1.02), zolmitriptan (0.97; 95% CI 0.88-1.06) and almotriptan (1.49; (95% CI 1.31-1.72). Similar profiles were seen for stringent-overuse. It should be noted that the absolute numbers of users and overusers for naratriptan and especially frovatriptan are very small, and that the duration of availability of especially frovatriptan was very short. These factors might have biased the results for these triptans (see discussion). The overuse in the

group of patients using more than one triptan is twice as high, compared to the use of just one triptan. The crude odds on overuse compared to sumatriptan (1.00) is 2.01 (95% CI 1.87-2.16) for the IHS criteria and for the stringent category it is 2.12 (95% CI 1.98-2.37). In the group of patients using more than one triptan, it is not possible to calculate the adjusted odds because of the differences between duration on the market of the different triptans.

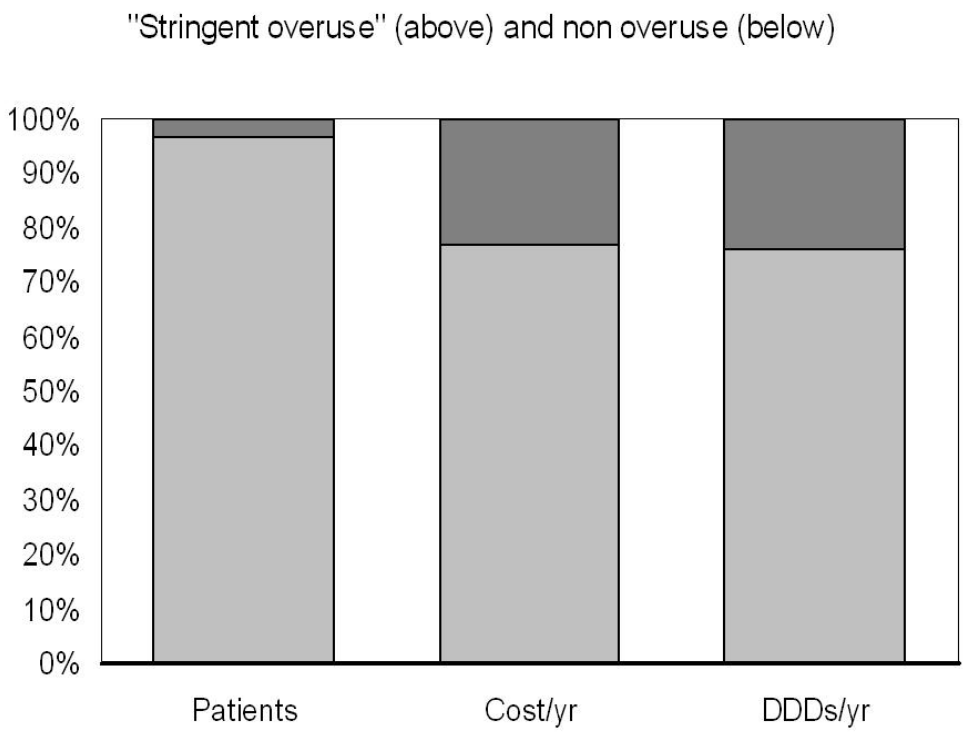
Figure 1. The part of patients with and without triptan overuse according to "IHS criteria", with the associated cost and drug use.



Percentage of patients with "IHS overuse", generated cost and DDDs (daily defined dose). On top the "IHS overuse" of ≥ 30 DDDs/qtr and below the non overusers. Source: GIP Database/ Health Care Insurance Board.

The costs of triptan-use and -overuse are shown in Figure 1 and 2. Total costs of triptan-use in 2005 were 29.7 million Euros, i.e. 349 Euros per triptan-user and 4.43 Euros per inhabitant. Patients overusing triptans accounted for 46% (IHS criteria) and 23% (stringent criteria) of the total costs, i.e. 1543 Euros per IHS-overuser and 2468 Euros per stringent-overuser.

Figure 2. The part of patients with and without triptan overuse according to "Stringent criteria", with the associated cost and drug use.



Percentage of patients with "Stringent overuse", generated cost and DDDs (daily defined dose). On top the "Stringent overuse" of ≥ 54 DDDs/qtr and below the non overusers. Source: GIP Database/ Health Care Insurance Board.

DISCUSSION

We analysed the use and overuse for all seven available triptans in the Dutch general population in the year 2005. We could make use of an unique national Health Care Insurance Board Database, which covered the medication use of 6.7 million people. Of these, 1.3% had used a triptan at least once in 2005 and 0.13% (10.4% of all triptan-users) was overusing triptans. Overusers accounted for almost half of the total costs for triptans. Remarkably, the level of overuse differed significantly per triptan. Users of rizatriptan, and possibly of frovatriptan and naratriptan, showed substantially lower levels of overuse. When patients use more than one triptan, the level of overuse is additional high: a doubling of levels of overuse compared to when the patient is only using one kind of triptan.

Table 5. Level of overuse for each triptan relative to sumatriptan.

	Total	**Non-overuse**		**Overuse**							
		< 30 DDD/qtr		**IHS criteria: ≥30 DDDs/qtr**		**IHS criteria: ≥30 DDDs/qtr**		**Stringent criteria* ≥54 DDDs/qtr**		**Stringent criteria* ≥54 DDDs/qtr**	
	N = 76,328	**n**	**(%)**	**n**	**(%)**	**Adjusted odds†**		**n**	**(%)**	**Adjusted odds†**	
Sumatriptan	41,352	35,798	(87)	5,554	(13)	1.00	(ref)	1,952	(5)	1.00	(ref)
Naratriptan	3,798	3,437	(91)	361	(10)	0.76	(0.68-0.85)	86	(2)	0.52	0.42-0.64
Zolmitriptan	4,983	4,397	(88)	586	(12)	0.97	(0.88-1.06)	134	(3)	0.63	0.53-0.75
Rizatriptan	25,796	24,770	(96)	1,026	(4)	0.34	(0.32-0.37)	182	(1)	0.17	0.15-0.20
Eletriptan	1,295	1,206	(93)	89	(7)	0.86	(0.72-1.02)	23	(2)	0.63	0.45-0.86
Almotriptan	1,455	1,289	(89)	166	(11)	1.49	(1.31-1.72)	37	(3)	0.95	0.73-1.22
Frovatriptan	957	940	(98)	17	(2)	0.26	(0.19-0.36)	2	(0)	0.08	0.03-0.22
>1 triptan§	5,536	4,491	(81)	1045	(19)	-#	-#	371	(7)	-#	-#

*Values are numbers (%). * 'Stringent overusers' are a subgroup of 'IHS overusers'. † Adjusted odds for duration of availability of the drug, by method of indirect standardisation. §When using more than one triptan, the adjusted odds can not be calculated (#) because of the variation in the duration of the availability of the triptan. Source: GIP Database/ Health Care Insurance Board.*

The results of the present study appear robust and representative because of the large number of patients included. We used an independent and unbiased nation-wide database with an accurate count of actual dispense of triptans at pharmacies, covering nearly half of the total population of The Netherlands. A potential limitation is that we couldn't measure the actual use of triptans by patients. It seems, however, very unlikely that with an average use of 210 DDDs in IHS overusers and of 420 DDDs in stringent overusers, many patients would not have used the dispensed medication.
With regard to these thresholds we can argue that overuse lies somewhere in between the two presented thresholds. The lower limit, the IHS criteria may give an overestimation, and the upper threshold, the stringent criteria, is probably an underestimation. With these stringent criteria, the existence of medication overuse headache is

evident. With the IHS criteria there is either overuse or eminent high risk on overuse. The results are in agreement with a smaller population-based study in Denmark. Here, 5% of sumatriptan-users used > 30 DDDs per month and were responsible for 38% of the total sumatriptan consumption and costs [26]. In two French studies, 25-30% of triptan users were overusers [27] and 12% became overusers (defined as ≥180 DDDs/yr) within one year from starting using triptans [28]. In an Italian study a much lower rate of overuse was found (3.2%), but this is probably due to a low overall use of triptans in this country [29].

