Incidence and determinants of antidepressant drug use in migraine patients

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The purpose of this retrospective, follow-up study was to characterise the use of antidepressant medication in a defined migraine population and evaluate the determinants thereof. Data was obtained from the PHARMO-RLS prescription database. Our migraine population (2,517 people) included patients having commenced specific migraine drugs, ergotamine or sumatriptan, for the first time from January 1 1992 to December 31 1998. The corresponding date was termed the 'index date'. Non-migraine patients, those not having used any medication specific for migraine, were selected and equally matched ($n=2,517$). The cumulative incidence of initiating antidepressant treatment was estimated during two-year observation periods prior to and after the index date. Several demographic and comedication characteristics were assessed as potential determinants of antidepressant drug use within the migraine population. Other determinants included usage patterns ("therapeutic intensity") of ergotamine and sumatriptan , defined as the absolute number of Defined Daily Doses (DDDs) dispensed per patient during one year prior to initiation of antidepressant therapy. A total of 300 migraine patients (11.9%) and 213 non-migraine patients (8.5%) had initiated antidepressant treatment in the two-year period prior to or in the two-year period after the index date (RR adj 1.4; 95% CI 1.2–1.7). The cumulative incidence of initiation of antidepressant treatment for the migraine population was 3.0% per year prior to and 3.2% per year after the initiation of specific migraine analgesia. The concomitant use of benzodiazepines (RR adj 4.7; 95% CI 3.5–6.3), migraine prophylactic medication (RR adj 2.1; 95% CI 1.6–2.8) and heavy therapeutic intensity use of specific migraine analgesia, defined as ≥ 150 DDDs per year were highly predictive of antidepressant drug use within the migraine population.

In conclusion, compared to the non-migraine population, the initiation of antidepressant treatment was only slightly higher in the migraine population. A number of determinants within the latter were found to be strongly associated with antidepressant drug use, the nature of which most likely reflects an increased severity of migraine whereby therapeutic needs are higher. *Int Clin Psychopharmacol* 18:331–339 © 2003 Lippincott Williams & Wilkins.

International Clinical Psychopharmacology 2003, 18:331–339

Keywords: ergotamine, sumatriptan, migraine, antidepressant, therapeutic intensity

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Received 10 December 2002 Accepted 4 September 2003

Introduction

Clinical and epidemiological evidence demonstrates a clear association between migraine and psychiatric disorders whereby the health related quality of life of the migraineur may further be compromised (Stewart *et al.*, 1994; Lipton *et al.*, 2000). Current evidence has established that the life-time prevalence of major depression in migraine, for example, is about three times higher (34%) than that estimated in the non-migraine population (10%) and that the prevalence of anxiety or panic disorders affects approximately 11% of the migraine population compared to 2% of the non-migraine population (Breslau *et al.*, 2000; Breslau *et al.*, 1991). The risk for psychiatric comorbidity seems to be strongest in women, migraineurs suffering from the aura symptoms or those with transformed migraine (Breslau *et al.*, 2000; Breslau *et al.*, 1991; Swartz *et al.*, 2000; Juang *et al.*, 2000).

It still remains unclear whether psychiatric comorbidity is primarily related to a unidirectional (cause or effect) psychological component or a bidirectional process (common environmental genetic etiology). By studying psychiatric comorbidity in migraine patients, Breslau *et al.* (2000; 1991) demonstrated a strong bidirectional relationship between major depression and migraine, meaning that migraine predicted first-onset depression and depression predicted first onset migraine (Breslau *et al.*, 2000; Breslau *et al.*, 1991; Breslau, 1998; Peroutka *et al.*, 1998). However, other studies could not support the shared mechanism hypothesis between migraine and

0268-1315

DOI: 10.1097/01.yic.0000097038.25861.3b

psychiatric comorbidity or whether in fact an association between these two disorders exits (Swartz *et al.*, 2000; Merikangas *et al.* 1990; Guillemn *et al.*, 1999; Mattsson *et al.*, 2002).

Although a clear association between migraine and major depression may exist, the phenomenon appears to be under recognised and under treated in clinical practice (Devlen, 1994). To what extent is unclear since only a few epidemiological studies have provided data concerning the patterns of antidepressant drug use in migraineurs suffering from coexisting psychiatric disorders. Putnam *et al.* (1999) by studying comedication characteristics in patients using sumatriptan estimated that antidepressants were used by approximately a third of the study patients. A recent study concerning the incidence and determinants of migraine prophylactic medication had shown that use of antidepressants and/or benzodiazepines was associated with an increased initiation of migraine prophylactic medication, possibly due to underlying psychiatric illness complicating migraine treatment (Rahimtoola *et al.*, 2002).

