

Use and safety of psychotropic drugs in elderly patients

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Use and Safety of Psychotropic Drugs in Elderly Patients

Gebruik en veiligheid van psychotropische medicaties in de oudere patienten

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To my Mother



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CHAPTER 1

General Introduction



1.1. RATIONALE FOR THIS RESEARCH

Late life neuropsychiatric disorders

By 2050 we expect two billion persons over 65 years worldwide [1]. As the proportion of the world's population in the older ages continues to increase, the burden of Alzheimer's disease (AD), Parkinson's disease (PD) and other neuropsychiatric disorders increase as well. The percentage of persons with Alzheimer's disease increases from 1% of 60-year-olds to about 30% of 85-year-olds [2].

Prevalence studies estimated that 24.3 million people have currently dementia worldwide, with 4.6 million new cases of dementia every year (one new case every 7 seconds). The number of people affected by dementia will double every 20 years to 81.1 million by 2040 [3]. The prevalence of Parkinson's disease in persons above 65 years is 1.8% in Europe, with an increase from 0.6% in those aged 65 to 69 years to 2.6% in those 85 to 89 years [4].

Alzheimer's disease is a progressive neurodegenerative disorder manifested by cognitive and memory deterioration leading to progressive impairment of activities in daily living. Behavioral and psychotic symptoms of dementia (BPSD), including agitation, aggression, and psychoses, frequently occur in patients with dementia, particularly in advanced stages of the disease [5].

Parkinson's disease is primarily considered a motor disease characterized by rest tremor, rigidity, bradykinesia and postural disturbances. However, neuropsychiatric complications, including mood and anxiety disorders, fatigue, apathy, psychosis, cognitive impairment, dementia, sleep disorders and addictions, frequently complicate the course of the illness [6].

Independent of these well defined neurodegenerative diseases, a variety of psychiatric disturbances commonly occur in advanced age, ranging from depressive symptoms to anxiety and psychotic disorders. The prevalence of depressive symptoms is 5–13%, but depression in elderly is often under-diagnosed and under-treated [7].

Anxiety disorders affect up to 20% of the community-dwelling elderly [8]. The prevalence of psychotic symptoms (i.e. hallucinations and delusions) in the geriatric population ranges from 0.2% to 4.8% in an outpatient setting, and are as high as 10–63% in elderly living in nursing home [9].

Overall, late life neuropsychiatric disorders are disabling conditions that result in a lower quality of life of elderly patients and their caregivers, earlier institutionalization, and excess mortality.

Use of psychotropic drugs in elderly

Appropriate and judicious use of psychotropic drugs may dramatically improve the quality of life and functional status of many elderly patients with neuropsychiatric disorders [10-12].

However, the decision to prescribe a psychotropic agent in elderly patients is a complex issue for a number of reasons. First, randomized clinical trials (RCTs) of psychotropic drugs in geriatric patients with mental illnesses are very scarce. Only recently a number of RCTs of mostly atypical antipsychotics have been conducted in demented patients [13]. Second, due to significant differences in pharmacokinetic and pharmacodynamic profiles, findings from RCTs of psychotropic drugs in younger persons may not be directly generalized to the geriatric population. Drug metabolism and clearance can be significantly reduced in older patients, as a result of impaired liver and renal functionality, which increases the potential for adverse drug reactions [14-16].

Third, the dose response effect is different in older patients since not only pharmacokinetics but also the pharmacodynamics change. Despite all these difficulties and the increased susceptibility to adverse drug reactions in elderly, one in five community-dwelling elderly persons receives currently psychotropic medications [17], and this rate is even higher in nursing home and long term facilities setting, where psychoactive agent overuse and disuse is the leading cause of preventable adverse drug reactions [18].

A brief overview of current knowledge and guidelines regarding the use and recommendations of specific psychotropic drugs (antipsychotics, antidepressants and anti-Parkinson drugs) in elderly is presented below.

Antipsychotic drugs

Antipsychotic (AP) drugs (comprising conventional and atypical agents) are widely used in late life psychiatric disorders, such as psychoses, agitation and behavioral and psychological symptoms of dementia [19].

