academicJournals

Vol. 7(41), pp. 2755-2762, 8 November, 2013
DOI 10.5897/AJPP2013.3893
ISSN 1996-0816 © 2013 Academic Journals
http://www.academicjournals.org/AJPP

African Journal of Pharmacy and Pharmacology

Full Length Research Paper

Antipsychotic drug prescribing to patients with dementia in a South African patient population

Ilse Truter

Drug Utilization Research Unit (DURU), Department of Pharmacy, Nelson Mandela Metropolitan University (NMMU), P. O. Box 77000, Port Elizabeth, 6031, South Africa.

Accepted 7 November, 2013

The primary aim of this study was to determine the prescribing pattern of antipsychotic drugs to patients with dementia in a South African patient population. A retrospective, cross-sectional drug utilisation study was conducted on 2010 prescription data of a national community pharmacy group. A total of 1231 patients were prescribed medication for dementia. The average age of patients was 75.10 (standard deviation (SD)=10.27) years, with 56.13% of female patients. A total of 5264 anti-dementia products were prescribed at an average cost of R584.06 per product. Donepezil accounted for 45.84% of prescriptions, followed by memantine (36.51%). Differences were observed between females and males with respect to the prescribing frequency of the different active ingredients (χ^2=48.491; d.f.=3; p<0.0001). Patients received on average 4.28 (SD=3.77) anti-dementia products over the year. Most patients (94.31%) received only one anti-dementia active ingredient during the year. Nearly a quarter of patients (23.23%) received one or more antipsychotic drugs despite "black box" warnings. Slightly more females were prescribed antipsychotic medication, with risperidone and quetiapine the most often prescribed antipsychotics. Older generation antipsychotics, such as haloperidol, were also prescribed. Despite warnings by health authorities, nearly a quarter of patients were prescribed antipsychotics. More comprehensive studies on antipsychotic use in dementia are needed to determine whether these drugs are used rationally and to ensure that the health of patients with dementia is not placed at risk.

Key words: Alzheimer's disease, dementia, antipsychotics, prescribing patterns, drug utilisation study, risperidone.

INTRODUCTION

The 2013 World Alzheimer Report (Prince et al., 2013) estimated that the numbers of dependent older people will increase nearly threefold from 101 million in 2010 to 277 million in 2050, and in addition, that nearly half of these older people with needs for care are likely to be living with and experiencing the effects of dementia. The most accurate number remains that 36 million people worldwide live with Alzheimer's disease or other dementias (Prince et al., 2013).

Alzheimer's disease is the most common component of dementia (Anderson, 2013). The prevalence of Alzheimer's disease increases with age, and is most prevalent in individuals older than 60 years. It has been shown to double every five years after the age of 65 years (Bridges-Webb and Wolk, 2003). Latin America, China and India are experiencing unprecedentedly rapid demographic aging with an increasing number of people with dementia (Prince et al., 2007). The International

*Corresponding author. E-mail: ilse.truter@nmmu.ac.za. Tel: +27-41-504 2131. Fax: +27-41-504 2744.

10/66). Dementia Research Group's (10/66 DRG) initiative aims to establish the prevalence of dementia worldwide. The 10/66 studies indicate that two-thirds (66%) of people with dementia live in low and middle income countries, yet 10% or less of population-based research has been carried out in these regions (Prince et al., 2007).

The exact prevalence of dementia and Alzheimer's disease in South Africa is not known. World Health Organization (WHO) estimates of the burden of disease in South Africa suggest that non-communicable diseases caused 28% of the total burden of disease measured by disability-adjusted life years (DALYs) in 2004 (Mayosi et al., 2009). Cardiovascular diseases, diabetes mellitus, respiratory diseases, and cancers together contributed to 12% of the overall disease burden, and neuropsychiatric disorders (such as schizophrenia, bipolar depression, epilepsy and dementia) accounted for 6% (Mayosi et al., 2009). However, dementia rates are predicted to increase at an alarming rate in the least developed and developing regions of the world despite mortality resulting from malnutrition, poverty, war and infectious diseases (Kalaria et al., 2008). WHO projections suggest that by 2025, about three-quarters of the estimated 1.2 billion people aged 60 years and older will reside in developing countries (Kalaria et al., 2008; Active Ageing: A Policy Framework, 2002; Health Report, 2002). Thus, by 2040, if growth in the older population continues, and there are no changes in mortality or burden reduction by preventive measures, 71% or 81.1 million dementia cases will be in the developing world (Kalaria et al., 2008; Ferri et al., 2005).