The question therefore arises as to whether the use of antidepressants by migraineurs is primarily a cause or consequence of onset of specific migraine drug treatment. The purpose of this study was to investigate the nature of the association between antidepressant and specific migraine analgesic drug use by estimating the incidence of initiation of antidepressants prior to and after the initiation of specific migraine analgesics. Furthermore a number of characteristics were explored within the migraine population in order to identify any potential determinants associated with the initiation of antidepressant medication.

Methods

Study setting

The study used prescription data from the PHARMO-RLS database covering the period 1985 to 1999. This database has been described in full by Herings *et al.* (1992). This database system provides relevant demographic and prescription data on an individual patient level for 8 medium sized cities ($n = 450{,}000$ inhabitants) in The Netherlands. 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 primary care 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), duration of use 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 or tension type headaches, or the complete registration of non-prescription medicines (e.g. OTC use of salicylates, NSAIDs or paracetamol), as patients may also purchase these drugs from non-pharmacy outlets.

Study population

As diagnostic and clinical data were lacking we were required to identify the migraine population by the use of specific abortive migraine drugs, including ergotamine and sumatriptan. Analysis of the data can only be valid for this particular population in whom a more severe form of headache, compared to other migraineurs who do not require these drugs, may exist. For this retrospective, follow-up study, patients having commenced a specific migraine drug, either ergotamine or sumatriptan, for the first time from January 1 1992 to December 31 1999, were initially identified. First time users were defined as patients possessing a drug free interval of abortive migraine drug use of at least two years. The date of first prescription of one of these drugs was termed the 'index date'. Patients were only included if they had presented more than one prescription during follow-up, as recent data suggest that one time use of one of these drugs is a partial indication of an uncertain diagnosis for migraine (Rahimtoola *et al.*, 2003). Furthermore, each patient was required to have possessed at least four years of prescription data, equivalent to two years before and after the index date. For this reason patients using one of the second generation triptans were not included. For each ergotamine or sumatriptan patient, one reference patient not having used migraine specific medication (i.e. ergotamine, triptans, pizotifen, flunarizine, clonidine, and methysergide) were randomly selected from eligible non-migraine patients from the PHARMO database and were matched on age, sex, locality, and index date ($\pm$ 90 days). For the purpose of this study reference patients were referred to as non-migraine patients.

Outcome definition

The primary outcome of interest was the initiation of antidepressant drug treatment. Each eligible patient was therefore screened for the first time use of an antidepressant during the two-year follow-up periods prior to or after the index date. First time use was defined as an antidepressant drug free interval of at least one year prior to commencing one of the corresponding drugs. The corresponding date was termed 'antidepressant start date'. Antidepressants included tricyclic antidepressants (TCAs–excluding amitryptiline), selective serotonin re-uptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and other non TCAs (trazadone, nafazodone, mianserine, mirtazipine and venlafaxine). Amitriptyline was not included as this drug was recommended in the

migraine prophylactic therapeutic guidelines for primary care physicians during the study period. Even though some SSRIs, such as fluoxetine and fluvoxamine, or MAOIs, such as moclobemide and quite recently nafazodone, have shown to display useful effects in migraine prevention, they were still included in our analysis as they were not included in international therapeutic guidelines for migraine prevention during the study period (Silberstein and Goadsby, 2002).