During the last two decades, the atypical antipsychotics, such as olanzapine, risperidone and quetiapine, have started to replace the older conventional antipsychotics, like phenothiazine (i.e. thioridazine and chlorpromazine) and butyrophenones (i.e. haloperidol) in the pharmacological management of psychotic disorders [20-21].

Several practice guidelines recommend atypical antipsychotics as the first line option in the treatment of chronic psychoses [22].

Reason is the better safety profile of atypicals as compared to conventional antipsychotics, especially regarding extrapyramidal adverse events [23].

However, the increasing use of atypical antipsychotics has resulted in a growing number of safety alerts, especially regarding off-label use. Based on a pooled analysis of available randomized placebo-controlled clinical trials (RCTs), the UK Committee on Safety of Medicines (CSM) has highlighted a 3-fold increased risk of cerebrovascular events in elderly with dementia, who were treated with risperidone or olanzapine in March 2004 [24].

In April 2005, another warning was issued by the Food and Drug Administration (FDA) to inform health professionals about the results of a pooled analysis of 17 RCTs reporting a 1.7 times increased risk of all-cause mortality associated with atypical antipsychotic use in elderly dementia patients [25]. Cerebrovascular events, pneumonia and arrhythmias were the most frequently reported causes of death. In June 2008, the FDA extended this warning also to the typical antipsychotics [26].

These safety alerts have ignited a very animated debate in the scientific community. Some authors judged the warnings on atypical antipsychotics as unnecessarily alarming and potentially detrimental for elderly patients with dementia, in light of a possible more widespread use of conventional antipsychotics, as recently documented by a Canadian study [27].

Given the extent of use and the safety concerns, epidemiologic evidence on the use and the risks of antipsychotic drugs in the geriatric population is urgently needed.

Antidepressant drugs

Antidepressants (ADs) are frequently prescribed for the treatment of depressive symptoms and anxiety disorders in elderly. Initially, the tricyclic antidepressants (TCAs) were mainly used for these indications, despite TCAs have poorly tolerated in elderly, mostly due to their anticholinergic effects.

The introduction of selective serotonin reuptake inhibitors (SSRIs) in the 80s has markedly changed the management of depression in elderly [28-29]. SSRIs, including sertraline, fluoxetine, paroxetine, fluvoxamine, citalopram, and escitalopram, are currently considered as first-line drugs in the treatment of late-life depression, due to similar efficacy but more favorable tolerability, compared to other antidepressants [30-31]. However, concerns about the safety of SSRIs are growing, due to their anti-platelet activity which may increase the risk of bleeding [32-33].

SSRIs decrease intracellular contents of serotonin in platelets by blocking serotonin transporter 5-HTT, thus inhibiting platelet function. Of particular interest is the relationship between antidepressant drug use and risk of both hemorrhagic and ischemic cerebrovascular events. These associations are difficult to study since

depression may be a risk factor and result of (minor) stroke [34]. Some previous studies failed to demonstrate an association between use of SSRIs and hemorrhagic stroke [35-37], while epidemiologic evidence on the risk of ischemic stroke in elderly patients is currently missing. Studying this relationship in an observational setting is complicated since elderly patients that are treated with antidepressants often have several cardiovascular risk factors and take many concomitant medications.

Polypharmacy may predispose elderly patients using antidepressants to develop drug-drug interactions. Older compounds, such as TCAs or Monoamine oxidase inhibitors (MAOIs), acting on a broad range of receptors and enzymes have a greater potential to interact pharmacodynamically with other medications affecting the same system(s) than newer agents (SSRIs) which have a more specific mechanisms of action [38]. On the other hand, SSRI use in the elderly is associated with the possibility of clinically relevant pharmacokinetic interactions with other medications due to their inhibitory effect on CYP enzymes. The differential effects of various SSRIs on CYPs are well characterized in vitro, with the potential to interact with other drugs being greater for fluvoxamine, fluoxetine and paroxetine and lower for sertraline, citalopram and escitalopram [39-40].

Therefore, the potential for drug-drug interactions should guide the selection of an appropriate antidepressant in elderly. Comprehensive reviews of antidepressant drug interactions in the elderly have been published, allowing for a better choice [41-42].