Psychotropic medicine is often used to treat secondary symptoms of Alzheimer's disease such as depression, agitation and sleep disorders (Anderson, 2013). These non-cognitive symptoms may prove more bothersome to patients and families than the cognitive impairment and can cause considerable stress on both patients and caregivers. Despite the potential value of psychotropic medicines, a particular concern is the use of excess anti-psychotics to control disruptive behaviour. Appropriate use of antipsychotic medication can relieve symptoms and reduce distress and can increase safety for patients and caregivers. However, their use may be associated with worsening cognitive impairment (Taylor et al., 2009), oversedation, falls, tardive dyskinesia, neuroleptic malignant syndrome, as well as with hyperlipidaemia, weight gain, diabetes mellitus, cerebrovascular accidents and death. An increased risk of especially cardiovascular symptoms, glucose intolerance, stroke and death has been associated with both the use of typical and atypical antipsychotics in some psychiatric disorders.

In April 2005, the USA Food and Drug Administration (FDA) issued an advisory and subsequent black box warning regarding the risks of atypical antipsychotic use among elderly patients with dementia (DeNoon, 2008; Dorsey et al., 2010). The FDA warned that clinical trial results strongly suggested that newer "atypical" antipsychotics increase the risk of death in dementia patients. The FDA required these drugs to carry its strongest black box warning on their labels. More recently, in 2008, based on observational studies, the FDA warned that older antipsychotics also seem to increase dementia patients' risk of death (DeNoon, 2008). These drugs therefore, too, will carry a black box warning.

An increased mortality risk therefore exists in elderly dementia patients receiving antipsychotic agents. There is an increased risk of fatal arrhythmias associated with several older and newer (atypical) antipsychotic agents due to the prolongation of the QT interval. The older antipsychotic drugs may even be more likely than the newer atypical antipsychotics to cause troublesome "extrapyramidal" symptoms such as tics and Parkinsonism. But the drugs, many in use since the 1950s, are still being prescribed. Older drugs that carry the FDA black box warning (not all available in South Africa) include prochlorperazine, haloperidol, loxapine, thioridazine, molindone, thiothixene, pimozide, fluphenazine, trifluoperazine, chlorpromazine and perphenazine. Newer drugs that continue to carry the FDA black box warning include aripiprazole, clozapine, paliperidone, risperidone, quetiapine, olanzapine, ziprasidone, and the combination of fluoxetine and olanzapine (DeNoon, 2008) (the combination is not available in South Africa).

The overuse of antipsychotics in dementia is reported to be a shared issue in Europe and several other countries in the world (Antipsychotics in Dementia, 2012). Although the exact extent of this exposure is not sufficiently documented, the rate of exposure is reported to range from 15% in the ambulatory setting to 20 to 40% in nursing homes, which is a much higher rate than in the general population (Antipsychotics in Dementia, 2012). A 2009 study suggested that 180000 people with dementia were taking antipsychotic medication in the UK and found that the drugs resulted in 1800 additional deaths (Huybrechts et al., 2012). The study published in the British Medical Journal in February 2012 (Huybrechts et al., 2012) concluded that although causality could not be proved and the possibility of residual confounding could not be ruled out, evidence was provided about the risk of using antipsychotic drugs in older patients and it reinforced the concept that antipsychotics should not be used in the absence of a clear need.