One might argue that the prevalence of triptan overuse was overestimated given the nature of sickness fund-based databases. Patients included in such databases generally tend to come from relatively lower socio-economic classes, compared to patients with private health insurance. Low educational level is known to be associated with a higher risk of medication overuse [12,30].

Given the nature of our sickfund-based database, our population had a relatively lower socio-economic status. However, our population represents 65% of the Dutch population in 2005 and other studies in this database revealed that data from these patients are similar to those in the general population. [31,32]. We also compared our data with those of a smaller database of dispensed drugs in pharmacies, including all income classes. Those data were very similar to the one in the present study. In particular, there was no evidence for socio-economic class major difference in use of triptans.

In our analysis we calculated the average triptan consumption, namely in a timeframe of 12 months, using the criteria that are based on a 3-month period. In this way we were able to provide more stable and reliable estimates than for shorter periods, since use and overuse of acute antimigraine medication are known to fluctuate substantially [12]. Indeed, we found 9,120 IHS-overusers (30 DDDs or more) in the first 3-month period, 10,287 in the second trimester, 10,128 in the third and 11,088 in the final trimester; the average was 10,156 overusers. Of all overusers in the first quarter, only 63-65% was also overuser in at least one of the subsequent three trimesters.

The most striking finding of our study was that level of overuse differed among the triptans. In particular, use of frovatriptan, rizatriptan, and to a lesser degree naratriptan, was associated with remarkably lower proportions of overusers compared to the reference agent sumatriptan and the other triptans. Several confounding factors could potentially explain this finding and need to be discussed.

First, for practical reasons, we used the number of DDDs to define overuse. However, triptan overuse is in fact defined by the number of days on which at least one dose of a triptan is taken, irrespective of the total number of dosages per day or the amount of mg per dose. In 2001, the DDD for sumatriptan was changed from 100 mg to 50 mg (http://www.whocc.no/atcddd/) [24]. Thus, one tablet of 100 mg sumatriptan suddenly was equal to 2DDD. As a result, patients using 61-107 tablets of 100 mg per year were assigned as "IHS overusers" (122-214 DDDs/yr), without necessarily fulfilling the IHS criteria for triptan overuse (use of at least one dose on ≥ 120 days per year). This could have potentially biased the results against sumatriptan in these patients. However,

the risk of incorrectly assigning someone (this applies to each type of triptan) to overusers group is negligible when applying the stringent criteria (≥ 216 DDDs/yr). The relative degree of overuse in this group was very similar to that when using the less stringent IHS criteria, with the understanding that the differences with sumatriptan are magnified to some extent. Use of almotriptan, sumatriptan and zolmitriptan was in both groups clearly associated with the highest level of overuse and use of rizatriptan, frovatriptan and naratriptan was associated with the lowest level of overuse. Furthermore, from clinical experience we know that, for a variety of reasons, many patients divide 100 mg tablets into two of 50 mg, thereby doubling the actual number of doses used. Also for another reason the extent of any possible bias by an erroneous classification of the WHO-DDD is small; only 27.6% of all sumatriptan is delivered by pharmacies as 100mg tablets. Consequently, any possible bias by an erroneous classification of the WHO-DDD is small in relation to the difference we found. We, therefore, are confident that the applied approach provides a reliable estimate of the relative levels of overuse for the various triptans.

A second potential confounding factor is that patients with cluster headache may sometimes use very high quantities of subcutaneous sumatriptan to treat their attacks, without necessarily being an overuser [33,34]. This could have biased the results towards overuse of sumatriptan. However, use of the subcutaneous formulation of sumatriptan made up for only 8.8% of the total use of sumatriptan in the IHS-overuse group and for only 5.7% in the stringent-overuse group. This is less than in the non-overuse group (10.5%), making a major impact of overuse of subcutaneous sumatriptan unlikely. In other countries than the Netherlands Cluster headache patients are sometimes treated with high dosages of oral sumatriptan because of cost considerations. All triptans are carefully reimbursed in the Netherlands, so this is unlikely in present study.

A third potential bias we need to discuss is the difference in duration of availability of the various triptans (Table 1). This might have led to preferential use of the earlier available agents by the most disabled patients who are likely to have a higher level of overuse. Sumatriptan was the first available triptan (1991), but because of complicated reimbursement issues in the Netherlands, the oral formulation became fully reimbursed only in 1996. Sales for sumatriptan really started only then. Overuse before that time was very rare in the Netherlands[35] The other triptans were always fully reimbursed from , frovatriptan and naratriptan were marketed as "gentle" triptans, with fewer adverse events and a slower onset of action, best suited for milder migraine attacks [16]. Combined with their significantly lower 2- and 24-hour efficacy rates[16], this might well have led to a preferential use of frovatriptan and naratriptan by patients with milder migraines, which are known to be associated with a lower level of overuse. These considerations do not seem to apply to rizatriptan, whose user numbers were very high ((N=25,796 users and N=1,026 overusers) and whose 2- and 24-hour efficacy rates are among the highest of all triptans [16].

One can ask whether the package size of the triptans can explain the differences.

However, triptans are used in such large quantities that each prescription usually involves multiple packages.The package size of the various triptans varies. Nevertheless, we found no correlation between the size of the package and the association with overuse for the various triptans (data not shown)."
Whether the observed differences also reflect a true clinical benefit, can only be tested in prospective randomized clinical trials.
Overusers accounted for almost half of the total costs of triptans. These costs could be significantly reduced if physicians would better monitor prescriptions and would consider prophylactic treatment earlier in case of increasing headache frequency to prevent overuse. Once overuse is established, withdrawal of overused medication is the most appropriate therapy[36].
To our knowledge, this is the first extensive study reporting the prevalence of overuse of all currently available triptans in the general population. Although the overall prevalence of overuse was low, overuse accounted for a large health burden and a substantial proportion of total costs of migraine therapy. The level of overuse differs per triptan. Whether this reflects a true clinical benefit needs to be investigated in prospective studies.