Anti-Parkinson drugs

Levodopa (L-Dopa) is the most effective drug for the treatment of Parkinson's disease (PD), although this medication is associated with limiting and poorly tolerated motor and non-motor side effects, particularly, in the advanced stages of the disease [43]. Other anti-Parkinson drugs (APDs) are commonly used in clinical practice, either as monotherapy or as adjunctive therapy with L-Dopa, to delay or reduce its motor and non-motor complications and to maximise drug effectiveness: ergot-derived (i.e. cabergoline, pergolide, and bromocriptine) and non ergot-derived (i.e. ropinirole and pramipexole) dopamine agonists (DAs), anticholinergic drugs, amantadine, selegiline and catechol-O-methyltransferase (COMT) inhibitors [44].

Dopamine agonists have been increasingly used as monotherapy in early PD to delay the start of L-Dopa treatment in the last decade [45]. Since 2002, a number of case reports of fibrosis valvular heart disease associated with pergolide and thereafter also with cabergoline have been published. This association was confirmed by several prevalence echocardiographic studies in patients with Parkinson's disease.

However, only one study looked at clinically diagnosed cardiac valve fibrosis using data from an electronic health record database [46-49]. Laboratory studies indicate that the effects of dopamine agonists may be linked to the activation of the serotonin 5-HT_{2B} receptor [50].

Since some ergot derived DAs are strong agonists of 5-HT_{2B} receptors, fibrotic valvular damage is thought to occur through preferential activation of this receptor expressed on heart valves.

As a consequence of the growing evidence about the risk of fibrotic heart valve disease, pergolide was withdrawn from the US market, and cabergoline as well as pergolide are now second line treatment for PD in Europe, and their use requires monitoring [51].

On the basis of these health policy interventions, a dramatic impact on the prescribing pattern of anti-Parkinson drugs is expected in the following years.

1.2. AIM AND OUTLINE OF THE THESIS

The general objective of the research described in the present thesis was to obtain a better understanding of the use and safety of antipsychotic (**chapter 2**), antidepressant (**chapter 3**), and anti-Parkinson drugs (**chapter 4**) in community dwelling elderly patients.

Specifically, with respect to antipsychotic drugs, we first analysed the trends in prescriptions in Italy with a special focus on patients with dementia (**chapter 2.1**). In the same setting it was measured if the safety warnings that have been issued by regulatory agencies changed the prescribing pattern of antipsychotics in elderly demented patients in the recent years (**chapter 2.2**). These safety alerts, together with a growing number of observational studies, questioned the actual tolerability of atypical and typical antipsychotic use in elderly patients. To further assess the safety risks, we first investigated the risk of stroke associated with the use of different antipsychotic drugs in Italy by using the electronic health record database Health-Search/Thales (HS) (**chapter 2.3**). Second, we analysed the risk of all cause mortality (**chapter 2.4**) and fatal and non-fatal pneumonia (**chapter 2.5**) in association with atypical either typical antipsychotics in a cohort of elderly outpatients, using data from the Integrated Primary Care Information (IPCI), which is a Dutch general practice database. Finally, we conducted a comprehensive review of the the safety of atypical and typical antipsychotics in elderly demented patients (**chapter 2.6**).

Regarding antidepressant drugs, we analysed their prescribing pattern in adults and elderly persons in Italian general practice (**chapter 3.1**). Subsequently we as-

essed the potential association between ischemic stroke and use of SSRIs, TCAs and other antidepressants in a cohort of Dutch elderly outpatients (**chapter 3.2**). Finally, we reviewed the state of the art and the strategies to prevent drug-drug interactions in older patients (**chapter 3.3**).

Concerning anti-Parkinson drugs (APDs), in **chapter 4.1** we described the prescribing pattern of APDs in Southern Italy, and, more in detail, we evaluated the burden of cardiovascular diseases in elderly with Parkinson's disease who start a dopamine agonist agent (**chapter 4.2**). Finally, to provide new insights on the risk of fibrotic valvular heart disease, we studied the association between ergot and non-ergot derived dopamine agonist use and cardiac valve regurgitation in elderly patients with Parkinson's disease, using data from multiple electronic health record databases (Health Search/Thales from Italy, IPCI from The Netherlands, THIN from United Kingdom) (**chapter 4.3**).

