Eur J Clin Pharmacol (2002) 58: 149–155
DOI 10.1007/s00228-002-0443-8

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

H. Rahimtoola · H. Buurma · C.C. Tijssen
H.G. Leufkens · A.C.G. Egberts

Incidence and determinants of migraine prophylactic medication in the Netherlands

Received: 26 November 2001 / Accepted: 30 January 2002 / Published online: 5 April 2002

Abstract *Objective*: To estimate and examine the incidence and determinants of initiation of migraine-prophylactic therapy as well as the corresponding drug of choice over a period of 5 years following the use of specific abortive migraine drugs.
Methods: By accessing data from a large prescription database, an identification of patients treated with ergotamine or a triptan from 1 January 1994 to 31 December 1998 was made. The cumulative incidence of initiation of migraine-prophylactic drugs (β-blockers, serotonin antagonists, specific calcium antagonists, amitriptyline, clonidine and valproic acid) was estimated in patients following the use of ergotamine or a triptan. An assessment of the migraine-prophylactic drug of first choice was also performed. A few baseline determinants were analysed to highlight a possible association with the initiation of prophylactic therapy: age, gender, type of abortive migraine drug use and year of prophylaxis. Additional determinants included the analysis of drug-utilisation patterns, such as the consumption and switch patterns of abortive migraine drug use as well as co-medication use prior to prophylaxis. For this particular analysis a reference group (patients not having commenced prophylaxis) was selected from the initial study population.
Results: After having satisfied eligibility criteria, a total of 3999 first-time users of ergotamine and triptans were included of whom 479 (12%) had initiated migraine-prophylactic therapy. This corresponded to an incidence density of 6.0 per 100 person-years and was highest for patients younger than 45 years and for multiple abortive migraine drug users. The incidence fell considerably from 12.0 person-years in 1994 to 5.1 person-years in 1998. More than half of the patients had been prescribed a β-blocker as the migraine-prophylactic drug of first choice by both general practitioners and neurologists. The use of antidepressants and/or benzodiazepines and oral contraceptives was significantly higher in patients starting prophylaxis compared with those who did not. The consumption of abortive migraine drug use (4.0 defined daily doses per month vs 3.7 defined daily doses per month), and switch patterns (27.1% vs 30.9%) were similar for patients starting and not starting prophylaxis.
Conclusion: The overall incidence of initiation of migraine-prophylactic therapy following the use of abortive migraine analgesics was 6.0% per year and fell considerably during 5 years of the study. Beta-blockers were the migraine-prophylactic drugs of first choice for general practitioners and neurologists. In our study we could not determine any factors clearly associated with the initiation of migraine prophylaxis besides prior use of antidepressants and benzodiazepines. A future assessment of the usage patterns of migraine-prophylactic drugs may provide detailed information concerning the effectiveness and tolerability.

Keywords Ergotamine · Triptans · Migraine

H. Rahimtoola (✉) · H. Buurma
SIR Institute for Pharmacy Practice Research,
Leiden, The Netherlands
E-mail: h.rahimtoola@pharm.uu.nl
Tel.: +31-30-2537324
Fax: +31-30-2539166

H. Rahimtoola · H.G. Leufkens · A.C.G. Egberts
Department of Pharmacoepidemiology and Pharmacotherapy,
Utrecht Institute for Pharmaceutical Sciences (UIPS),
PO Box 80082, 3508TB, Utrecht, The Netherlands

C.C. Tijssen
Department of Neurology, St Elisabeth Hospital,
Tilburg, The Netherlands

A.C.G. Egberts
Hospital Pharmacy Midden Brabant,
Twee Steden Hospital & St Elisabeth Hospital,
Tilburg, The Netherlands

Introduction

Migraine is a common disabling condition that can significantly limit and impair the health-related quality of life of the migraineur [1]. Despite the recent advances in migraine-abortive therapy, such as the availability of sumatriptan and the second-generation triptans, some

migraine patients are unable to achieve satisfactory results from specific or non-specific abortive migraine therapy. In these patients the initiation of prophylactic medication can, therefore, be considered a therapeutic option. This treatment is likewise often recommended for those suffering from two migraine attacks or more per month [2]. The medications available for migraine prophylaxis, though not curative, have shown to reduce the frequency of migraine attacks by about 50% compared with placebo. The few controlled clinical trials available so far have failed to prove any superiority of one migraine-prophylactic medication to another. Therefore, the initiation of a specific medication for migraine prophylaxis, though guided by migraine therapeutic guidelines, is often based upon a physician's beliefs and experiences with a particular drug, scientific proof for efficacy, side-effect profile and specific patient characteristics, such as co-morbidity [2, 3, 4].