The Medicines Control Council (MCC) in South Africa published a Medicine Safety Alert in December 2008 which was updated in June 2009 entitled: "Atypical Antipsychotics in Elderly Patients with Dementia" in which they informed prescribers of increased risks of cerebrovascular adverse events (including strokes and transient ischaemic attacks) and mortality, associated with

the use of atypical antipsychotics in elderly patients with dementia. The atypical antipsychotics to which this medicine safety alert referred to included clozapine, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole (Medicine Safety Alert: Atypical Antipsychotics in Elderly Patients with Dementia, 2009).

Risperidone is currently the only drug licenced in the UK for the behavioural and psychological symptoms of dementia (Taylor et al., 2009). It is only indicated for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is harm to self or others (Use of Atypical Antipsychotics in Treatment of Dementia Declined after FDA Warning, 2011). The MCC in South Africa has also subsequently deleted risperidone from the list of antipsychotic drugs not indicated for use in the elderly (Medicine Safety Alert: Atypical Antipsychotics in Elderly Patients with Dementia, 2009).

During February 2011, it was reported that, in the USA, the warning issued by the FDA regarding the use of atypical antipsychotics for the treatment of dementia resulted in a significant decline in the use of these medicines for treating dementia symptoms in elderly patients (Taylor et al., 2009; Kales et al., 2011). Extreme caution should be exercised in using these drugs, although their judicious use can have a positive impact on problematic behavioural symptoms. A dose decrease or discontinuation should be considered periodically for all dementia patients receiving antipsychotic medicine. No data are available for South Africa. The hypothesis for the study was therefore that despite warnings by health authorities, patients with dementia were still being prescribed antipsychotics. Studies on antipsychotic use in dementia are needed in South Africa to determine whether these drugs are used rationally and to ensure that the health of patients with dementia is not placed at risk. This is not only important for patients with dementia, but also for the health care system to ensure that scarce health care resources are used optimally and rationally.

The primary aim of the study was to determine the prescribing of antipsychotic drugs to patients with dementia in a South African patient population.

MATERIALS AND METHODS

A retrospective, cross-sectional drug utilisation study was conducted on prescription data for 2010 of a national community pharmacy group in South Africa. The pharmacies in this group are distributed throughout South Africa, and are located in all nine provinces of South Africa. These pharmacies are mostly located in urban areas, and therefore have the same pattern of distribution as the majority of pharmacies in South Africa.

The database contained 2,665,025 records of central nervous system medicine for 575469 patients for the year 2010. Each medication record contained information on the age and gender of the patient, with a unique number to identify each patient, the date of the prescription, detailed information on the dispensed drug (name, package size, formulation, strength and quantity), price and various reimbursement variables.

The Anatomical Therapeutic Chemical (ATC) Classification System (ATC/DDD Index 2011, 2011), MIMS (Snyman, 2011) and the South African Medicines Formulary (Rossiter, 2012) were used to identify the medicines that were prescribed. All prescriptions for Alzheimer's disease (MIMS Category 1.10 (Snyman, 2011) or ATC Group N06D (ATC/DDD Index 2011, 2011; Rossiter, 2012)) were extracted and analysed. No diagnoses were available in the database, therefore MIMS and the ATC drug classification system were used to identify the active ingredients used most commonly for Alzheimer's disease and dementia (the active ingredients analysed included donepezil, galantamine, rivastigmine and memantine). The dementia patients in this study were therefore identified using a proxy measure, namely anti-dementia drug prescriptions since no diagnoses were available in the database. Microsoft Access® and Excel® were used to analyse the data. Descriptive statistics were calculated. Ethical approval to conduct the study was granted by the Research Ethics Committee (Human) of the Nelson Mandela Metropolitan University.

One Euro (€1.00) was equal to R9.38 (South African Rands), one US Dollar ($1.00) was equal to R7.64 and one British Pound (£1.00) was equal to R11.48 at the time of the study (30 June 2010).