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CHAPTER 2

Antipsychotic drugs in elderly: use and safety



2.1. Antipsychotic prescribing pattern among Italian general practitioners: a population-based study during 1999-2002 years

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ABSTRACT

Objectives: To assess the antipsychotic use and the prevalence/incidence of antipsychotic drug users in Italy during the 1999-2002 years. To estimate the persistence with antipsychotic medications and to measure their off-label use.

Methods: We selected 465,061 individuals registered at June 2002 in the lists of 320 general practitioners, homogenously distributed throughout Italy, from the Health Search Database. We measured the antipsychotic drugs consumption, calculated as defined daily dose (DDD) per 1,000 inhabitants per day. We also calculated the number of individuals receiving at least one antipsychotic prescription, to estimate the annual prevalence and incidence of antipsychotics users. Among incident users, we evaluated the percentage of patients that were adherent to drug label indications and the average duration of treatment, estimated as Medical Possession Ratio (MPR).

Results: Atypical antipsychotic use has been continuously increased from 1999 to 2002. Women, older people and patients affected by psychotic disorders, other than schizophrenia, were more likely to receive antipsychotic prescriptions. Persistence to atypical drugs treatment (MPR=0.213 in 2002) appeared longer, compared to the typical ones (0.169). The percentage of patients adherent to drug label indications was significantly higher among typical antipsychotic users ($P < 0.001$). The most common off-label use for atypical drug was senile dementia.

Conclusion: Atypical drugs use is continuously growing up along the years 1999-2002, particularly in older people with dementia. The rapidly increasing use of this new class of antipsychotics highlights the need of a better evaluation about their safety profile, and a better definition of their role in psychiatric treatments.

INTRODUCTION

In the last decade the management of schizophrenia was modified by the marketing of second generation antipsychotics (SGAs). In different practice guidelines, SGAs have been considered as the first therapeutical option in schizophrenia [1-2] because they would provide a better safety profile with respect to traditional drugs. Several studies have reported that SGAs are associated to a reduction in the occurrence of extrapyramidal side-effects, major adverse event in the antipsychotic treatment [3], despite the growing concern about the SGAs metabolic effects, including diabetes, hyperlipidemia and obesity [4]. However, the debate about the role for these medications still remains, because of their frequent use off-labelled [5]. Recently, the Committee on Safety of Medicines (CSM), after reviewing the available data from clinical trials of risperidone and olanzapine, has highlighted an increased risk of stroke in elderly patients with dementia who are treated with these drugs. In fact, although no atypical antipsychotic drug is licensed in Italy for the treatment of behavioural disturbances in dementia, risperidone and olanzapine are often used for such indication [6]. Nevertheless several previous studies reported a substantial increase of atypical antipsychotics prescriptions in primary care over the last years [7]. Particularly, a recent population-based study, performed in the UK from 1991 to 2000 [8], showed a continuously growing up consumption for such medications, partially attributable to the increased average annual duration of treatment. As far as Italy is concerned, few recent papers were published on this issue. The last study by Barbui et al [9] in the year 2000, reported a rate of off-label SGAs prescriptions of 52%.

The present study was therefore performed to investigate possible changes in prescribing pattern for antipsychotic drugs in general practice during the years 1999-2002, and to explore the duration of treatment, with the purpose to observe whether persistence could contribute in drug consumption variations. We have also estimated the off-label use for each antipsychotic drug.

METHODS

Data source

Primary care-based data were obtained by the Health Search Database (HSD), which was set up by the Italian College of General Practitioners (SIMG) in 1998. Characteristics of the database have been described in previous studies [10-11]. Briefly, the HSD contains information about patient demographics, medical diagnoses coded according to the ninth edition of *International Classification of*

Diseases (ICD-9), drug prescriptions coded according to the Anatomical Chemical Classification system (ATC), hospital referrals, and diagnostic investigations from 550 general practitioners (GPs) with a total patients population of over 800,000 individuals. Every 3 months, the HSD is subject to a range of quality checks, particularly aimed to assess the completeness of all information collected. Physicians who fail to meet standard quality criteria are not considered for epidemiological studies [12].