GLOSSARY OF ABBREVIATIONS

- ATC: Anatomical Therapeutic Chemical classification, designed for drug utilization studies, developed and maintained by the WHO Collaborating Centre for Drug Statistics Methodology
- CVZ: Health Care Insurance Board; independent non-profit governing body in the Netherlands
- DDD: Defined Daily Dose, standardized dosage per day according to the WHO
- GIP database: Drug Information Project, database monitoring conditions in health insurance, owned by the CVZ
- IHS: International Headache Society, responsible for the International Classification of Headache Disorders (ICHD-2)
- MOH: Medication Overuse Headache
- TOH: Triptan Overuse Headache

References

1. Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. *Neurology* 1999;53(3):537-542.
2. Lipton RB, Scher AI, Kolodner K, Liberman J, Steiner TJ, Stewart WF. Migraine in the United States: epidemiology and patterns of health care use. *Neurology* 2002; 58(6):885-894.
3. Dodick DW, Silberstein SD. How clinicians can detect, prevent and treat medication overuse headache. *Cephalalgia* 2008;28(11):1207-1217.
4. Menken M, Munsat TL, Toole JF. The global burden of disease study: implications for neurology. *Arch Neurol* 2000;57(3):418-420.
5. Andlin-Sobocki P, Jonsson B, Wittchen HU, Olesen J. Cost of disorders of the brain in Europe. *Eur J Neurol* 2005;12 Suppl 11-27.
6. Ferrari MD. Migraine. *Lancet* 1998;351(9108):1043-1051.
7. Bigal ME, Lipton RB. Clinical course in migraine: conceptualizing migraine transformation. *Neurology* 2008;71(11):848-855.
8. Terwindt GM, Ferrari MD, Tijhuis M, Groenen SM, Picavet HS, Launer LJ. The impact of migraine on quality of life in the general population: the GEM study. *Neurology* 2000;55(5):624-629.
9. Lampl C, Buzath A, Yazdi K, Sandor PS. Ergot and triptan overuse in Austria--an evaluation of clinical data and cost. *Cephalalgia* 2002;22(10):807-811.
10. Kruit MC, van Buchem MA, Hofman PA, Bakkers JT, Terwindt GM, Ferrari MD, Launer LJ. Migraine as a risk factor for subclinical brain lesions. *JAMA* 2004; 291(4):427-434.
11. Kruit MC, Launer LJ, Ferrari MD, van Buchem MA. Infarcts in the posterior circulation territory in migraine. The population-based MRI CAMERA study. *Brain* 2005;128(Pt 9):2068-2077.
12. Wiendels NJ, Knuistingh Neven A, Rosendaal FR, Spinhoven P, Zitman FG, Assendelft WJJ, Ferrari MD. Chronic frequent headache in the general population: prevalence and associated factors. *Cephalalgia* 2006;26(12):1434-1442.
13. Silberstein SD, Olesen J, Bousser MG, Diener HC, Dodick D, First M, Goadsby PJ, Gobel H, Lainez MJ, Lance JW, Lipton RB, Nappi G, Sakai F, Schoenen J, Steiner TJ. The International Classification of Headache Disorders, 2nd Edition (ICHD-II)--revision of criteria for 8.2 Medication-overuse headache. *Cephalalgia* 2005;25 (6):460-465.
14. Diener HC, Limmroth V. Medication-overuse headache: a worldwide problem. *Lancet Neurol* 2004;3(8):475-483.
15. Katsarava Z, Fritsche G, Muessig M, Diener HC, Limmroth V. Clinical features of withdrawal headache following overuse of triptans and other headache drugs. *Neurology* 2001;57(9):1694-1698.
16. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 2001;358 (9294):1668-1675.

17. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. *Cephalalgia* 2002;22(8):633-658.
18. Goadsby PJ, Lipton RB, Ferrari MD. Migraine--current understanding and treatment. *N Engl J Med* 2002;346(4):257-270.
19. Limmroth V, Katsarava Z, Fritsche G, Przywara S, Diener HC. Features of medication overuse headache following overuse of different acute headache drugs. *Neurology* 2002;59(7):1011-1014.
20. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. *Headache* 2008;48(8):1157-1168.
21. Ferrari MD. Should we advise patients to treat migraine attacks early? *Cephalalgia* 2004;24(11):915-917.
22. Guitera V, Munoz P, Castillo J, Pascual J. Quality of life in chronic daily headache: A study in a general population. *Neurology* 2002;58(7):1062-1065.
23. Wiendels NJ, van Haestregt A, Knuistingh Neven A, Spinhoven P, Zitman FG, Assendelft WJJ, Ferrari MD. Chronic frequent headache in the general population: comorbidity and quality of life. *Cephalalgia* 2006;26(12):1443-1450.
24. World Health Organisation, Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment. 1998. Oslo.
25. Wammes-van der Heijden EA, Rahimtoola H, Leufkens HG, Tijssen CC, Egberts AC. Risk of ischemic complications related to the intensity of triptan and ergotamine use. *Neurology* 2006;67(7):1128-1134.
26. Gaist D. Use and overuse of sumatriptan. Pharmacoepidemiological studies based on prescription register and interview data. *Cephalalgia* 1999;19(8):735-761.
27. Perearnau P, Vuillemet F, Schick J, Weill G. [Patterns of prescription and usage of triptans in Alsace (France): misuse is frequent and avoidable]. *Rev Neurol (Paris)* 2006;162(3):347-357.
28. Lugardon S, Roussel H, Sciortino V, Montastruc JL, Lapeyre-Mestre M. Triptan use and risk of cardiovascular events: a nested-case-control study from the French health system database. *Eur J Clin Pharmacol* 2007;63(8):801-807.
29. Pavone E, Banfi R, Vaiani M, Panconesi A. Patterns of triptans use: a study based on the records of a community pharmaceutical department. *Cephalalgia* 2007.
30. Hagen K, Vatten L, Stovner LJ, Zwart JA, Krokstad S, Bovim G. Low socio-economic status is associated with increased risk of frequent headache: a prospective study of 22718 adults in Norway. *Cephalalgia* 2002;22(8):672-679.
31. Langendam MW, Hooijkaas C, Piepenbrink JF. [The increase in the use of drug treatment for diabetes mellitus in the Netherlands, 1998-2003] *Ned Tijdschr Geneeskd* 2006;150(25):1396-1401.
32. Akkerman AE, Kuyvenhoven MM, Verheij TJ, van DL. Antibiotics in Dutch general practice: nationwide electronic GP database and national reimbursement rates. *Pharmacoepidemiol Drug Saf* 2008;17(4):378-383.

33. Ekbom K, Waldenlind E, Cole J, Pilgrim A, Kirkham A. Sumatriptan in chronic cluster headache: results of continuous treatment for eleven months. *Cephalalgia* 1992;12(4):254-256.
34. Dahlof C, Ekbom K, Persson L. Clinical experiences from Sweden on the use of subcutaneously administered sumatriptan in migraine and cluster headache. *Arch Neurol* 1994;51(12):1256-1261.
35. Visser WH, de Vriend RH, Jaspers MW, Ferrari MD. Sumatriptan in clinical practice: a 2-year review of 453 migraine patients. *Neurology* 1996;47(1):46-51.
36. Diener HC, Limmroth V. Medication-overuse headache: a worldwide problem. *Lancet Neurol* 2004;3(8):475-483.