However, the use of migraine-prophylactic medicines in daily practice particularly by patients suffering from moderate to severe forms of migraine is relatively low [5]. One study estimated that only 38% of eligible migraineurs were receiving prophylactic medication [6]. The non-life threatening nature of migraine, low consultation rates, intolerable side effects of current prophylactic medications and patient unawareness of the availability of other therapeutic options are few of the various reasons that may explain this phenomenon [7].

So far, the few studies examining the prescribing patterns of migraine-prophylactic medication in different countries have not revealed any substantial differences in the preferential selection of a particular medication; β-blocking drugs, serotonin antagonists, specific calcium antagonists, antidepressants and more recently valproic acid seem to be the preferred drugs for patients initiating migraine-prophylactic treatment [5, 8, 9, 10]. Even though these studies have provided some information concerning the extent of migraine-prophylactic drug use in their study populations, detailed data on the incidence and determinants of commencing migraine-prophylactic therapy are, as we are aware, lacking.

The purpose of this observational, retrospective, 5-year follow-up study was to estimate the incidence of initiation of migraine-prophylactic therapy and to examine the corresponding drug of first choice in patients using a specific abortive migraine drug by means of extensive computerised prescription data. In addition, a number of potential determinants were examined in order to highlight a possible association with the initiation of prophylactic therapy.

Methods

Study setting

The study used prescription data from the PHARMO-RLS database covering the period 1985–1998. This database has been described in full elsewhere [11]. In brief, the system was designed in 1985 to provide relevant demographic and prescription data at an individual level for five medium-sized cities in The Netherlands from 1985 to 1989. Since 1990 it has been further updated, covering a total of six cities ($n = 300{,}000$) and from 1993 to 1998 for eight cities ($n = 450{,}000$). In view of a high patient–pharmacy registration commitment in The Netherlands, in addition to sophisticated pharmacy software currently available, the medication information for each patient is virtually complete.

Each registered person is identified with an anonymous unique patient-identification code that allows for the observation of patient medication use in time. Retrievable information per prescribed medicine includes date of dispensing, drug, dosage regimen, quantity supplied [Defined Daily Doses (DDDs)] and type of prescriber. Patient information per prescribed medicine includes gender and date of birth. The database does not provide information concerning the indications for use of the medicines, in this case the diagnosis of migraine versus cluster headache, or complete registration of non-prescription medicines [e.g. over-the-counter (OTC) use of salicylates, non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol].

Study population

For this study, all patients who began taking an abortive migraine drug, either ergotamine or a triptan, for the first time from 1 January 1994 to 31 December 1998, were included ($n = 4959$). First-time users were defined as patients possessing a drug-free interval of abortive migraine analgesic use of at least 2 years. Sumatriptan was registered in The Netherlands from June 1991. Prescriptions were retrieved using the World Health Organization Anatomical Therapeutical Classification system (ATC system) for ergotamine, alone (N02CA02) or combination (N02CA52), sumatriptan (N02CC01), naratriptan (N02CC02), zolmitriptan (N02CC03) and rizatriptan (N02CC04) [12]. The date of first prescription of one of these drugs was termed the "start date analgesia". Patients who were already using migraine-prophylactic medications at the "start date analgesia" or who had a prophylactic drug-free interval of less than 1 year prior to the start date analgesia were excluded from further analysis ($n = 225$). Furthermore, patients in whom prescription follow-up data of less than 90 days were present were excluded ($n = 735$).

The main outcome of interest was initiation of migraine-prophylactic treatment for the first time, after commencing ergotamine or a triptan, during our follow-up period (1 January 1994 until 31 December 1998). With reference to the clinical and therapeutic guidelines of the Dutch College of General Practitioners (NHG formulary) and the Dutch Association of Neurologists [13, 14], each eligible patient was subsequently screened for the use of one of the following prophylactic medications after their start date analgesia: β-blockers (propranolol or metoprolol), serotonin antagonists (pizotifen or methysergide), calcium antagonists (flunarizine or verapamil), amitriptyline, clonidine or valproic acid. The corresponding date was termed "index date prophylaxis". Even though some selective serotonin reuptake inhibitors and quite recently angiotensin-converting enzyme (ACE) inhibitors have shown to display useful effects in migraine prevention, they were not included in our analysis as they were and are as yet not included in international therapeutic guidelines for migraine prevention during the study period.