Study population

For this study, we selected 465,061 patients registered at the end of June 2002 in the lists of 320 GPs, homogeneously distributed throughout Italy (142 GPs from northern Italy, 60 from central, and 118 from southern) in order to include a number of patients proportional (0.9%) to the size of their respective population.

We identified patients receiving at least one antipsychotic prescription, during the years 1999-2002. For each patient selected, the following information was included: age, gender, antipsychotic prescriptions, including brand name of the medication, ATC code, prescription date, number of prescribed packages, and indication codified by ICD-9.

We excluded from the study sample subjects aged <15 years, and patients without almost one year of recorded data in HSD before the first antipsychotic prescription (i.e. INDEX DATE).

Antipsychotic drugs

Antipsychotics were classified, according to the British National Formulary [8], into the following groups: (1) atypical, which consisted of clozapine, olanzapine, risperidone, and quetiapine; (2) typical, including all the other antipsychotic drugs. We excluded from the analysis amisulpride because until 2002 in Italy, it was exclusively used to treat dysthymia. Such compound was, in fact, classified as atypical antipsychotic after the end of the observation.

Drug utilization was expressed by using the defined daily dose (DDD) per 1,000 inhabitants per day, where DDD is the assumed average dose per day for a drug used for its main indication in adults [13]. Results have been standardized by age group according with Italian population reported by Italian Office of National Statistics (ISTAT) in 2002 [14].

Prevalence/incidence of antipsychotic treatment

Prevalence and incidence of antipsychotic treatment were assessed by drug type and by molecule for each year. We considered an antipsychotic user as a patient who had at least one recorded antipsychotic prescription during the study period.

We measured the prevalence of antipsychotic treatment, defined as the number of antipsychotic drugs users divided by the number of subjects alive and registered in the GP lists of the study population. We defined “new user” as a patient receiving the first antipsychotic prescription without any recorded antipsychotic treatment in the previous year. The incidence rate was measured as the number of “new users” divided by the person-time free from antipsychotic drug use in the current year.

Analysis of persistence

Among new users, the persistence to antipsychotic drug therapy was annually quantified as a Medication Possession Ratio (MPR). MPR was calculated by dividing the cumulative duration of any antipsychotic treatment during follow-up (numerator) with the duration of “possible treatment” (denominator) [15]. Any subject who had an MPR greater than one had their records modified to reflect a maximum value of one [16].

The cumulative duration of each medication was calculated by dividing the total prescribed amount of antipsychotic drug with the recommended daily dose, according to the Italian Defined Daily Doses. The duration of “possible treatment” corresponded to the number of days from the index date to the end of each year.

Adherence to drug label indications

Among new users, we analysed the indications (ICD-9 codes) linked to the first antipsychotic prescription being recorded. Thus, we compared such indications with those reported on drug label for each molecule in order to measure the percentage of adherence. Stratification by gender, age groups, and drug type was performed to observe factors associated with major adherence.

Statistical analysis

Chi-square test for proportions, with a significance level of $P \leq 0.05$ was used for assessing the demographic variables more likely to be associated to an antipsychotic prescription, and for evaluating possible changes in the prescribing pattern during observation years. The same test was also used to explore differences among drug types concerning prescription rate and adherence to indications.

RESULTS

Antipsychotic prescriptions

Among neuropsychiatric drugs, antipsychotics (8.3% of total psychoactive drugs use) result the fourth drug category more prescribed during the year 2002 in the HSD, following antidepressants (45.7%), anticonvulsivants (17.8%), and sedatives/hypnotics (17.4%).

Antipsychotic use was relatively stable over the years 1999-2002 (Table 1). However, among the different therapeutic subgroups, atypical drugs consumption varied from 10.5% of total antipsychotics in 1999 to 38.0% in 2002, whereas traditional medications use decreased during the 4-year study period. Out of 21 different molecules being used, 10 accounted for almost 90% of total antipsychotic consumption. Haloperidol was the most commonly prescribed drug during 2002 (21.4%), followed by olanzapine (19.8%) and risperidone (13.0%). Among traditional drugs, long-acting antipsychotics use remained stable over 4 years and accounted for only 9% of total antipsychotics use (data not shown).

Table 1. Use of antipsychotic drugs, stratified by calendar year.