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.

References

1. Dekker F, van Duyn NP, Ongering JEP, Bartelink MEL, Boelman L, Burgers J, Bouma M, Kurver M. NHG-Standaard Hoofdpijn (derde herziening). *Huisarts en Wetenschap* 2014;57(1):2-21.
2. Yu J, Smith KJ, Brixner DI. Cost effectiveness of pharmacotherapy for the prevention of migraine: a Markov model application. *CNS Drugs* 2010;24(8):695-712.
3. Smelt AF, Blom JW, Dekker F, van den Akker ME, Knuistingh NA, Zitman FG, Ferrari MD, Assendelft P. A proactive approach to migraine in primary care: a pragmatic randomized controlled trial. *CMAJ* 2012;184(4):E224-E231.
4. Cevoli S, D'Amico D, Martelletti P, Valguarnera F, Del BE, De SR, Sarchielli P, Narbone M, Testa L, Genco S, Bussone G, Cortelli P. Underdiagnosis and undertreatment of migraine in Italy: a survey of patients attending for the first time 10 headache centres. *Cephalalgia* 2009;29(12):1285-1293.
5. Diamond S, Bigal ME, Silberstein S, Loder E, Reed M, Lipton RB. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention study. *Headache* 2007;47 (3):355-363.
6. Lafata JE, Tunceli O, Cerghet M, Sharma KP, Lipton RB. The use of migraine preventive medications among patients with and without migraine headaches. *Cephalalgia* 2010;30(1):97-104.
7. Lipton RB, Scher AI, Kolodner K, Liberman J, Steiner TJ, Stewart WF. Migraine in the United States: epidemiology and patterns of health care use. *Neurology* 2002;58 (6):885-894.
8. Lipton RB, Bigal ME. Ten lessons on the epidemiology of migraine. *Headache* 2007; 47 Suppl 1S2-S9.

9. Lucas C, Auray JP, Gaudin AF, Dartigues JF, Duru G, Henry P, Lanteri-Minet M, Pradalier A, Chazot G, El Hasnaoui A. Use and misuse of triptans in France: data from the GRIM2000 population survey *Cephalalgia* 2004;24(3):197-205.
10. Rahimtoola H, Buurma H, Tijssen CC, Leufkens HG, Egberts AC. Incidence and determinants of migraine prophylactic medication in the Netherlands. *Eur J Clin Pharmacol* 2002;58(2):149-155.
11. Rahimtoola H, Buurma H, Tijssen CC, Leufkens HG, Egberts AC. Migraine prophylactic medication usage patterns in The Netherlands. *Cephalalgia* 2003;23(4):293-301.
12. Valade D, Lanteri-Minet M, Radat F, Mekies C, Lucas C, Vives E, Joubert JM, Geraud G. Clinical determinants of migraine preventive treatment: contribution of SMILE, an observational survey of primary care migraine management in France. *Cephalalgia* 2010;30(10):1207-1213.
13. Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. *Neurology* 1999;53(3):537-542.
14. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 2001;358(9294):1668-1675.
15. Lipton RB, Bigal ME, Goadsby PJ. Double-blind clinical trials of oral triptans vs other classes of acute migraine medication - a review. *Cephalalgia* 2004;24(5):321-332.
16. Dodick DW, Sandrini G, Williams P. Use of the sustained pain-free plus no adverse events endpoint in clinical trials of triptans in acute migraine. *CNS Drugs* 2007;21(1):73-82.
17. Tfelt-Hansen P. Is sustained pain freedom and no adverse events a clinically relevant endpoint in acute migraine treatment? *Cephalalgia* 2011.
18. Tfelt-Hansen P, Block G, Dahlof C, Diener HC, Ferrari MD, Goadsby PJ, Guidetti V, Jones B, Lipton RB, Massiou H, Meinert C, Sandrini G, Steiner T, Winter PB. Guidelines for controlled trials of drugs in migraine: second edition. *Cephalalgia* 2000;20(9):765-786.
19. Tfelt-Hansen P, Pascual J, Ramadan N, Dahlof C, D'Amico D, Diener HC, Hansen JM, Lanteri-Minet M, Loder E, McCrory D, Plancade S, Schwedt T. Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators. *Cephalalgia* 2012;32(1):6-38.
20. Diez FI, Straube A, Zanchin G. Patient preference in migraine therapy. A randomized, open-label, crossover clinical trial of acute treatment of migraine with oral almotriptan and rizatriptan. *J Neurol* 2007;254(2):242-249.
21. Lainez MJ, Evers S, Kinge E, Allais G, Allen C, Rao NA, Massaad R, Lis K. Preference for rizatriptan 10-mg wafer vs. eletriptan 40-mg tablet for acute treatment of migraine. *Cephalalgia* 2006;26(3):246-256.

22. Loder E, Brandes JL, Silberstein S, Skobieranda F, Bohidar N, Wang L, Boyle D, Kolodny A, Guerra F, Santanello N, Johnson-Pratt L. Preference comparison of rizatriptan ODT 10-mg and sumatriptan 50-mg tablet in migraine. *Headache* 2001;41(8):745-753.
23. Pascual J, Munoz R., Leira R. An open preference study with sumatriptan 50 mg and zolmitriptan 2,5 mg in 100 migraine patients. *Cephalalgia* 2001;21(6):680-684.
24. Savi L, Omboni S, Lisotto C, Zanchin G, Ferrari MD, Zava D, Pinessi L. A double-blind, randomized, multicenter, Italian study of frovatriptan versus rizatriptan for the acute treatment of migraine. *J Headache Pain* 2010.
25. Schoenen J, Pascual J, Rasmussen S, Sun W, Sikes C, Hettiarachchi J. Patient preference for eletriptan 80 mg versus subcutaneous sumatriptan 6 mg: results of a crossover study in patients who have recently used subcutaneous sumatriptan. *Eur J Neurol* 2005;12(2):108-117.
26. Tullo V, Allais G, Ferrari MD, Curone M, Mea E, Omboni S, Benedetto C, Zava D, Bussone G. Frovatriptan versus zolmitriptan for the acute treatment of migraine: a double-blind, randomized, multicenter, Italian study. *Neurol Sci* 2010;31 Suppl 1S51-S54.

CHAPTER 11

Summary

SUMMARY

Chapter 1 provides the general introduction of this thesis. Headache is a problem for which patients occasionally attend a GP. Only a small proportion of people with headache visit the GP, although there is often a high disease burden.
This thesis is mainly about migraine, a disabling headache disorder which is characterized by unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.
Addressed in this thesis are three elements of migraine. Firstly, the preventive treatment of migraine, which is often undervalued and not frequently used. Secondly, attack treatment of migraine. In the third and last part follows attention for medication overuse headache.