Data analysis and potential confounders

The cumulative incidence (cumulative incidence per year) of initiating antidepressant treatment by migraineurs and non-migraineurs during the two-year follow-up periods prior to and after the index dates were estimated per six-monthly interval. The incidence within the migraine population was also compared during the two-year follow-up periods prior to and after the initiation of specific abortive migraine therapy. Baseline characteristics of the study migraine ($n = 2,517$) and non-migraine population ($n = 2,517$) were examined and included gender, age, and "comorbidity index". The presence of coexisting chronic conditions has shown to lead to a higher occurrence of depressive disorders and corresponding antidepressant drug use in the general population. Since migraine patients are substantially more likely than non-migraine patients to be diagnosed with a variety of comorbid condition(s) we included the comorbidity index in order to adjust for the potential burden of coexisting illness as a potential confounder for the risk of antidepressant treatment (Joish *et al.*, 2000). The latter was derived from a chronic disease score estimated for each patient by assigning scores (0–5) to specific classes of drugs according to the severity of the disease for which they were prescribed during the total observation period (Korff *et al.*, 1992). The latter included drugs used for cardiovascular, respiratory disorders, rheumatoid arthritis, chemotherapy, Parkinson's disease, epilepsy, diabetes mellitus, gastrointestinal ulcer, gout, hypercholesterolemia, and glaucoma. In order to adjust for an increased exposure to prescription medication within the migraine population due to a possible increase in physician consultation after having initiated ergotamine or sumatriptan, we estimated the total number of prescriptions dispensed per six-monthly interval during each two year observation period as an estimation of potential patient-physician contact. Both comorbidity index and patient-physician contact estimate in addition to the type of prescriber of the first antidepressant prescription were analysed as differential factors for the use of antidepressant drugs in the two populations.

The second approach to our study was to identify any potential determinants predictive of the initiation of an antidepressant within the migraine population for which several patient and medication related characteristics were analysed. These included age and gender, type of abortive migraine medication used, co-medication used during the total observation period, comorbidity index and prescription exposure index. Comedication included cardiovascular drugs (ACE inhibitors, calcium channel antagonists, β-adrenergic blockers – excluding propranolol and metoprolol, nitrates, digoxin, diuretics, vitamin-K antagonists, HMG COA reductase inhibitors), diabetes, benzodiazepines, gastrointestinal agents (proton pump inhibitors, H2 antagonists), migraine prophylactic drugs (propranolol, metoprolol, pizotifen, flunarizine, clonidine, methysergide, and amitriptyline), NSAIDs, and oral contraceptives.

A level of severity of migraine was likewise analysed as a potential determinant and was indirectly correlated to the consumption and switch patterns (change from ergotamine to sumatript and visa versa) of abortive migraine analgesia. Consumption patterns ("therapeutic intensity") were estimated by calculating the absolute consumption of ergotamine and sumatriptan based upon the sum of DDDs of ergotamine and sumatriptan dispensed during a one-year observation period prior to the antidepressant start date. Therefore, this particular analysis included only those patients who had commenced antidepressant treatment after having initiated ergotamine or sumatriptan (index group) and the reference group included those patients who had not. The latter were matched with the index group by a prescription date that corresponded to the antidepressant start date of the cases, (± 90 days). Patients were subsequently categorised according to < 30, $\geq 30 - < 90$, $\geq 90 - < 150$, and ≥ 150 DDDs. Even though an established definition for excessive use of specific abortive migraine analgesics is lacking we defined this as the use exceeding 150 DDDs or more, which has also been applied in other drug utilization studies involving sumatriptan and ergotamine (Evers *et al.*, 1999; Gaist, 1999). The following provides the DDDs of ergotamine and sumatriptan recommended by the World Health Organization (WHO, 1993):

> 1 DDD sumatriptan corresponded to one 100 mg tablet, one 6 mg subcutaneous injection or one 20 mg nasal spray
>
> 1 DDD ergotamine corresponded to one 4 mg single preparation by any route or one 2 mg combination preparation by any route.

In order to test the strength of the association between the various determinants studied and the initiation of antidepressant treatment between the migraine and non-migraine populations, logistic analysis was applied (adjustments for age, gender, type of abortive migraine drug used and comorbidity index). Odds ratios were used

Table 1 Baseline characteristics of the study population (migraine and non-migraine patients)

Characteristic	Migraine N=2,517 (%)	Non-migraine N=2,517 (%)
Gender		
Female	2,089 (83.0)	2,086 (82.9)
Male	428 (17.0)	431 (17.1)
Age		
Mean (SD) in years	44.5 (12.6)	44.6 (12.8)
<25	156 (6.2)	156 (6.2)
25–44	1092 (43.4)	1110 (44.1)
45–64	1106 (43.9)	1080 (42.9)
>64	163 (6.5)	171 (6.8)
Chronic disease score		
0	1,265 (50.3)	1349 (53.6)
<2	661 (26.3)	746 (29.6)
≥2	591 (23.5)	422 (16.8)
Comedication		
Asthma/COPD	296 (11.8)	318 (12.6)
Benzodiazepines	1,126 (44.7)	885 (35.2)
Cardiovascular	579 (23.0)	581 (23.1)
Diabetes	123 (4.9)	145 (5.8)
Epilepsy	102 (4.1)	67 (2.7)
Gastrointestinal	416 (16.6)	322 (12.8)
Antidepressant use*	348 (13.8)	247 (9.8)
Physician contact estimate		
Mean (sem) Rxs presented:		
Prior index date	8.0 (0.3)	8.3 (0.2)
After index date	9.9 (0.3)	9.4 (0.2)

*irrespective of first time use

to express the strength of the associations and were interpreted as relative risks (RR 95% CI).