RESULTS

Age and gender distribution of patients

A total of 1231 patients were prescribed medication for dementia. The age and gender distribution of patients is as shown in Figure 1. More than half (56.13%) of the patients were females. The average age of patients was 75.10 (standard deviation (SD)=10.27) years (range: 21 to 98 years). The average age of females was 75.05 (SD=9.99) years and of males 75.16 (SD=10.63) years. Most patients (41.27%) were between 70 and 79 years of age, followed by patients between 90 and 89 years (32.58%). A small percentage (2.44%) of patients receiving anti-dementia products was younger than 50 or 90 years and above (3.49%).

Anti-dementia products prescribed

A total of 5264 anti-dementia prescriptions (products) was prescribed at a cost of R3 074 487 (average cost of R584.06 per prescription). The four active ingredients prescribed were donepezil, rivastigmine, galantamine and memantine. Patients received on average 4.28 (SD=3.77) prescriptions for anti-dementia products over the year. The AChEIs accounted for 63.49% of prescriptions and the NMDA-receptor antagonist (memantine) for 36.51%. Donepezil accounted for 45.84% of prescriptions for

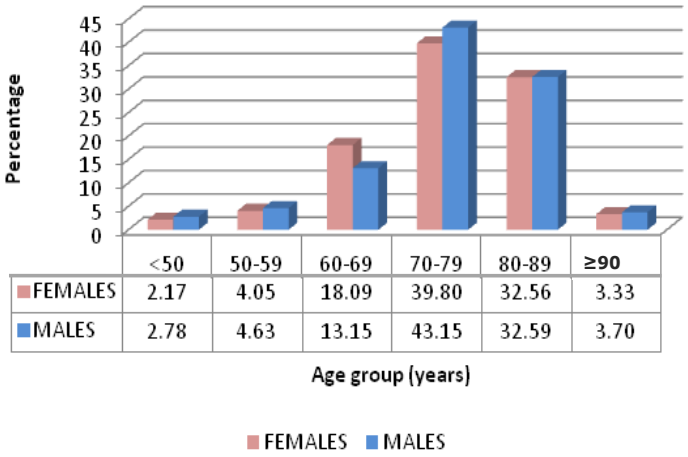

Figure 1. Age and gender distribution of patients (n=1231).

anti-dementia medicine, followed by memantine (36.51%) (Table 1). Differences were observed between females and males with respect to the prescribing frequency of the different active ingredients (χ^2=48.491; d.f.=3; p<0.0001). Donepezil was more often prescribed to female patients and memantine to male patients.

Only one trade name product for memantine (Ebixa®, Lundbeck) is available on the South African market. Ebixa® 10 mg tablets was the single most often prescribed trade name product accounting for 36.47% of trade name products prescribed for dementia. Only two prescriptions for Ebixa® oral drops 10 mg/g were prescribed (accounting for 0.04% of trade name products prescribed for dementia).

Most patients (94.31%) received only one active ingredient over the year, while 69 patients received two different active ingredients, and one patient three different active ingredients. The most often prescribed combination was memantine and donepezil (37 patients), followed by memantine and galantamine (21 patients).

Prescribing of antipsychotic products

A total of 1505 antipsychotic products were prescribed to 286 of the 1231 patients in the study (23.23% of patients) at a cost of R633 655. The average cost per anti-psychotic product was R421.03. Slightly, more females were prescribed antipsychotic medication (24.89% females versus 21.11% males). Patients received on average 5.26 (SD=4.39) antipsychotic products over the year. Female patients received on average 4.97 (SD=4.41) antipsychotic products and male patients 5.70 (SD=4.36) products over the year. The average age of patients that prescribed psychotropic drugs was 71.69 (SD=14.44) years.

Risperidone was the most often prescribed antipsychotic (53.16%) followed by quetiapine (31.10%) (Table 2). Older generation antipsychotics, such as haloperidol, were also prescribed although at low prescribing frequencies.