Data analysis

Baseline characteristics of the study population ($n = 3999$) were examined and included gender, age, type of abortive migraine drug user, prescriber who started ergotamine or the specific triptan treatment and co-medication use during a 2-year period prior to start date analgesia. Analysis of co-medication included the analysis of the most common prescribed therapeutic groups in The Netherlands. This included antidepressant drugs (excluding amitriptyline), benzodiazepines, cardiovascular drugs (β-blockers

– excluding propranolol and metoprolol, ACE inhibitors, calcium antagonists – excluding verapamil, nitrates), hormonal drugs (oral contraceptives), non-steroidal anti-inflammatory drugs (NSAIDs) and anti-ulcer drugs (H2 antagonists and proton-pump inhibitors).

The choice of the migraine-prophylactic medication was determined and stratified according to type of prescriber, either general practitioner or specialist. The cumulative incidence of initiating migraine prophylaxis by ergotamine and triptan recipients was estimated using life-table analysis. By implementing Cox regression analysis, general patient and medication characteristics were examined in order to investigate certain factors possibly associated with the initiation of migraine-prophylactic medication. These again included gender, age, type of abortive migraine drug user, prescriber of the first abortive migraine drug prescription and year in which prophylactic medication began. The strength of these factors was expressed as an incidence-density ratio with 95% confidence interval (95% CI), which can be interpreted as a relative risk (RR).

Additional determinants examined included the consumption of abortive migraine drug use, switch patterns (ergotamine to a triptan or vice-versa) and co-medication use, following the start date analgesia and prior to the index date prophylaxis. In order to assess the frequency of migraine attacks of our study population, we measured the consumption (''therapeutic intensity'') of abortive migraine drug use. The therapeutic intensity of ergotamine or triptans, expressed as the number of DDDs per month, was estimated by dividing the total number of DDDs dispensed per ergotamine/triptan prescription by the number of days between the first and last prescription presented by each patient before migraine-prophylactic treatment. A maximum follow-up period of 2 years preceding the index date prophylaxis was used. For this evaluation, patients were required to have presented at least three prescriptions for ergotamine/triptan as well as possessing a minimum follow-up of abortive migraine drug use of 15 days.

- 1 DDD sumatriptan corresponded to one 100-mg tablet or one 6-mg subcutaneous injection.
- 1 DDD naratriptan or zolmitriptan corresponded to one 2.5-mg tablet, respectively.
- 1 DDD rizatriptan corresponded to one 10-mg tablet.
- 1 DDD ergotamine corresponded to one 4-mg single preparation by any route or one 2-mg combination preparation by any route [12].

Patients were subsequently categorised into defined therapeutic intensity classifications: (≤ 3, 3–6, >6) DDDs per month. A similar approach examining sumatriptan consumption and heavy use has been used elsewhere [15].

For these three evaluations, a reference group, patients not having commenced migraine-prophylactic treatment during the study period, was sampled from the initial study population by matching a date of an abortive migraine drug prescription (''reference index date'') with the index dates of prophylaxis. By applying logistic regression analysis, the strength of these factors was expressed as odds ratios (ORs) with 95% CI.

Microsoft Access, a relational database software package, was used for database management and internal quality and validation procedures. The statistical package, SPSS for Windows (version 10.0) was used for data analysis.

Results

After satisfying initial eligibility criteria, a total of 3999 first-time users of ergotamine or sumatriptan were identified during the study period 1994–1998. The corresponding baseline characteristics are provided in Table 1. The 3999 patients contributed to a total of 7947 person-years corresponding to a mean follow-up time of 2.0 years per patient. Approximately 80% of the population was female, and the mean age was 41.4 years. More than half (56%) of this population received ergotamine. During the 2-year observation period prior to the ''start date analgesia'' we identified 3293 (82%) patients who were using at least one of the drugs belonging to the co-medication categories analysed. NSAIDs, oral contraceptives and benzodiazepines were by far the most common of the co-medications used.