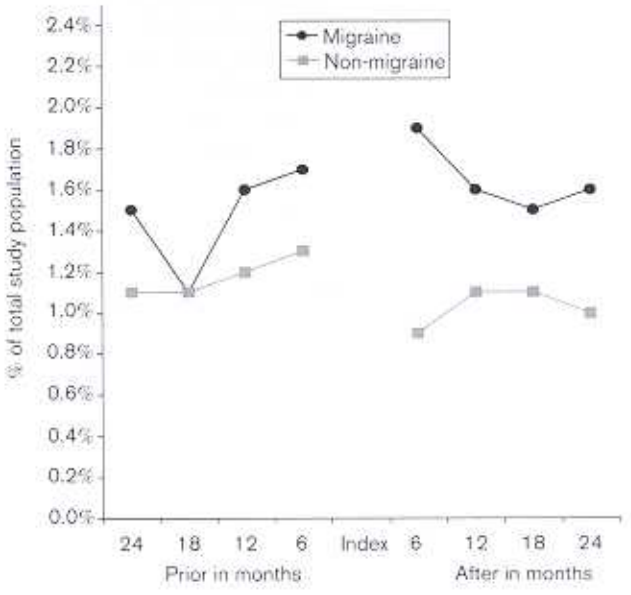
Microsoft Access, a relational database software package, was used for database management and internal quality and validation procedures. The statistical package, SPSS for Windows (version 10.0) was used for data analysis (Table 1).

Results

After fulfilling eligibilty criteria, a total of 2,517 patients had commenced either ergotamine or sumatriptan for the first time after 1992. Matching criteria identified 2,517 patients as the reference group. The majority of the study population included females (82.9%) and the mean age was 44.6 years (SD: 12.7).

A total of 513 patients (10.2%) of the total study population had been prescribed an antidepressant drug for the first time during the four-year observation period. This corresponded to an average cumulative incidence of 2.7% per year. Antidepressant drug use was observed in 348 and 247 migraine and non-migraine patients, respectively, of whom a total of 82 were excluded from further analysis as they were considered non first time users. A total of 300 migraine patients (11.9%) had initiated antidepressant treatment prior to or after the index date as opposed to 213 reference patients (8.5%), (RR adj 1.4; 95% CI 1.2–1.7). (Figure 1 and Table 2).

Fig. 1



Incidence of initiation of antidepressant drugs prior to and after index date.

There were no striking fluctuations in the initiation of antidepressant treatment prior (5.8%) or after (6.2%) the initiation of ergotamine or sumatriptan. This incidence pattern was similarly observed for the non-migraine population. Notably, for the migraine patients the cumulative incidence per six-monthly interval had reached its highest level shortly prior to (1.7%) and after (1.8%) the index date, respectively. For the reference group, the incidence remained consistent throughout the observation period at 1.1%, for which minimal fluctuation during the six monthly intervals, prior to and after the index dates, was found.

Although, the initiation of antidepressive treatment was predominantly prescribed by general practitioners for all patients (Table 2), a weaker involvement by neurologists compared to general practitioners was observed in migraine patients (RR adj 0.6; 95% CI 0.4–0.9). Furthermore migraineurs having started antidepressant therapy demonstrated a stronger comorbidity index, as defined by the chronic disease score of > 2, compared to non-migraine patients (RR adj 2.7; 95% CI 1.7–4.2). There were no large differences observed between both groups in terms of gender, age or physician contact (or prescription exposure). A weaker preference for an SSRI as a first line antidepressant, however, was in fact observed for the migraine population (RR adj 0.5; 95% CI 0.3–0.7).