The percentage prescription of anti-dementia and anti-psychotic products over the year is illustrated in Figure 2. There was a small increase in the prescribing rate of antipsychotic products, but the study was too small to make any definite conclusions from this finding.

DISCUSSION

Donepezil, rivastigmine, galantamine and memantine were the drugs prescribed in this study for the treatment of dementia. Anti-dementia drugs appear to be equally efficacious, have a similar side effect profile, their cost is approximately equivalent and there is little evidence to recommend one over the other. They appear to provide a modest enhancement of cognitive function in patients with Alzheimer's disease, but do not seem to have a significant impact on the underlying pathophysiology of Alzheimer's disease.

A total of 1231 patients were prescribed medication for dementia. This represented less than one percent of the patients in the total database. The exact reason for this apparently low percentage is not clear. It may have been that patients may have had dementia but were not prescribed anti-dementia drugs that patients with dementia may not have been diagnosed with dementia, or that patients may have been prescribed anti-dementia drugs but were not claiming the products from their medical insurance schemes and were therefore not included in the study. It is therefore possible that a potentially large proportion of dementia patients was overlooked and did not receive anti-dementia drugs. The diagnosis of dementia is also not always accurate, which can lead to a misclassification of disease. The findings of this study are therefore not necessarily generalisable to the whole of South Africa as far as the prevalence of dementia is concerned.

Further limitations of the study were that no clinical information and diagnoses were available in the database. These medicines are, however, nearly exclusively indicated for the treatment of dementia of Alzheimer's disease (Rossiter, 2012), except in the cases where it is used off-label. The possibility of off-label use is supported by the fact that a small percentage of younger patients received anti-dementia medicines. These younger patients received once-off prescriptions for dementia medicines, which was probably for off-label use. Memantine, for example, is according to the literature used off-label for various psychiatric disorders,

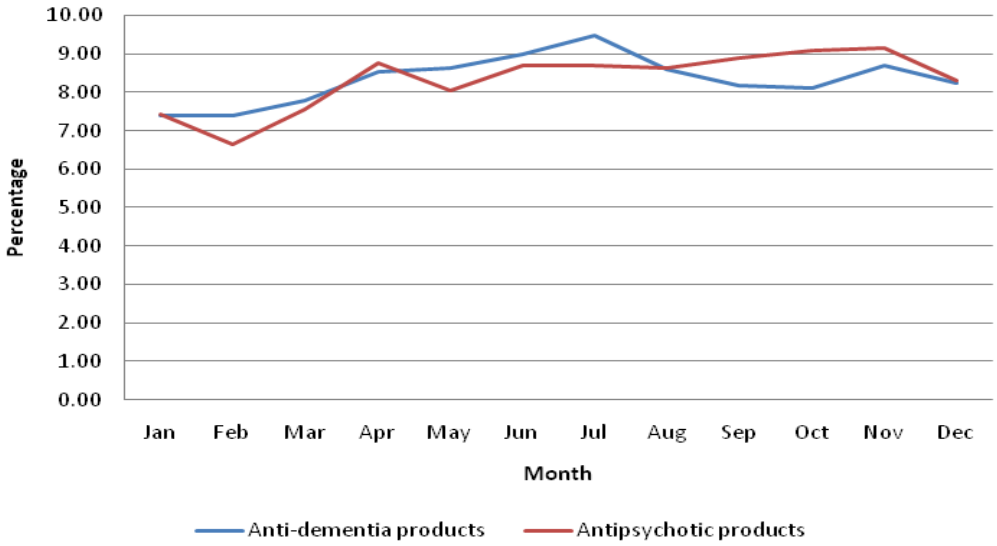

Figure 2. Percentage prescribing frequency of anti-dementia and antipsychotic products over the 12 months*. *The line diagram illustrates the monthly number of anti-dementia products expressed as a percentage of the total number of anti-dementia products (blue line) and the monthly number of antipsychotic products as a percentage of the total number of antipsychotic products (red line).

Table 1. Prescribing frequency of anti-dementia active ingredients according to gender groups (n = 5264)*.