Table 1. Baseline characteristics of the study population (prophylactic and non-prophylactic users: $n = 3999$)

Characteristic	Number	%	Mean (SD)
Female gender	3108	78	
Age (years)	–	–	41.4 ± 13.7
Follow-up (years)			2.0 ± 1.4
Abortive migraine analgesia			
Ergotamine	2253	56	
Sumatriptan	1489	37	
Naratriptan	93	2	
Zolmitriptan	152	4	
Rizatriptan	12	0.3	
One-time use[a]	1673	42	
General practitioner[b]	3613	90	
Neurologist[b]	355	9	
Unknown[b]	31	1	
Co-medication[c]			
Antidepressants	282	7	
Benzodiazepines	1234	31	
Antidepressants and benzodiazepines	206	5	
Cardiovascular drugs	319	8	
Oral contraceptives	1821	46	
Antacids	507	13	
Non-steroidal anti-inflammatory drugs	2190	55	

[a]Corresponds to the registration of only one abortive migraine prescription during follow-up

[b]Prescriber of the first abortive migraine drug prescription

[c]Use on ''start date analgesia'' or during 2 years prior to start date analgesia

We identified 479 patients (12.0%) who initiated migraine-prophylactic treatment after having commenced abortive migraine analgesia during the follow-up period. Overall (Fig. 1), the incidence density for commencing migraine-prophylactic therapy in our population was 6.0 per 100 person-years.

The most common (53%) prescribed prophylactic drug was a β-blocker (propranolol or metoprolol), of which propranolol was the preferred drug to be prescribed by general physicians as well as neurologists (Fig. 2). This prescribing pattern was consistent across all domains studied (gender, age and type of abortive migraine drug recipient). Amitriptyline (14.6%) and pizotifen (13.2%), clonidine (5.2%), valproic acid (5.0%), flunarizine (4.6%) verapamil (3.5%) and methysergide (1.0%) were the following drugs of choice to be prescribed.

Although there was a clear preference to prescribe β-blockers by both types of physicians there were a few differences noted for the choice of the other prophylactic

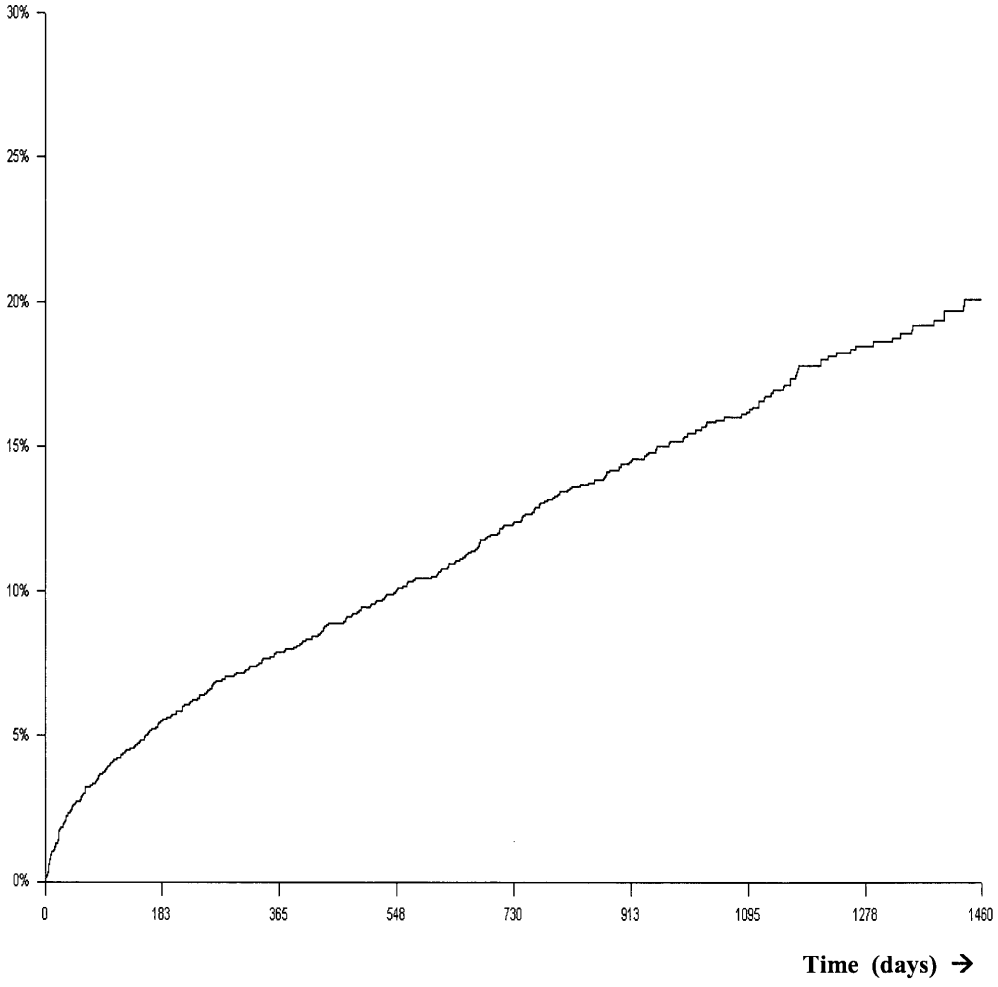

Fig. 1. Incidence density of initiation of migraine-prophylactic therapy (1994–1998)