Table 3 displays the strength of the association between various determinants examined and initiation of anti-

Table 2 Determinants of initiation of antidepressant medication for migraine versus non migraine patients

	Migraine *N* (%)	Non-migraine *N* (%)	RR crude [95% CI]	RR adj [95% CI]
Overall	300 (12.2)	213 (8.6)	1.5 [1.2–1.8]	1.4 [1.2–1.7]
Period of initiation				
Prior	145 (5.9)	115 (4.6)	1.0 [reference]	1.0 [reference]
Post	155 (6.3)	98 (3.9)	1.3 [0.9–1.8]	1.3 [0.9–1.8]
Type of antidepressant				
TCA	195 (65.0)	97 (45.5)	1.0 [reference]	1.0 [reference]
SSRI	94 (31.3)	102 (47.9)	0.5 [0.3–0.7]	0.5 [0.3–0.7]
MAOI	2 (0.7)	2 (0.9)	0.5 [0.1–3.6]	0.5 [0.1–3.4]
Other	9 (3.0)	12 (5.6)	0.4 [0.2–0.9]	0.3 [0.1–0.8]
Prescriber				
General practitioner	242 (80.7)	154 (72.3)	1.0 [reference]	1.0 [reference]
Specialist	58 (19.3)	59 (27.7)	0.6 [0.4–0.9]	0.6 [0.4–0.9]
Comorbidity index				
0	106 (35.3)	112 (52.6)	1.0 [reference]	1.0 [reference]
≤ 2	89 (29.7)	60 (28.2)	1.6 [1.0–2.4]	1.6 [1.0–2.4]
>2	105 (35.0)	41 (19.2)	2.7 [1.7–4.2]	2.7 [1.7–4.2]
Physician contact				
Rx exposure				
≤ 3	17 (5.7)	15 (7.0)	1.0 [reference]	1.0 [reference]
>3–6	51 (17.0)	48 (22.5)	0.9 [0.4–2.1]	1.0 [0.4–2.2]
>6–9	61 (20.3)	42 (19.7)	1.3 [0.6–2.8]	1.4 [0.6–2.6]
>9	171 (57.0)	108 (50.7)	1.4 [0.7–2.9]	1.2 [1.1–1.3]

RR adjusted for comorbidity index score; TCA: tricyclic antidepressant; SSRI: selective serotonin reuptake inhibitor; MAOI: monamine oxidase inhibitor; other: non SSRI drug.

depressants only within our migraine population. Female gender (RR adj 1.3; 95% CI 1.1–1.7) and the use of gastrointestinal drugs (RR adj 1.6; 95% CI 1.2–2.3) were found to be weakly associated with the initiation of antidepressant drug treatment after adjusting for age, gender, type of abortive migraine drug and comorbidity index score. The concomitant use of benzodiazepines (RR adj 4.7; 95% CI 3.5–6.3), migraine prophylactic drugs (RR adj 2.1; 95% CI 1.6–2.8) and NSAIDs (RR adj 1.8; 95% CI 1.4–2.3) was considerably higher in patients having initiated an antidepressant. This was further highlighted by an increased comorbidity index score >2 (RR adj 2.5; 95% CI 1.8–3.3). An assessment of severity of migraine as a potential determinant for the initiation of antidepressant therapy was indirectly estimated by the consumption (therapeutic intensity) and switch patterns of ergotamine and sumatriptan displayed during a one year period prior to initiating antidepressant therapy. Heavy use of ergotamine and sumatriptan, defined by a therapeutic intensity of ≥ 150 DDDs, was more pronounced in the index group than in the reference group (RR adj 3.4; 95% CI 1.4–8.5) as well as an increased tendency to switch treatment from ergotamine to sumatriptan or visa versa during this period (RR adjusted 2.5; 95% CI 1.6–4.0).

Discussion

The initiation of antidepressants within our migraine patient population was only slightly higher to that found in the reference group, 12% compared to 9%. Characteristics most clearly and independently associated with the use of antidepressants within the migraine population were the high burden of comorbidity, concomitant use of benzodiazepines, migraine prophylactic medication, NSAIDs, and heavy as well as switching use of specific migraine analgesia.

The prescribing of (migraine and non-migraine) antidepressant treatment for the total study population was approximately 3% per year and similar to data obtained from other European studies is considered low (Rouillon *et al.*, 1996; Bellantuono *et al.*, 2002). Rouillon *et al.* (1996) determined that 2.75% of their study population had been prescribed antidepressant therapy, far lower to the actual prevalence estimated for depression in the general population which is about 10%. Possible reasons for under treatment of the population suffering from depressive disorders may be the underreporting of related symptoms to physicians and general problems with access to medical care (Druss *et al.*, 2000).