Molecules	1999		2000		2001		2002	
	DDD*/1,000 inhab./day	% on total	DDD*/1,000 inhab./day	% on total	DDD*/1,000 inhab./day	% on total	DDD*/1,000 inhab./day	% on total
Typical	1.53	89.5	1.26	81.3	1.25	68.7	1.19	62.0
Haloperidol	0.49	28.7	0.42	27.1	0.42	23.1	0.41	21.4
Clotiapine	0.14	8.2	0.12	7.7	0.12	6.6	0.13	6.8
Levosulpiride	0.16	9.4	0.13	8.4	0.13	7.1	0.10	5.2
Fluphenazine	0.12	7.0	0.10	6.5	0.10	5.5	0.10	5.2
Thioridazine	0.15	8.8	0.12	7.7	0.09	4.9	0.08	4.2
Chlorpromazine	0.06	3.5	0.05	3.2	0.06	3.3	0.06	3.1
Other typicals#	0.41	24.0	0.32	20.6	0.33	18.1	0.31	16.1
Atypical	0.18	10.5	0.29	18.7	0.57	31.3	0.73	38.0
Olanzapine	0.06	3.5	0.11	7.1	0.27	14.8	0.38	19.8
Risperidone	0.10	5.8	0.15	9.7	0.23	12.6	0.25	13.0
Quetiapine [^]	-	-	0.01	0.6	0.03	1.6	0.06	3.1
Clozapine	0.02	1.2	0.02	1.3	0.04	2.2	0.04	2.1
Total	1.71	100.0	1.55	100.0	1.82	100.0	1.92	100.0

[^] Molecule introduced in drug market starting from 2000.

*Italian DDD values expressed in grams: Haloperidol (0.008, os formulation; 0.0033, depot); Clotiapine (0.12); Levosulpiride (0.15); Fluphenazine (0.01, os; 0.001, parenteral); Thioridazine (0.3); Chlorpromazine (0.3, os; 0.1, parenteral); Olanzapine (0.01); Risperidone (0.005); Quetiapine (0.4); Clozapine (0.3);

#Other typicals: Levomeprazine (0.3), Promazine (0.3, os; 0.1, parenteral), Perphenazine (0.03, os; 0.01, parenteral; 0.007, depot), Pimozide (0.004), Trifluoroperazine (0.02), Pericyazine (0.05), Zuclopenthixol (0.03, os; 0.015, depot), Bromperidol (0.01), Pipamperon (0.2).

Description of study sample

Percentage of subjects treated with antipsychotic drugs was constant over the years (about 1.4% of total sample population). Among these, the number of patients receiving at least one prescription of both atypical and typical drugs in each year increased from 1.8% of total antipsychotic users in 1999 to 8.6% in 2002. Women and elders were more likely to receive typical antipsychotics, although, across the study years, the differences in the patients demographics between the antipsychotic groups tended to narrow (Table 2). Among typical users, percentage of males varied from 37.1% in 1999 to 40.5% in 2002 ($P < 0.001$), while it dropped off from 48.9% to 45.9% among SGAs users. Similarly, typical users older than 65 years decreased from 54.0% in 1999 to 50.3% in 2002, whereas SGAs users varied from 27.6% to 49.1% ($P < 0.001$).

Table 2 also shows the main indications for antipsychotic prescription over the years, where psychosis disorders other than schizophrenia and affective disorders reported the higher frequency. Interestingly, the percentage of patients with dementia treated with atypical drugs, continuously increased along the study years (3.7% in 1999 vs. 19.8% in 2002).

Table 2. Demographic and clinical characteristics of patients in treatment with antipsychotic drugs, stratified by drug type and calendar year.