Part 1 Preventive therapy for migraine

In **chapter 2** we present a narrative 'umbrella' review on the preventive treatment of migraine, based on a search in Medline and Embase, including an overview of indications for preventive treatment mentioned in guidelines.
According to most sources, patients with an average of two or more attacks per month, when using attack treatment, are eligible for preventive treatment. This decision is also based on the (average) duration of attack, severity of attacks, and the response to attack treatment. In the present guidelines there is only limited involvement of patients, whereas this is an essential condition for treatment continuation and success. Before starting prevention, the average attack frequency should be determined, preferably using a headache diary for 2-3 months, because of the highly variable frequency of migraine attacks. None of the currently available preventive medications (such as beta-blockers, sodium valproate, topiramate and candesartan) are specific for migraine. To obtain a good outcome, preventive treatment should be titrated up step-by-step to the highest possible dose without side effects.
According to literature, for about 50% of patients with preventive treatment, a 50% reduction in attack frequency can be achieved and the remaining attacks tend to become less severe.
In conclusion, preventive treatment of migraine is a worthwhile intervention in primary care, for which beta-blockers and anti-epileptic drugs can be used. For many patients preventive treatment will contribute to a greater reduction in disease burden than can be established with attack treatment alone.

In **chapter 3** we present an insight into the actual preventive treatment of migraine in general practice in the Netherlands. We present an observational population-based study, assessing current use, previous use, duration and course of preventive treatment of migraine in Dutch general practice conducted between 1997 and 2007 in the

Interdisciplinary Processing of Clinical Information (IPCI) database, a GP research database. All prevalent and incident migraine patients (N = 7367) were included.
About 13% of all migraine patients currently use preventive therapy. 44% of all migraine patients started with preventive therapy in the study period. Therefore this large primary care database reveals, that a limited number of patients are current users of preventive treatment, but many patients have prior use.
Of those starting with preventive treatment 56% still used it after 9 months, meaning that once preventive therapy is started the therapy adherence is mainly good.
There was a long delay between migraine diagnosis and start of preventive treatment. Thus it often takes a long time before a patient is willing to embrace preventive treatment.
When preventive treatment is applied, usually there is only one effort carried out with one type of medication. Therefore more attempts with various medications per patient can be made.

In **chapter 4** we present a focus group study in Dutch general practice on the preventive treatment of migraine by exploring the opinions of GPs. Four focus groups (6 GPs each) were formed. GPs were purposively sampled to acquire a range of participants, reflecting the more general GP population.
Six themes emerged: GPs general views on migraine, reluctance to start preventive therapy, initiating preventive medication, taking the initiative for preventive therapy, patient or physician, starting and managing preventive therapy, and the expectations of the benefit of preventive therapy. GPs were aware of the functional impact of migraine and the benefits of preventive therapy. However, some were hesitant to start prescribing prophylaxis due to doubts about effectiveness, potential side effects and the risk of developing drug dependency. GPs' decisions were often based on considerations other than those presented in national guidelines, e.g. the patient's need to control their own problem. Many GPs consider the responsibility for initiating preventive therapy to lie with the patient.
We conclude that various considerations hamper GPs from managing migraine with preventive medication, and various patient-related concerns cause GPs to deviate from national headache guidelines.

In **chapter 5** a qualitative study is presented on the patient's view on the preventive treatment of migraine. This qualitative study explores the opinions, motives and expectations of patients regarding preventive migraine therapy. Three focus group meetings were held with 6-7 migraine patients per group (2 female and 1 male group, total 20 patients) recruited from urban and rural Dutch general practices. All participants were migraine patients according to the IHS-criteria (International Headache Society); 9 had experience with prophylactic medication. The focus group meetings were analysed using a general thematic analysis.
For patients several distinguished factors count when making a decision on preven-

tive treatment. The decision of a patient on preventive medication depends on experience and perspectives, grouped into five categories, namely the context of being active or passive in taking the initiative to start prophylaxis; assessing the advantages and disadvantages of prophylaxis; satisfaction with current attack migraine treatment; the relationship with the physician and the feeling to be heard; and previous steps taken to prevent migraine.
In addition to the functional impact of migraine, the decision to start prophylaxis is based on a complex of considerations from the patient's perspective (e.g. perceived burden of migraine, expected benefits or disadvantages, interaction with relatives, colleagues and physician). Therefore**,** when advising migraine patients about prophylaxis, their opinions should be taken into account. Patients need to be open to advice and information and prophylaxis has to be offered at an appropriate moment in the course of migraine.

In **chapter 6** a cross-sectional questionnaire study on migraine patients' acceptance or rejection of preventive treatment is presented. Most patients with two or more migraine attacks per month (indication for preventive treatment) do not use preventive medication. We investigated how many patients use preventive treatment or would like to use it, and which aspects of migraine contribute to the choice whether to use preventive treatment treatment.
In three general practices, patients were selected who were diagnosed with migraine or had prescriptions for migraine medication. A questionnaire was sent to 283 patients and completed by 166 patients (58.7%), of whom 15 were excluded. A total of 129 females and 22 males were included (median age 41 years). Most patients had two or more attacks per month (66.2%). Fifty-five per cent of patients with two or more attacks per month wanted to use prophylaxis; only 8% actually used this treatment. The migraine frequency contributed most to the acceptation of preventive therapy. To a lesser extend the measured impact of migraine contributed to the acceptation of preventive therapy (measured with the HIT-6-score, a validated impact score). Patients who had seen their GP in the previous year were more likely to report an interest in preventive therapy.
In conclusion: interest in preventive therapy can be explained by an increased concern about migraine symptoms and the findings suggest that physicians can play a more active role in optimising migraine therapy.

Part 2 Attack treatment of migraine

In **chapter 7** we present a patient preference study. In this randomized, crossover, blinded rizatriptan-ibuprofen multi-migraine attack trial we used a novel patient centred endpoint, the 'patient preference'. After the first three attacks treated with either a triptan or NSAID, the patients were asked to treat another three attacks with the opposite medication. The double-dummy technique ensured that neither patient

nor researcher could distinguish the verum from placebo and each patient still had active treatment.
29 triptan-naive patients expressed a quantified preference (0-5) after treating three attacks with rizatriptan 10 mg and three with ibuprofen 400 mg. Ten (35%) patients expressed strong preference for rizatriptan and six (21%) for ibuprofen, which was not a significant difference. Thirteen (45%) had no or only a moderate preference. Mean overall preference (on a 10 point scale in cm) was 0.62 cm in favour of rizatriptan. Patients with high migraine-specific baseline disability on the MIDAS scale had stronger preference for rizatriptan.
Most patients had a clear preference for one of both treatments, which was correlated only moderately to the usually reported "two-hour pain free responses".
The two-hour pain free rate after treating a single migraine attack in a parallel-group study design is the recommended primary endpoint to establish acute antimigraine efficacy versus placebo. However, when comparing established treatments, the clinical validity of this approach seems limited. Multi-attack, crossover, patient-preference trials, may better detect clinically meaningful differences between established treatments.