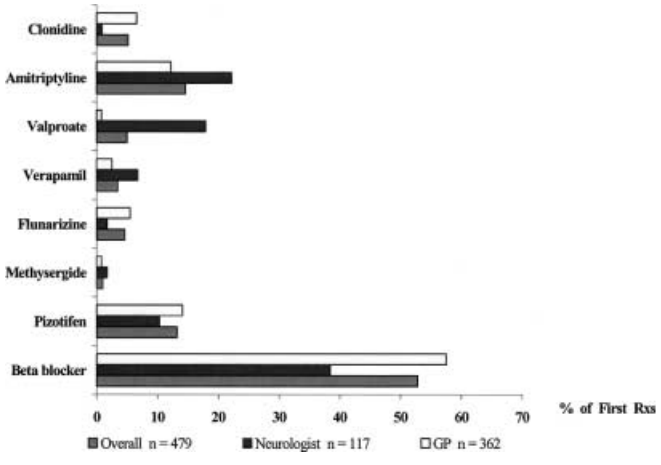

Fig. 2. Migraine-prophylactic drug of first choice amongst prescribers

drugs. General physicians preferred flunarizine or pizotifen whereas a preference by neurologists to prescribe valproic acid, amitriptyline or verapamil was observed.

Determinants associated with the initiation of migraine-prophylactic treatment, expressed as incidence-density ratios, are shown in Table 2. The incidence in men was almost equivalent to that estimated in women (RR 0.88; 95% CI 0.70, 1.39) and was higher for patients aged 45 years or younger (RR 1.37; 95% CI 1.13, 1.66). Multiple abortive migraine drug use, presentation of more than one abortive migraine analgesic prescription, was found to be clearly associated with the initiation of migraine-prophylactic treatment (RR 1.51; 95% CI 1.24, 1.82). The prescriber of initiation of abortive migraine treatment was not considered predictive for the initiation of prophylactic treatment. Large variations in the year in which prophylaxis was started were observed: there was a significant reduction from 1994 onwards to 1998.

The mean overall consumption of ergotamine and triptans (Table 3), defined as the ''therapeutic intensity'', was estimated at 4.0 DDDs per month prior to the initiation of migraine prophylaxis (case group). This estimation was similar to that measured for the reference group, 3.7 DDDs per month ($P = 0.1$). The proportion of case patients classified within the higher categories of therapeutic intensity (> 6 DDDs per month) did not differ from that observed within the reference group, 18.8% (OR 1.4; 95% CI 0.8, 2.5). Switch in abortive migraine drug treatment, from the original abortive migraine drug prescription to another prior to the date

Table 2. Determinants of migraine-prophylactic drug initiation. *pyrs* person years, *RR* relative risk, *CI* confidence interval

Characteristics	Follow-up (pyrs)	Initiation of migraine prophylaxis (number)	Incidence density (per 100 pyrs)	Incidence-density ratio RR (95% CI)
Overall	7947	479	6.0	
Gender				
Women	6206	384	6.2	1 (reference)
Men	1741	95	5.5	0.88 (0.70, 1.10)
Age (years)				
< 25	742	54	7.3	1.03 (0.77, 1.39)
25–44	3904	263	6.7	1 (reference)
45–64	2839	144	5.1	0.75 (0.61, 0.93)
> 64	462	18	3.9	0.57 (0.35, 0.91)
Migraine analgesic use				
Ergotamine	5600	312	5.6	1 (reference)
Sumatriptan	2192	159	7.3	1.12 (0.92, 1.35)
Naratriptan	50	3	6.0	1.08 (0.82, 1.42)
Zolmitriptan	100	4	4.0	0.42 (0.16, 1.15)
Rizatriptan	5	1	20.0	2.0 (0.30, 14.2)
One-time use[a]	3252	152	4.7	1 (reference)
Multiple use[b]	4695	327	7.0	1.51 (1.24, 1.82)
General practitioner	7261	438	6.0	1 (reference)
Consultant	640	38	5.9	0.95 (0.68, 1.32)
Year of prophylaxis				
1994	465	56	12.0	4.15 (2.90, 5.95)
1995	1,270	97	7.6	1.87 (1.40, 2.51)
1996	1,666	90	5.4	1 (reference)
1997	2,126	113	5.3	0.67 (0.51, 0.89)
1998	2,422	123	5.1	0.45 (0.33, 0.61)