	1999 (N=4,505)		2000 (N=5,590)		2001 (N=6,081)		2002 (N=6,064)	
	Typicals (N=4,284)	Atypicals (N=221)	Typicals (N=5,034)	Atypicals (N=556)	Typicals (N=4,784)	Atypicals (N=1,297)	Typicals (N=4,490)	Atypicals (N=1,574)
Gender (%)								
Male	1,588 (37.1)	108 (48.9)	1,891 (37.6)	271 (48.7)	1,975 (41.3)	623 (48.0)	1,820 (40.5)	712 (45.2)
Female	2,696 (62.9)	113 (51.1)	3,143 (62.4)	285 (51.3)	2,809 (58.7)	674 (52.0)	2,670 (59.5)	862 (54.8)
Mean Age (DS)	65.5 (19.5)	52.1 (20.1)	65.6 (18.9)	52.6 (20.8)	64.5 (19.4)	57.9 (21.6)	63.6 (19.6)	60.1 (21.9)
Age groups (%)								
15-29	159 (3.7)	34 (15.4)	203 (4.0)	74 (13.3)	212 (4.4)	124 (9.6)	231 (5.1)	156 (9.9)
30-49	846 (19.7)	90 (40.7)	929 (18.5)	187 (33.6)	1,008 (21.1)	394 (30.4)	998 (22.2)	415 (26.4)
50-64	968 (22.6)	36 (16.3)	1,127 (22.4)	88 (15.8)	1,061 (22.2)	186 (14.3)	1,002 (22.3)	230 (14.6)
65-79	1,083 (25.3)	37 (16.7)	1,396 (27.7)	107 (19.2)	1,191 (24.9)	295 (22.7)	1,111 (24.7)	387 (24.6)
≥80	1,228 (28.7)	24 (10.9)	1,369 (27.2)	90 (16.2)	1,312 (27.4)	298 (23.0)	1,148 (25.6)	386 (24.5)
Diagnostic groups (%)								
Other or no diagnosis	961 (22.4)	27 (12.2)	929 (18.4)	42 (7.6)	808 (16.9)	78 (6.0)	658 (14.7)	91 (5.7)
Schizophrenia	296 (6.9)	71 (32.1)	344 (6.8)	134 (24.1)	354 (7.4)	259 (20.0)	332 (7.4)	294 (18.7)
Affective disorders	1,408 (32.9)	43 (19.4)	1,729 (34.3)	131 (23.5)	1,383 (28.9)	324 (24.9)	1,365 (30.4)	378 (24.0)
Other psychotic disorders *	1,245 (29.1)	72 (32.6)	1,497 (29.7)	173 (31.1)	1,607 (33.6)	398 (30.7)	1,533 (34.1)	501 (31.8)
Dementia	374 (8.7)	8 (3.7)	536 (10.6)	76 (13.7)	631 (13.2)	238 (18.4)	601 (13.4)	311 (19.8)

*Psychosis not otherwise specified, paranoid disorders, reactive psychosis, personality disorders, alcohol or drug-related psychosis, psychosomatic disturbances.

Prevalent and incident users

Prevalence of antipsychotic users resulted relatively stable over the years, varying from 13.7 (per 1,000 inhabitants) in 1999 to 12.9 in 2002 (Figure 1 a-b). Prevalence decreased among females (16.4 in 1999 vs. 14.6 in 2002), whereas it remained stable among males (10.9 in 1999 vs. 11.2 in 2002). Prevalence of typical drug users decreased from 13.0 in 1999 to 9.6 in 2002, whilst it increased approximately 5-fold for SGAs (0.7 in 1999 vs. 3.4 in 2002). Incidence rate of overall antipsychotic users was rather stable over the years (10.1 per 1,000 person-years in 1999 and in 2002). However, such trend substantially varied between the drug types with a decrease of typical users (9.7 in 1999 vs. 8.8 in 2002), and a slight increase of atypical users (0.4 in 1999 vs. 1.3 in 2002), as reported in figures 2 a-b.

Figures 1 a-b. Prevalence of antipsychotic drugs users, stratified by calendar year and drug type and gender