The design of the study in **chapter 8** was very similar to the study in chapter 7. We performed a randomized, blinded, crossover study with double-dummy medication between a triptan and a painkiller. Primary outcome measure was direction and strength of patient preference (10 point scale).
31 triptan-naive participants were randomised to naratriptan 2.5 mg or paracetamol 1000 mg with a crossover after three attacks. 28 participants were able to make a preference assessment. Preference score was 0.17 in favour of naratriptan. Nine (32%) participants strongly preferred naratriptan, and also nine (32%) paracetamol. When looking at all the preferences 16 (57%) participants preferred naratriptan and 11 (42.1%) preferred paracetamol. The two-hour pain-free attack rates were 15/76 (20%; naratriptan) and 9/74 (12%; paracetamol) for all attacks ($p = 0.25$). When treating the first attack use of naratriptan has a higher pain-free rate. Correlation of two-hour pain-free response with preference was poor ($r = 0.27$).
The preference from patients as a group for either naratriptan or paracetamol in the acute attack treatment of migraine is similar, but individual patients have a strong preference for one or the other, with no relation to attack severity or migraine impact. Multi-attack, crossover, patient-preference trials better detect clinically meaningful differences between established treatments.

Part 3 Medication overuse headache

In **chapter 9** a large observational analysis of the Dutch Health Care Insurance Board Database for the year 2005 is presented, which included prescriptions for 6.7 million people (46% of the total Dutch population). We assessed the prevalence, demograph-

ics, risk factors, and costs of triptan-overuse, defined as more than 30 (IHS Criteria) or 54 (Stringent Criteria) “defined daily doses” (DDD) per 3 months.

Triptans were used by 85,172 (1.3%) people; 8,844 (10.4%) were IHS-overusers and 2,787 (3.3%) were ‘stringent’-overusers.
The triptan-specific odds ratios adjusted for durations of availability for the rate of IHS-overuse, compared to sumatriptan, were: 0.26 (95% CI 0.19–0.36) for frovatriptan, 0.34 (95% CI 0.32–0.37) for rizatriptan, 0.76 (95% CI 0.68–0.85) for naratriptan, 0.86 995% CI 0.72–1.02) for eletriptan, 0.97 (95% CI 0.88–1.06) for zolmitriptan and 1.49 (95% CI 1.31–1.72) for almotriptan (an OR < 1 means a higher lower probability on overuse and an OR > 1 indicates a smaller higher probability of overuse). Costs for overuse were 29.7 million Euros per year for the Netherlands. The IHS criteria overusers used 46% of the total expenditure on triptans, and for stringent overusers this was 23% of the total expenditure. Users of frovatriptan, rizatriptan and naratriptan had a lower level of overuse.
We conclude that overuse of triptans, resulting in chronic headache, occur frequent and creates unnecessary high cost.

In the general discussion in **chapter 10** findings and conclusions from the various chapters of this thesis are discussed.
The common thread through all parts of this thesis is what patients want in migraine and which interventions do have their preference: patient’s preference in migraine.

CHAPTER 12

Samenvatting

SAMENVATTING

Hoofdstuk 1 bevat de algemene introductie van dit proefschrift. Hoofdpijn is een probleem waarvoor patiënten af en toe een huisarts raadplegen. Slechts een klein deel van de mensen met hoofdpijn bezoekt de huisarts, maar vaak is er een hoge ziektelast.
Dit proefschrift gaat vooral over migraine, een invaliderende hoofdpijnsoort, gekenmerkt door eenzijdige locatie, bonzend, matige of ernstige intensiteit, verergering door fysieke activiteit en waarbij misselijkheid en / of fotofobie en fonofobie voorkomt.
In dit proefschrift komen drie elementen van migraine aan bod. Als eerste de preventieve behandeling van migraine, die vaak wordt ondergewaardeerd en weinig gebruikt. Als tweede aanvalsbehandeling van migraine. In het derde en laatste deel volgt aandacht voor medicatieovergebruikshoofdpijn.

Deel 1 Preventieve therapie voor migraine

In **hoofdstuk 2** presenteren we een narratieve 'paraplu' review over de preventieve behandeling van migraine, op basis van een zoekacties in Medline en Embase. Er wordt ook een overzicht gegeven van de aanbevelingen in richtlijnen ten aanzien van preventieve behandeling.
Volgens de meeste richtlijnen komen patiënten met een gemiddelde van twee of meer aanvallen per maand in aanmerking voor preventieve behandeling. De beslissing om te starten met preventieve behandeling wordt af en toe ook gebaseerd op de (gemiddelde) duur van de aanval, de ernst van de aanvallen, en de respons op de behandeling. In deze richtlijnen is er slechts beperkte betrokkenheid van de patiënten, terwijl dit een essentiële voorwaarde voor de continuïteit en van de behandeling en daarmee het succes er van.
Voordat preventie medicatie wordt gestart, dient de gemiddelde aanval frequentie te worden bepaald, bij voorkeur met een hoofdpijndagboek gedurende 2-3 maanden, vanwege de zeer variabele frequentie van migraineaanvallen. Geen van de momenteel beschikbare preventieve medicijnen (zoals bètablokkers, natriumvalproaat, topiramaat en candesartan) zijn specifiek voor migraine. Om een goed resultaat te krijgen, moet preventieve behandeling stap voor stap worden getitreerd tot aan de hoogst mogelijke dosis zonder bijwerkingen.
Volgens de literatuur wordt bij ongeveer 50% van de patiënten door preventieve behandeling een vermindering van 50% in de aanval frequentie bereikt en worden de resterende aanvallen meestal minder ernstig.
Concluderend is de preventieve behandeling van migraine een waardevolle interventie in de eerste lijn, waarbij bètablokkers en anti-epileptica worden gebruikt. Voor veel patiënten kan preventieve behandeling bijdragen aan een grotere vermindering van ziektelast dan kunnen alleen met aanval behandeling bereikt kan worden.

In **hoofdstuk 3** presenteren we een inzage in de feitelijk toegepaste preventieve behandeling van migraine in de huisartsenpraktijk in Nederland. We presenteren in een observationele studie het huidige gebruik, eerder gebruik, duur en het verloop van de preventieve behandeling van migraine in de Nederlandse huisartsenpraktijk, zoals het heeft plaats gevonden tussen 1997 en 2007. We gebruikten de Interdisciplinary Processing of Clinical Information (IPCI)-database, een huisarts research database. Alle prevalente en incidente migrainepatiënten (N = 7367) werden opgenomen.
Ongeveer 13% van alle migrainepatiënten maakt op enig moment gebruik van preventieve therapie. 44% van alle migrainepatiënten zijn in de onderzoeksperiode gestart met preventieve therapie. Uit deze grote eerstelijns database blijkt dat er op enig moment maar een beperkt aantal patiënten actieve gebruikers zijn, maar veel patiënten er wel ervaring mee hebben.
Diegene die starten met preventieve behandeling gebruikt 56% het nog steeds na 9 maanden, wat betekent dat wanneer preventieve therapie wordt gestart de therapietrouw is meestal goed is.
Er was een lang tijdsverloop tussen de migrainediagnose en de start van de preventieve behandeling. Het blijkt dus vaak lang te duren voordat een patiënt bereid is om tot preventieve behandeling.
Als preventieve behandeling wordt toegepast, wordt er meestal slechts één poging met één soort medicatie uitgevoerd. Het verdient aanbeveling om vaker profylaxe te proberen met verschillende medicijnen.