Active ingredient	Percentage		Both genders	
	Female (n = 2969)	Male (n = 2295)	Number	%
Donepezil	49.98	40.48	2413	45.84
Memantine	33.98	39.78	1922	36.51
Galantamine	15.59	19.39	908	17.25
Rivastigmine	0.44	0.35	21	0.40
Total	100.00	100.00	5264	100.00

*χ^2=48.491; d.f.=3; p<0.0001.

Table 2. Antipsychotic active ingredient prescribing frequency according to gender groups (n = 1505).

Active ingredient	Percentage		Both genders	
	Female (n = 855)	Male (n = 650)	Number	(%)
Risperidone	60.12	44.00	800	53.16
Quetiapine	25.73	38.15	468	31.10
Olanzapine	5.15	7.54	93	6.18
Haloperidol	2.46	2.00	34	2.26
Aripiprazole	1.52	2.92	32	2.13
Chlorpromazine	1.64	0.92	20	1.33
Amisulpiride	0.58	1.85	17	1.13
Trifluoperazine	0.58	1.54	15	1.00
Clozapine	1.17	0.46	13	0.86
Ziprasidone	0.70	0.62	10	0.66
Clothiapine	0.35	0.00	3	0.20
Total	100.00	100.00	1505	100.00

such as depression, schizophrenia, obsessive-compulsive disorder, substance abuse and binge eating disorder (Zdanys et al., 2008).

The age and gender distribution of patients given in Table 1 was similar to that of a previous South African retrospective database study on pharmacy records (Truter, 2010) conducted on 588 patients using 2008 data. In the study (Truter, 2010), the average age of patients was 75.54 years and 55.44% of patients were female (compared to 75.10 years and 56.13% in this study), and patients received on average of 4.28 (SD=3.77) prescriptions for anti-dementia products over the year.

The AChEIs accounted for 75.30% of prescriptions in this study, compared to 63.49% of prescriptions in the 2008 study (Truter, 2010). There was an increase in the prescription of the NMDA-receptor antagonist (memantine) from 24.70 to 36.51%. Donepezil accounted for 37.09% in the 2008 study compared to 45.84% in the 2010 study. There are three trade name products of donepezil available (the originator plus two generic products), whilst the other products have no generic equivalents on the South African market. The lower cost of the generic equivalents may have impacted on their increased prescription. The prescription of rivastigmine remained low.

Continuity of prescription was investigated, and it was observed that nearly a half of the patients (586 of the 1231 patients) received only one or two anti-dementia prescriptions during the year, which means that not all patients were using these products on a chronic or continual basis. Only 30.87% of the patients were prescribed six or more anti-dementia products during the year. There are various reasons why this may be the case. These products are relatively expensive and not all medical insurance schemes reimburse these products, so affordability may have played a role. It may also be because patients or caregivers may feel these products are not effective or making a big enough improvement on their quality of life.

Combination therapy with an AChEI and memantine is sometimes indicated in South Africa if the patient can afford it. The rationale for the combination therapy is based on the fact that the two drugs have different and complementary mechanisms of action. The National Institute for Clinical Excellence (NICE, 2011) guidelines did not find any additional benefit of combination therapy, although a study by Atri et al. (2013) did find that combination therapy has benefit. Generally therefore, combination therapy is not indicated by clinical guidelines although it may be used. Similar to the 2008 study (Truter, 2010) in which 5.27% of patients were prescribed more than one anti-dementia active ingredient, only 5.69% of patients in this study were prescribed a combination (the most often prescribed combination was memantine and donepezil). The cost of combination therapy and the lack of cost-effectiveness data may be reasons why combination therapy was not utilised more in this study.