A number of cross-sectional and longitudinal studies have estimated that the lifetime prevalence of major depression in migraineurs may range from 30% to 40% (Breslau *et al.*, 2000; Juang *et al.*, 2000; Breslau, 1998; Mattsson and Ekeslius, 2002; Fasmer, 2001). The incidence of antidepressant drug use, as an indication of co-existing depression, in our study is, therefore, far lower. Data from

Table 3 Determinants of antidepressant drug use within ergotamine and sumatriptan patients

Determinant	Initiation of antidepressant medication		OR (95% CI)	OR adj (95% CI)
	Yes $n=300$ (%)	No $n=2,169$ (%)		
Gender				
Male	43 (14.3)	380 (17.5)	1.0 [reference]	1.0 [reference]
Female	257 (85.7)	1789 (82.4)	1.3 [0.9–1.8]	1.3 [1.1–1.9]
Mean age (SD) in years[*]	45.1 (12.5)	44.3 (12.3)		
<45 years	152 (50.6)	1081 (49.8)	1.0 [reference]	1.0 [reference]
≥ 45 years	148 (49.3)	1088 (50.2)	1.0 [0.8–1.2]	0.9 [0.7–1.1]
Type of migraine analgesia				
Ergotamine	218 (72.7)	1680 (77.5)	1.0 [reference]	1.0 [reference]
Sumatriptan	82 (27.3)	489 (22.5)	1.3 [1.0–1.7]	1.3 [1.0–1.8]
Comedication				
Cardiovascular	21 (7.0)	172 (7.9)	0.9 [0.5–1.4]	1.2 [0.7–2.0]
Benzodiazepines	234 (78.0)	892 (41.1)	5.1 [3.8–6.8]	4.7 [3.5–6.3]
Diabetes	13 (4.3)	68 (3.1)	1.4 [0.8–2.6]	1.4 [0.8–2.6]
Gastrointestinal	47 (15.7)	222 (10.2)	1.6 [1.2–2.3]	1.6 [1.2–2.3]
Migraine prophylaxis	104 (34.7)	423 (19.5)	2.2 [1.7–2.8]	2.1 [1.6–2.8]
NSAIDs	191 (63.7)	1060 (48.9)	1.8 [1.4–2.4]	1.8 [1.4–2.3]
Oral contraception	151 (50.3)	974 (44.9)	1.2 [1.0–1.6]	1.3 [1.0–1.8]
Comorbidity index				
0	106 (35.3)	1149 (53.0)	1.0 [reference]	1.0 [reference]
1–2	89 (29.7)	553 (25.5)	1.7 [1.3–2.4]	1.7 [1.3–2.4]
>2	105 (35.0)	467 (21.5)	2.4 [1.8–3.3]	2.5 [1.8–3.3]
Physician contact				
Rx exposure				
≤ 3	17 (5.7)	518 (23.9)	1.0 [reference]	1.0 [reference]
3–6	51 (17.0)	745 (34.3)	2.1 [1.2–3.7]	2.1 [1.2–3.6]
6–9	61 (20.3)	417 (19.2)	4.5 [2.6–7.7]	4.6 [2.6–8.0]
>9	171 (57.0)	489 (22.5)	10.7 [6.4–17.8]	11.4 [6.8–19.2]
Therapeutic intensity				
Mean DDDs (sem)[**]	28.1 (2.7)	19.3 (0.8)		
<30	121 (78.1)	1554 (81.0)	1.0 [reference]	1.0 [reference]
30–<90	20 (12.9)	286 (14.9)	0.9 [0.6–1.5]	0.9 [0.5–1.5]
90–<150	7 (4.5)	56 (2.9)	1.6 [0.7–3.6]	1.6 [0.7–3.6]
150	7 (4.5)	23 (1.2)	3.9 [1.6–9.3]	3.4 [1.4–8.5]
Switch use[†]	28 (18.1)	115 (7.3)	2.8 [1.8–4.4]	2.5 [1.6–4.0]

OR adjusted for age, gender, type of abortive migraine analgesia, comorbidity index score.
[*]$P=0.3$; [**]$P=0.004$; adjusted univariate analysis for age, gender, type of abortive migraine analgesia, comorbidity index, and physician contact estimate.
[†]ergotamine →sumatriptan or sumatriptan →ergotamine.