In **hoofdstuk 4** presenteren we een focusgroepstudie in de Nederlandse huisartspraktijk over de preventieve behandeling van migraine door onderzoek naar de meningen van huisartsen. Vier focusgroepen (elk 6 huisartsen) werden gevormd. Bij de huisartsen werd een brede steekproef genomen met een diversiteit aan deelnemers, met als doel een goede weergave van meningen onder huisartsen in het algemeen.
Zes thema's kwamen naar voren: algemene opvattingen van huisartsen over migraine, terughoudendheid om preventieve therapie te starten, het nemen van het initiatief voor preventieve therapie door patiënt of huisarts, het starten en uitvoeren van preventieve therapie, en de verwachtingen over van het nut van preventieve therapie. Huisartsen waren goed op de hoogte van de functionele impact van migraine en de voordelen van preventieve therapie. Echter, sommige waren terughoudend om te beginnen met het voorschrijven van preventie vanwege twijfels over de effectiviteit, de mogelijke bijwerkingen en het risico op het ontwikkelen afhankelijkheid. Beslissingen van huisartsen werden vaak op basis van andere overwegingen genomen, dan die welke in de nationale richtlijnen staan. Bijvoorbeeld zoals in welke mate patiënten voor zich op kunnen komen. Soms vinden huisartsen dat de verantwoordelijkheid voor het initiëren van preventieve therapie bij de patiënt ligt.
We concluderen dat verschillende overwegingen de huisartsen belemmeren om migraine middels preventieve medicatie aan te pakken, en diverse patiënt-gerelateerde aspecten zorgen er voor dat de huisarts afwijkt van de landelijke richtlijnen.

In **hoofdstuk 5** wordt een kwalitatieve studie gepresenteerd over de meningen van patiënten over de preventieve behandeling van migraine. Deze studie verkent de meningen, motieven en verwachtingen van patiënten ten aanzien van preventieve behandeling van migraine. Drie focusgroepbijeenkomsten vonden plaats met 6-7 migrainepatiënten per groep (twee vrouwen- en een mannengroep, totaal 20 patiënten) gerekruteerd uit stedelijke en landelijke Nederlandse huisartspraktijken. Alle deelnemers waren migrainepatiënten volgens de IHS-criteria (International Headache Society); negen hadden ervaring met preventieve medicatie. De focusgroepen werden geanalyseerd met behulp van thematische analyse.
Voor patiënten tellen verschillende factoren mee bij het maken van een beslissing over preventieve behandeling. De beslissing van een patiënt over preventieve medicatie is afhankelijk van eerdere ervaringen en vooruitzichten, gegroepeerd in vijf categorieën: het actief of passief zijn in het nemen van het initiatief om preventie te beginnen, het beoordelen van de voor-en nadelen van preventie, de tevredenheid met de huidige aanvalsbehandeling van migraine, de relatie met de arts en het gevoel te worden gehoord, en voorafgaande stappen om migraine te voorkomen.
Naast de functionele gevolgen van migraine is de beslissing om profylaxe te beginnen op basis van een complex van overwegingen vanuit de patiënt (bijv. ervaren last van migraine, verwachte voordelen en nadelen, interactie met familieleden, collega's en arts).
Naast de functionele impact van migraine wordt de beslissing om met preventie te beginnen genomen op basis van een complex aan overwegingen vanuit de patiënt (bijv. ervaren last van migraine, verwachte voor- en nadelen en interactie met familieleden, collega's en huisarts).
Daarom moet bij het adviseren van migrainepatiënten over preventie rekening worden gehouden met hun mening. Patiënten moeten openstaan voor advies en informatie en preventie moet worden aangeboden op het juiste moment in het beloop van migraine.

In **hoofdstuk 6** wordt een vragenlijststudie over aanvaarding of verwerping van preventieve behandeling van migraine onder een dwarsdoorsnede van patiënten in de huisartspraktijk gepresenteerd. De meeste patiënten met twee of meer migraineaanvallen per maand (indicatie voor profylaxe) gebruiken geen preventieve medicatie. We hebben onderzocht hoeveel patiënten preventieve medicatie gebruiken of deze willen gaan gebruiken, en welke aspecten van migraine bijdragen aan de keuze voor preventieve behandeling.
In drie huisartspraktijken werden patiënten geselecteerd, met de diagnose migraine of die recepten voor migrainemedicatie hadden gekregen. Er werd een vragenlijst gestuurd naar 283 patiënten en ingevuld door 166 patiënten (58,7%), van wie er 15 werden uitgesloten. In totaal 129 vrouwen en 22 mannen antwoordden (gemiddelde leeftijd 41 jaar). De meeste patiënten hadden twee of meer aanvallen per maand (66,2%). Vijfenvijftig procent van de patiënten met twee of meer aanvallen per maand wilde preventieve behandeling, slechts 8% gebruikte daadwerkelijk deze behandeling. De

migrainefrequentie draagt het meest bij aan de acceptatie van preventieve therapie. In mindere mate speelt de gemeten impact van migraine een rol in de acceptatie van preventieve therapie (gemeten met de HIT-6-score, een gevalideerde impactscore). Patiënten die de huisarts in het voorgaande jaar hadden bezocht, rapporteerden vaker belangstelling voor preventieve behandeling.
Concluderend: interesse in preventieve therapie kan worden verklaard door een toegenomen bezorgdheid over migraine symptomen en de bevindingen suggereren dat artsen een meer actieve rol in het optimaliseren van migraine therapie kunnen spelen.

Deel 2 Aanvalsbehandeling van migraine

In **hoofdstuk 7** presenteren we een 'patient preferentie' studie. In deze gerandomiseerde, cross-over, geblindeerde rizatriptan-ibuprofen multi-migraineaanval studie gebruikten we een nieuwe patiëntgerichte eindmaat, de 'voorkeur van de patiënt'. Na eerst drie aanvallen met of een triptaan of NSAID te hebben behandeld werden de patiënten gevraagd nog eens drie aanvallen met het andere medicament te behandelen. De dubbel-dummy techniek zorgde ervoor dat noch de patiënt noch onderzoeker de verum kon onderscheiden van de placebo en elke patiënt nog steeds (gedeeltelijk) actieve behandeling kreeg.
29 triptaan-naïeve patiënten uitten een kwantitatieve voorkeur (0-5) na de behandeling van drie aanvallen met rizatriptan 10 mg en drie aanvallen met ibuprofen 400 mg. Tien (35%) van de patiënten hadden een sterke voorkeur voor rizatriptan en zes (21%) voor ibuprofen, hetgeen geen significant verschil was. Dertien (45%) hadden geen of slechts een matige voorkeur. De gemiddelde algemene voorkeur (op een 10-puntsschaal in cm) was 0,62 cm in het voordeel van rizatriptan. Patiënten met hoge MIDAS-score (grotere impact van migraine) hadden een sterkere voorkeur voor rizatriptan.
De meeste patiënten hadden een duidelijke voorkeur voor een van beide behandelingen. De voorkeur correleerde slechts matig met de meestal gebruikte "2-uur pijnvrij score".
Multi-aanval, cross-over, 'patient-preferentie' studies zijn zeer goed in staat om klinisch relevante verschillen tussen bestaande behandelingen te detecteren.