[a]Presentation of only one ergotamine or triptan prescription throughout study period
[b]Presentation of more than one ergotamine or triptan prescription throughout study period

Table 3. Additional determinants: therapeutic intensity of ergotamine and triptan, switch patterns and co-medication use in prophylactic (cases) and non-prophylactic users (reference) prior to index dates. *DDDs* defined daily doses, *OR* odds ratio, *CI* confidence interval

Therapeutic intensity (DDDs per month)	Cases ($n = 165$)	Reference ($n = 165$)	OR (95% CI)
< 3.0	62.4%	67.3%	1.0 (reference)
3.0–6.0	18.8%	18.2%	1.1 (0.6, 2.0)
> 6.0	18.8%	14.5%	1.4 (0.8, 2.5)
Additional determinants	($n = 479$)	($n = 479$)	
Switch	27.1%	30.9%	0.8 (0.6, 1.0)
Co-medication			
Antidepressants	9.6%	5.4%	1.9 (1.1, 3.0)
Benzodiazepines	28.8%	18.8%	1.7 (1.3, 2.4)
Antidepressants and benzodiazepines	6.3%	3.8%	1.7 (0.9, 3.1)
Cardiovascular drugs	6.3%	5.0%	1.3 (0.7, 2.2)
Oral contraceptives	39.7%	30.5%	1.5 (1.1, 2.0)
Antacids	10.9%	9.0%	1.2 (0.8, 1.9)
Non-steroidal anti-inflammatory drugs	40.1%	35.5%	1.2 (0.9, 1.6)

of index, occurred in 30.9% of the reference patients and was slightly lower for case patients, 27.1% (OR 0.78; 95% CI 0.60, 1.0).

The use of some co-medication categories was associated with the initiation of migraine prophylaxis (Table 3). A larger proportion of case patients compared with reference patients was using an antidepressant and/or benzodiazepine prior to the respective index dates, 38.4% versus 24.2% (OR 1.95; 95% CI 1.46, 2.60) and oral contraceptives 39.7% versus 30.5% (OR 1.50; 95% CI 1.1, 2.0).

Discussion

The overall incidence of initiation of migraine-prophylactic therapy following the use of specific abortive migraine analgesics was 6.0% per year and fell considerably during the 5 years of the study. Beta-blockers were the migraine-prophylactic drugs of first choice for general practitioners and neurologists. In our study we could not determine any factors clearly associated with the initiation of migraine prophylaxis besides prior use of antidepressants and benzodiazepines.

Von Korff et al. found that 21% of the migraine population was using preventive medication, which according to the authors was considered low [5]. We found that only 12% of our migraine population had commenced prophylactic therapy during the 5-year observation period. These findings may be related to low physician-consultation rates by migraineurs, more favourable patient satisfaction from the newer abortive migraine drugs or reluctance by physicians to initiate prophylactic treatment for fear of side effects, limited efficacy of prophylactic drugs or poor patient compliance [7, 16, 17]. The reason for the considerable decline in the initiation of migraine-prophylactic treatment from 1994 to 1998 is unclear. However, the increased use and

availability of the triptans in The Netherlands during the study period may have delayed the intent to initiate migraine-prophylactic treatment following treatment failure of the first abortive migraine drug.

One of the aims of this study was to determine the prescribing patterns of migraine-prophylactic medication in patients taking this form of treatment for the first time. A substantial preference for β-blocking drugs, followed by amitriptyline and pizotifen was observed. This overall preference is consistent with that observed in other international studies [5, 6, 8, 9, 10, 18]. Surprisingly, a relatively large number of patients was prescribed amitriptyline by general practitioners (GPs) as a drug of first choice, even though this drug is considered one of the last options in their respective guidelines. This may seem to have been a deliberate approach by GPs to treat both migraine and co-existing depression in certain patients [4, 13]. Valproic acid was formally recommended only by neurologists during the study period [13, 14]. The preference to prescribe valproic acid primarily by neurologists is consistent with that seen in other countries [3, 8] and highlights an earlier recognition by neurologists towards the positive effects of valproic acid in migraine prevention [14]. Despite its promising efficacy in migraine and cluster headaches, methysergide should be reserved for severe cases in which other options are no longer effective due to the severe side effects, such as retroperitoneal fibrosis [2, 3, 4]. Despite its proven efficacy the relatively low prescribing rate of flunarizine differs from that seen in other international studies and is an indication of its therapeutic place in the guidelines of GPs and neurologists in The Netherlands [8, 13, 18].