the same studies have shown that migraineurs have a two or three fold increase in the risk of major depression (Breslau *et al.*, 2000; Swartz *et al.*, 2000; Merikangas *et al.*, 1990). However, contrary to our a priori expectations, the relative risk of antidepressant drug use in our migraine population compared to the non-migraine population was estimated at 1.4, far lower to that seen in these studies. Finally, Millson *et al.* (2000) found that that between 1993 and 1997 23% of all triptan patients studied were diagnosed by a general practitioner with depression and was found to be significantly higher to that observed in non-triptan patients (16.8%). According to this study, this is most likely attributed to an increasing consultation with the physician due to an increasing severity of migraine. Of the ergotamine and sumatriptan patients in our study an estimated 12% had initiated antidepressant treatment during the observation period (either prior to or after the initiation of ergotamine or sumatriptan), far lower than those who had been diagnosed and treated with depression in the former study. This available data suggests a relative under treatment of depression in patients suffering from migraine within our study area, for which various underlying reasons are plausible.

Firstly, the use of antidepressants offers only one of the available treatments for depression. For example, cognitive behaviour therapy or other psychotherapies can be as effective for specific individuals, either alone or in conjunction with medication. Furthermore, our migraine population was restricted to those patients who had been using specific abortive migraine drugs. A few drug utilization studies conducted in the migraine population have consistently found that the prescribing of these drugs is low (Edmeads *et al.*, 1993; Furlong *et al.*, 1996). von Korff *et al.* (1999) found that only 17% of a group of primary care migraine patients were using these drugs

and that the majority were using OTC and/or non-specific prescription analgesics. Our migraine population can therefore only represent a portion of the overall migraine population, whereby the prevalence of depressive comorbidity compared to the general population may be underestimated.

The relatively high level of under consultation frequently observed within the migraine population may lead to under diagnosis and under treatment for migraine itself as well as potential neurological disorders and can be considered an alternative explanation (Furlong *et al.*, 1996). Recognition and treatment of psychiatric comorbidity in migraine patients, as noted within the general population, should be emphasised as the quality of life of many migraineurs can be further compromised in the presence of comorbid psychiatric illnesses (Lipton *et al.*, 2000).

The presence of coexisting migraine and depression will certainly provide the prescriber opportunities but also limitations for treatment. Preliminary findings have demonstrated that some antidepressants, such as fluoxetine, nefazodone, and moclobemide have shown promising results in the preventive treatment of migraine and chronic daily headaches (Silberstein and Goadsby, 2002). They may, therefore, allow the physician to effectively treat both migraine and depression. However, the combination of an SSRI or MAOI with sumatriptan are not devoid of serious side-effects, such as the serotonin syndrome, and as such should be used with caution when indicated (Putnam *et al.*, 1999; Joffe and Sokolov, 1997). Evidence of adherence to this precautionary measure can distinctly be observed in our study as the prescribing of a TCA was clearly preferred to an SSRI as a first line antidepressant in the majority of our ergotamine and sumatriptan treated patients. Nevertheless, since the SSRIs are the most commonly prescribed of antidepressants, the prescribing of these drugs to a migraineur using sumatriptan will be unavoidable, as we had observed in approximately one third of treated migraineurs (Rouillon *et al.*, 1996).

Variations in the incidence of antidepressant use prior to and after the initiation of specific abortive drug treatment could not be found, suggesting that the risk of initiation of treatment of the two conditions is bi-directional (i.e. treatment of each disorder increases the risk of treating the other). This is further supported by our findings that a gradual increase in the initiation of psychotropic drug use was observed shortly prior to as well as after the initiation of ergotamine and sumatriptan. However, due to the lack of clinical data, we cannot claim whether the association between the onset of migraine and psychiatric comorbidity is bi-directional, as confirmed in other studies (Breslau *et al.*, 2000; Breslau *et al.*, 1991; Breslau, 1998), as the initiation of specific abortive migraine treatment cannot be considered an indication of the initial diagnosis of migraine for a patient, but more likely an indication of an increasing severity of the headache.