Het design van de studie in **hoofdstuk 8** was vergelijkbaar met de studie in hoofdstuk 7. We voerden een gerandomiseerde, geblindeerde, cross-over studie met dubbeldummy medicatie uit tussen een triptaan en een pijnstiller. Primaire uitkomstmaat was de richting en de sterkte van voorkeur van de patiënt (10 puntenschaal).
31 triptaan-naïeve deelnemers werden gerandomiseerd in een groep die drie aanvallen behandelde met 2,5 mg naratriptan en een groep die drie aanvallen behandelde met paracetamol 1000 mg, met daarna een cross-over. 28 deelnemers waren in staat om een voorkeur uit te spreken. De voorkeur score was 0.17 in het voordeel van naratriptan. Negen (32%) deelnemers hadden een sterke voorkeur naratriptan en ook

negen (32%) voor paracetamol. Wanneer we kijken naar alle voorkeuren toonden 16 (57%) deelnemers de voorkeur voor naratriptan en 11 (42,1%) de voorkeur voor paracetamol. De 2-uur pijnvrij aanval ratio's waren 15/76 (20%; naratriptan) en 9/74 (12%; paracetamol) voor alle aanvallen (p = 0.25). Bij de behandeling van de eerste aanval resulteerde gebruik van naratriptan in een hogere mate van pijnvrij na 2 uur. Correlatie van 2-uur pijnvrij respons met 'patient-preference' was slecht (r = 0,27).
De voorkeur van patiënten als groep voor naratriptan of paracetamol bij de behandeling van de acute migraineaanval is even groot, maar de individuele patiënt heeft een sterke voorkeur voor het ene of het andere. Deze voorkeur wordt niet bepaald door de ernst van de migraineaanval of de impact van migraine. Ook hier is de multi-aanval, cross-over, 'patient-preferentie' trial beter in staat om klinisch relevante verschillen tussen bestaande behandelingen te detecteren.

Deel 3 Medicatieovergebruikshoofdpijn

In **hoofdstuk 9** is een grote observationele analyse uitgevoerd met gebruik van de GIPdatabank van het College voor Zorgverzekeringen, met gegevens uit het jaar 2005. De databank bevat voorschriften van 6,7 miljoen mensen (46% van de totale Nederlandse bevolking). Wij hebben de prevalentie, demografie, risicofactoren, en de kosten van triptaan overgebruik, gedefinieerd als meer dan 30 ('IHS'-criteria) of 54 ('strikte'-criteria) "defined daily doses" (DDD) per 3 maanden.
Triptanen werden gebruikt door 85.172 (1,3%) mensen, 8.844 (10,4%) waren 'IHS'-overgebruikers en 2787 (3,3%) waren 'strikte'-overgebruikers.
De triptaan-specifieke odds ratio's gecorrigeerd voor duur van beschikbaarheid, voor de mate van 'IHS'-overgebruik, vergeleken met sumatriptan, waren: 0.26 (95% BI 0,19-0,36) voor frovatriptan, 0.34 (95% BI 0,32-0,37) voor rizatriptan, 0.76 (95% BI 0,68-0,85) voor naratriptan, 0,86 (95% CI 0,72-1,02) voor eletriptan, 0.97 (95% BI 0,88-1,06) voor zolmitriptan en 1.49 (95% BI 1,31-1,72) voor almotriptan (een OR <1 betekent een lagere kans op overgebruik en een OR> 1 geeft een hogere waarschijnlijkheid van overgebruik). Kosten voor overmatig gebruik waren 29,7 miljoen euro per jaar voor Nederland. De 'IHS'-criteria overgebruikers gebruikten 46% van de totale uitgaven voor triptanen en voor 'strikte '`overgebruikers was dit 23% van de totale uitgaven. Gebruikers van frovatriptan, rizatriptan en naratriptan hadden een lager overgebruik.
We concluderen dat overgebruik van triptanen, wat resulteert in chronische hoofdpijn, vaak voorkomt en onnodig hoge kosten veroorzaakt.

In de algemene discussie in **hoofdstuk 10** worden de bevindingen en conclusies uit de verschillende hoofdstukken van dit proefschrift besproken.
De rode draad door alle onderdelen van dit proefschrift is wat patiënten willen bij migraine en welke interventies hun voorkeur hebben: 'patient preference in migraine'.

Dankwoord

Na een aantal jaren werk ligt er nu dan een proefschrift, dat slechts een paar summiere vragen over hoofdpijn beantwoordt. Gelukkig wel op een voor huisartsen belangrijk terrein. Nu is het dan zover om alle mensen te bedanken, die aan dit onderzoek en proefschrift hebben bijgedragen en het mij hebben mogelijk gemaakt er aan te werken.
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Curriculum vitae

Frans Dekker (François) was born in 1953 in a small village called Retranchement, at the very southern most part of the Dutch coast. After high school (Koningin Wilhelmina Lyceum in Sluis) and military services he studied medicine at the Vrije Universiteit Medical Centre in Amsterdam. Jobs during his study were many; from being a courier in the world of advertising and design up to organizing courses in nursing homes and student-teacher at the university in general practice and public health. He did additional training in epidemiology (Wageningen University). After finishing medical school (1982) he has been working at the 'Blood Bank' in the center of Amsterdam and as lecturer at the University of Applied Sciences Amsterdam (Hogeschool van Amsterdam, bachelor course).
His vocational training for general practice (Vrije Universiteit Medical Centre and internship in a general practice at Leiderdorp and in psychiatry). Thereafter he had various jobs, such as repatriation of casualties, physician in a nursing home, fill in jobs in general practice and as coordinator of a cluster of healthcare centers, charged with starting a new health care center in Purmerend. After two years he started as GP in the newly founded health care center Molentocht in Purmerend and continued his job as lecturer at the University of Applied Sciences Amsterdam.
He kept on working as a GP for 3-4 days a week and combined this with a second job, which changed several times. After a short period of working as a coordinator of pharmacotherapy-counseling groups in the northern part of Holland, he started in 1992 as staff-member of the Dutch College of General Practitioners (NHG) until 1999, working on 'implementation' and CME (Continuing Medical Education). After that he worked until 2004 at the Health Care Insurance Board (CVZ), involved in the making of the websi te of the Farmacotherapeutisch Kompas (the most used source of drug information on the web in the Netherlands). From 1990 until now he was involved in many local, regional and nationwide activities on CME and implementation and development of the electronic patient record (EPR) for GPs. He is a member of Hoofdpijn-PCN, a special Dutch interest group for GPs on headache.
From 2004 up until now, he has been working on his thesis at the Leiden University Medical Center (LUMC), department of Public Health and Primary Care, in addition to his work as a GP in 'General practice Molentocht' in Purmerend.
Frans Dekker is married to Irene Haverbeke. They live in Ilpendam, a small village in the region Waterland, north of Amsterdam. They have two sons, Edial en Floris, both working abroad in web-supported organizing of individualized activities and/or products.