The use of antipsychotic drugs in patients with dementia has been debated extensively yet little information is available in South Africa. Nearly a quarter of patients in this study (23.23% or 286 patients) received one or more antipsychotic drugs despite the black box warning issued in 2003 by the FDA and a warning in December 2008 by the MCC that antipsychotic drugs are best avoided in patients with dementia of the Alzheimer's type. Risperidone was the most often prescribed antipsychotic in this study and is currently also the only drug licenced in the UK for the behavioural and psychological symptoms of dementia (Use of Atypical Antipsychotics in Treatment of Dementia Declined after FDA Warning, 2011). It is indicated for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is harm to self or others (Taylor et al., 2009). The MCC in South Africa has also deleted risperidone from the list of antipsychotic drugs not indicated for use in the elderly (Medicine Safety Alert: Atypical Antipsychotics in Elderly patients with Dementia, 2009). It is therefore positive that risperidone was the active ingredient of choice in South Africa when antipsychotics were prescribed. A low percentage (4.78%) of the antipsychotics prescribed was conventional or first-generation antipsychotics.

These results were fairly similar to other studies (Ilyas et al., 2012; Kales et al., 2011). In a study examining the trends in prescriptions and costs of drugs for mental disorders in England between 1998 and 2010, it was observed that the bulk of antipsychotic prescription in 2010 was for olanzapine, quetiapine and risperidone, which accounted for 24, 23 and 17% of antipsychotic prescription items, respectively (Ilyas et al., 2012). In this study, the same three antipsychotic active ingredients were the most commonly prescribed although in different proportions (risperidone accounted for 53.16%, quetiapine for 31.20% and olanzapine for 6.18% in this study). In a study by Kales et al. (2011) on National Veterans Affairs data in the USA, trends in antipsychotic use in outpatients with dementia between 1999 and 2007 were investigated. These investigators found that olanzapine and risperidone showed declining rates and quetiapine showed an increase during the early warning period, but rates of use for all three antipsychotics declined during the black box warning period. Interestingly, there was a small but significant increase in anticonvulsant prescriptions in the black box warning period. The current study only investigated prescribing trends in 2010, and the exact effect of the FDA and MCC warnings can therefore not be detected over time.

It was, however, of concern that for every 3.50 anti-dementia products in this study, one antipsychotic product was prescribed (a total of 5264 anti-dementia and 1505 antipsychotic products were prescribed, that is, a ratio of 3.50 anti-dementia products for every one antipsychotic product). Although the anti-dementia prescriptions and the antipsychotic prescriptions did not always coincide exactly in terms of dates dispensed or issued, there was definite overlap for many patients indicating that patients were using these medicines concurrently. The use of antipsychotics in dementia needs a case-by-case evaluation weighing up the benefits and risks in order to ensure the best possible treatment for the patient. Because of the lack of clinical information, it is difficult to determine whether the prescription of antipsychotic drugs in dementia patients in this South Africa population is reasonable or excessive. More comprehensive studies on antipsychotic use in dementia are needed to determine whether these drugs are used rationally and to ensure that the health of patients with dementia is not placed at risk.

Conclusion

The results of this study regarding the prescription patterns of anti-dementia products were generally similar to that of a previous South African study. However, the prescription of antipsychotic drugs together with products for dementia has not been investigated previously in South Africa. Despite serious warnings by health authorities, nearly a quarter of patients on medication for Alzheimer's disease were prescribed antipsychotic drugs in this study. It is difficult to make definite conclusions since the study was firstly, too small, and secondly, there are no previous studies on antipsychotic prescription in dementia in South Africa to compare the findings of this study with. Also, it was not known what percentage of patients was living in nursing homes, the severity of their condition or the stage of Alzheimer's disease, or any information on co-morbid conditions. Further investigation is needed, and it is recommended that clinical studies as well as qualitative studies be conducted where the actual symptoms of patients can be evaluated against the effectiveness of treatment with antipsychotic drugs.

ACKNOWLEDGEMENTS

The authors acknowledged the pharmacy group for providing the data for the study. This work is based upon research supported by the National Research Foundation (NRF). Any opinion, findings and conclusions or recommendations expressed in this paper are those of the author and therefore the NRF do not accept any liability liability in regard thereto.

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