Females are more likely than males to regularly seek medical advice for migraine and other headache symptoms, which can lead to higher prescription-medication use for migraine in this population [19]. However, we could not identify a strong correlation between prophylactic use and gender type. In contrast, an association between young age and initiation of migraine prophylaxis was determined, which possibly reflects a higher reluctance by physicians to prescribe the corresponding drugs to older patients in view of fear for adverse drug reactions, drug–drug or drug–disease interactions [20, 21].

Since prophylactic therapy is recommended for patients suffering from two or more migraine attacks a month and for those who obtain inadequate relief from acute medication [2], we initially assumed that the consumption as well as the switch patterns of ergotamine and the triptans would have been significantly higher in patients who had commenced prophylaxis. These patterns, however, did not differ from those patients not starting prophylactic medication. Apparently, these two criteria were not the most relevant for the initiation of migraine prophylaxis in daily practice.

A higher prevalence of anxiety and depression has been associated with patients suffering from severe forms of migraine and/or chronic use of acute migraine medication. As a result the frequency and severity of migraine attacks can be increased requiring such patients to seek more regular medical advice than other migraineurs, which in turn increases their likelihood to be prescribed migraine-prophylactic treatment [22, 23, 24, 25]. These findings may therefore provide an explanation concerning the strong association between migraine-prophylactic treatment and prior antidepressant and/or benzodiazepine use in some of our patients. If a segment of our population initiating migraine prophylaxis was suffering from chronic analgesic use then the initiation of this treatment to these patients would be inappropriate as the efficacy of this treatment is often compromised by concomitant overuse of migraine analgesics [26].

The use of oral contraceptives, substantially higher than that observed in other population-based migraine studies [27, 28], was found to be associated with future migraine-prophylactic treatment. However, since oral contraceptive use possesses negative as well as beneficial effects on the severity of migraines [29], it is difficult to claim such an association.

There are several limitations to this study. First, we estimated the incidence of migraine prophylaxis by the initiation of prescription drugs most commonly used for this indication. However, the therapeutic indications of many of the drugs analysed are not exclusive to migraine prevention but also extend to the treatment of cardiovascular complications, depression, epilepsy and other vascular headaches (i.e. misclassification). Second, since access to clinical information and use of OTC medication information was limited, we were required to identify patients suffering from migraine by their use of specific migraine analgesics, such as ergotamine or the triptans. This can likewise lead to an underestimation of the migraine population residing in the study area, since only a minority of migraineurs have been found to use ergotamine or sumatriptan to treat their headaches [6]. Finally, the investigated population is nonhomogeneous, meaning that a proportion of the patients were suffering from tension-type or cluster headaches in whom preventive treatment such as amitriptyline or verapamil is required [30].

Some imprecision in our estimation of therapeutic intensity as an indication of the frequency of migraine attacks may exist as an assumption was made that a prescription presented at the pharmacy correlates with consumption of the drug. However, estimation of drug consumption need not be a problem for recipients of multiple prescriptions, since prescriptions repeated consistently can serve as strong evidence of drug use by patients [31]. Our analysis of therapeutic intensity included only those patients who presented multiple prescriptions of ergotamine or triptans.

Despite some limitations to this study, we believe that our study adds to existing evidence that only a minority of migraineurs is treated with migraine-prophylactic medications. Contrary to expectations only a few determinants were considered clearly predictive of future migraine-prophylactic treatment. A future assessment of

the usage patterns of migraine-prophylactic drugs may provide detailed information concerning the effectiveness and tolerability.

Acknowledgements This study was funded by a grant from The Royal Dutch Association for the Advancement of Pharmaceutical Sciences (KNMP), The Hague, The Netherlands, and SIR Institute for Pharmacy Practice Research, Leiden, The Netherlands.