The presence of chronic diseases, as defined by the chronic disease score was strongly associated with the use of antidepressants within the migraine population. Of particular interest was the higher usage of NSAIDs, migraine prophylactic medications (including amitriptyline), and benzodiazepines by migraine patients initiating antidepressants as compared to those who did not. A recent study found that the use of antidepressants and benzodiazepines was predictive for the initiation of migraine prophylactic medication, which indirectly highlights the relationship between increased severity of migraine and psychiatric comorbidity (Rahimtoola *et al.*, 2002; Radat *et al.*, 1999). The elevated use of benzodiazepines may best be explained by the fact that migraineurs suffering from co-existing depression are also likely to suffer from anxiety disorders whereby the use of benzodiazepines may be required (Juang *et al.*, 2000; Birkenhaeger *et al.*, 1995).

A higher severity index indirectly characterised by a heavy consumption (>150 DDDs per year) and increased concomitant use of specific abortive migraine drugs was likewise found to be strongly associated with the initiation of antidepressants in our study. A higher prevalence of anxiety and depression has been associated with patients suffering from severe forms of migraine and chronic use of acute migraine medication (Stewart *et al.*, 1994; Lipton *et al.*, 2000; Juang *et al.*, 2000; Radat *et al.*, 1999). Mitsikostas *et al.* (1999) found that the risk of depressive disorders was dramatically elevated in patients with drug overuse headache and may be the result of prexisting comorbidity of severe migraine and depression or vice versa. Based upon these and our findings it can be implied that the need for antidepressive treatment by our patients is strongly related to patients in whom the severity of migraine and therapeutic demands are increased. Furthermore, these patients, particularly those suffering from migraine with aura and depression are at increased risk for attempted suicide compared to patients with depression or migraine alone (Breslau, 1998). Our study further emphasises the importance of recognising and treating psychiatric comorbidity in migraineurs.

A major limitation to our study was attributed to the lack of diagnostic or clinical information. For this reason, we were unable to differentiate between migraine and cluster headache among sumatriptan patients or migraine patients actually suffering from depression. Patients suffering from cluster headache compared to migraine patients often require increased use of abortive medications, such as sumatriptan preferably by the subcutaneous

dosage form, due to the increased frequency of headache attacks. Therefore our claim that heavy use of specific abortive medication is an indirect estimation of increasing severity of migraine may be misleading due to the fact that the higher therapeutic intensity categories defined in this study may have largely included patients suffering from cluster headache. However, in view that the prevalence of this syndrome in the general population is extremely low (0.05%–0.2%) compared to migraine (10%–15%) and the fact that almost all heavy users were tablet-only users, we believe that this potential limitation is of minor significance (Tomkins *et al.*, 2001; Tonon *et al.*, 2002).

In order to identify migraineurs suffering from depression we were required to use specific antidepressant drugs as markers for the latter which will without doubt exert a confounding effect on our analysis. Most importantly, the use of other antidepressants, such as fluvoxamine or fluoxetine, with or without specific anti-migraine drugs may have been a deliberate approach of the physician to treat migraine alone or both migraine and depression in certain patients. However, since these drugs were not recommended by national and international therapeutic guidelines for migraine during the study period, we did not include them as established migraine prophylactic agents. Furthermore, antidepressants are used for a variety of other disorders including obsessive-compulsive disorder, sleeping disorders and neuropathic pain, therefore leading to potential misclassification of depression in some patients. Since amitriptyline was recommended as a migraine prophylactic drug of choice by therapeutic guidelines for general practitioners in The Netherlands and elsewhere we were faced with the dilemma whether or not to include this drug in the analysis, as our estimation of the incidence of antidepressant treatment in our migraine population will certainly have been effected. Nevertheless our estimations should be viewed with caution and the overall incidence of antidepressant treatment should be restricted to those drugs selected in our study. Finally, some imprecision in our analysis of the different usage patterns of and estimation of therapeutic intensity as a measure of specific abortive migraine drug consumption 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 (Petri *et al.*, 1988). Our analysis of therapeutic intensity for example included only those patients who presented more than one prescription for ergotamine or sumatriptan during the total follow-up period.

In conclusion, although a slight increased use of antidepressants was found in our migraine population compared to the non-migraine population, the difference was far lower than that estimated for the prevalence of depression in migraine. Despite the limitations surrounding our study, we believe this adds to existing evidence that psychiatric comorbidity is under treated in general practice for patients suffering from migraine. Increased efforts should be made to identify migraineurs at heightened risk for psychiatric co-morbidity as this group probably represents that segment of the migraine population in whom medical and therapeutic management is problematic.

Acknowledgements

This study is funded by a grant from the 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.

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