References

1. Lipton RB, Stewart WF, von Korff M (1997) Burden of migraine: societal costs and therapeutic opportunities. Neurology 48[Suppl 3]:S4–S9
2. Tfelt-Hansen P (1997) Prophylactic pharmacotherapy of migraine. Neurol Clin 15:153–165
3. Limmroth V, Michel MC (2001) The prevention of migraine: a critical review with special emphasis on β-adrenoceptor blockers. Br J Clin Pharmacol 52:237–243
4. Ramadan NM, Schultz LL, Gilkey SJ (1997) Migraine prophylactic drugs: proof of efficacy, utilization and cost. Cephalalgia 17:73–80
5. von Korff M, Black LK, Saunders K, Galer BS (1999) Headache medication use among primary care headache patients in a health maintenance organisation. Cephalalgia 19:575–580
6. Celentano DD, Stewart WF, Lipton RB, et al (1992) Medication use and disability among migraineurs: a national probability sample. Headache 32:223–228
7. MacGregor EA (1997) The doctor and the migraine patient: improving compliance. Neurology 48[Suppl 3]:S16–S20
8. Furlong S, Pryse-Phillips W, Crowley M, Turner C (1996) Prescribing practices for the management of headache in Newfoundland and Labrador. Headache 36:542–546
9. Edmeads J, Findlay H, Tugwell P, et al (1993) Impact of migraine and tension-type headache on life-style, consulting behaviour, and medication use: a Canadian population survey. Can J Neurol Sci 20:131–137
10. Lanteri-Minet M, Alchaar H, Besson G, et al (2000) Prophylaxis for migraine headache: a pharmacoepidemiologic study of practices used by primary care physicians and neurologists in France. Rev Neurol 156:1106–1112
11. Herings RMC (1993) PHARMO: a record linkage system for postmarketing surveillance of prescription drugs in The Netherlands. Thesis, Utrecht University
12. Anonymous (1993) Anatomical Therapeutic Chemical (ATC) classification index. WHO Collaborating Centre for Drug Statistics Methodology, Oslo
13. Bartelink MEL, Van Duijn NP, Knuistingh NA, et al (1991) NHG-formulary for migraine. Huisarts Wetenschap 34:504–508
14. Koehler PJ (1999) Chronic headache without neurological disturbances. Guidelines according to the Dutch Neurological Society. Ned Tijdschr Geneeskd 143:295–300
15. Gaist D, Halls J, Sindrup SH, Gram LF (1996) Is overuse of sumatriptan a problem? A population based study. Eur J Clin Pharmacol 50:161–165
16. Diener HC, Kaube H, Limmroth V (1998) A practical guide to the management and prevention of migraine. Drugs 56:811–818
17. Lipton RB, Amatniek JC, Ferrari MD, et al (1994) Migraine – identifying and removing barriers to care. Neurology 44[Suppl 4]:S63–S67
18. Pasqual J, Leira R, Lainez JM, et al (1999) Spanish study of quality of life in migraine (II). Profile of medication consumption and subjective efficacy. Neurologia 14:205–209
19. Stewart WF, Celentano DD, Linet MS (1999) Disability, physician consultation, and use of prescription medications in a population-based study of headache. Biomed Pharmacother 43:711–718
20. Rasmussen BK, Jensen R, Schroll M, et al (1991) Epidemiology of headache in a general population – a prevalence study. J Clin Epidemiol 44:1147–1157
21. Passmore AP, Crwaford VLS, Beringer TRO, et al (1995) Determinants of drug utilisation in an elderly population in North and West Belfast. Pharmacoepidemiol Drug Saf 4:147–160
22. Siberstein SD (1998) Comprehensive management of headache and depression. Cephalalgia 18[Suppl 21]: S50–S55
23. Karen L, Swartz MD, Laura A, Haroutune K, Li Ching Lee, et al (2000) Mental disorders and the incidence of migraine headaches in a community sample. Arch Gen Psychiatry 57:945–950
24. Lipton RB, Hamelsky SW, Kolodner KB, Steiner TJ, Stewart WF (2000) Migraine, quality of life, and depression: a population-based case-control study. Neurology 55:629–635
25. Radat F, Sakh D, Lutz G, el Amrani M, Ferreri M et al (1999) Psychiatric comorbidity is related to headache induced by chronic substance use in migraineurs. Headache 39:477–480
26. Edmeads J (1990) Analgesic-induced headaches: an unrecognised epidemic. Headache 30:614–615
27. Putnam GP, O'Quinn S, Bolden-Watson CP, et al (1999) Migraine polypharmacy and the tolerability of sumatriptan: a large-scale, prospective study. Cephalalgia 19:668–675
28. Fox AW, Davis RL (1998) Migraine chronobiology. Headache 38:436–441
29. Becker WJ (1999) Use of oral contraceptives in patients with migraine. Neurology 53[Suppl 1]:S19–25
30. D'Alessandro R, Gamberini G, Benassi G, et al (1986) Cluster headache in the Rebublic of San Marino. Cephalalgia 6:159–162
31. Petri H, de Vet CW, Naus J, et al (1988) Prescription sequence analysis: a new and fast method for assessing certain adverse reactions of prescription drugs in large populations. Stat Med 7:1171–1175