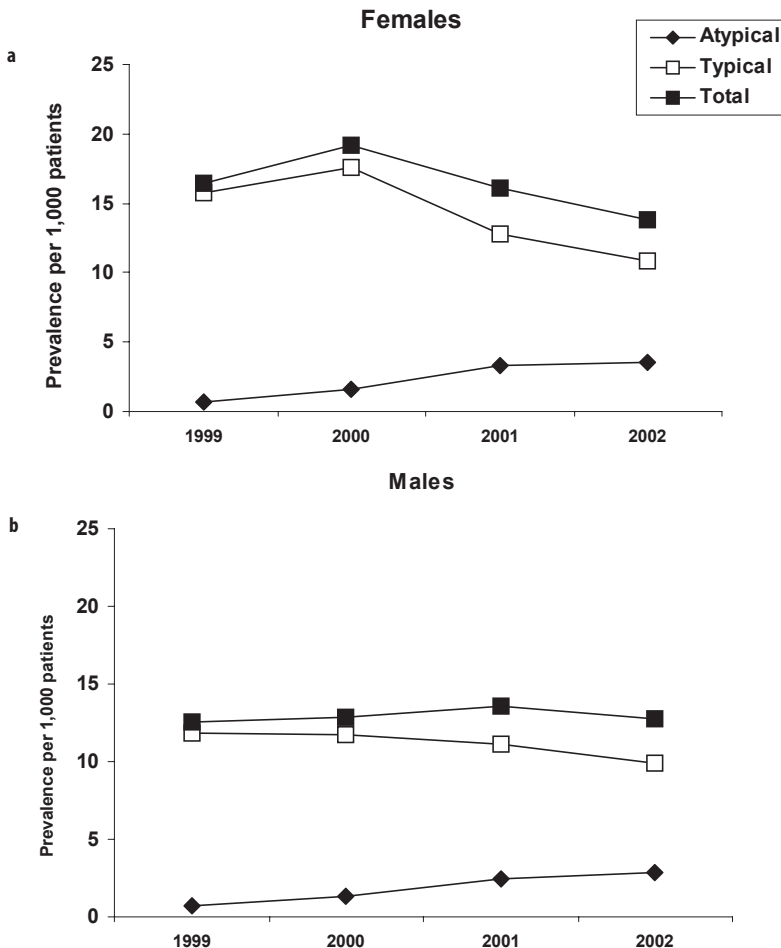
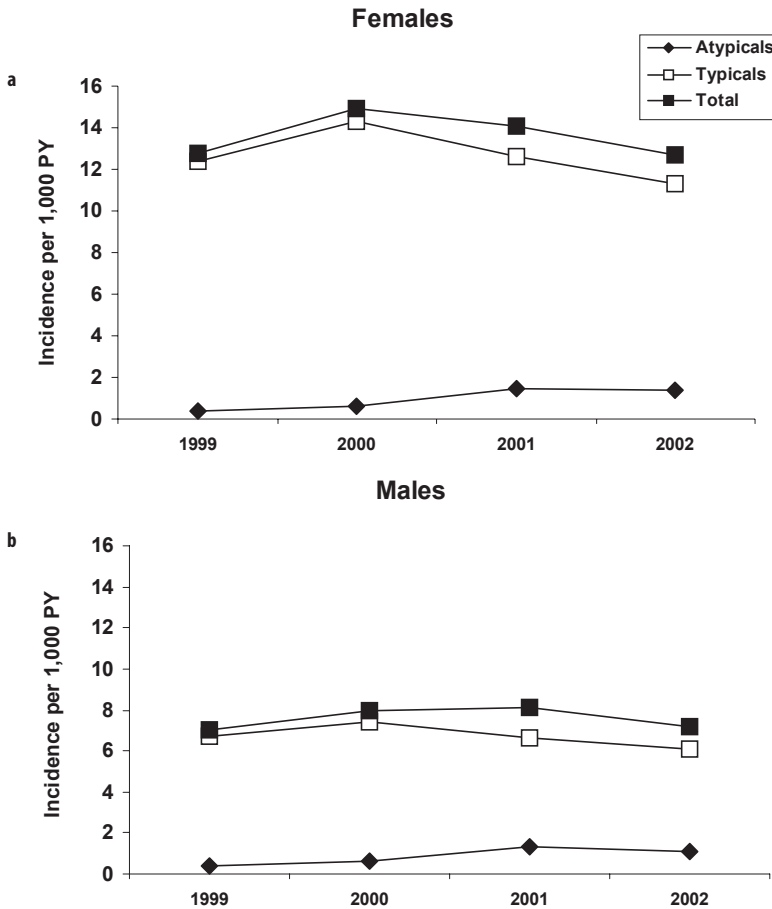


Figure 2 a-b. Incidence of antipsychotic drug use per 1,000 Person/Years (P/Y) in females (A) and males (B), stratified by calendar year and drug class.

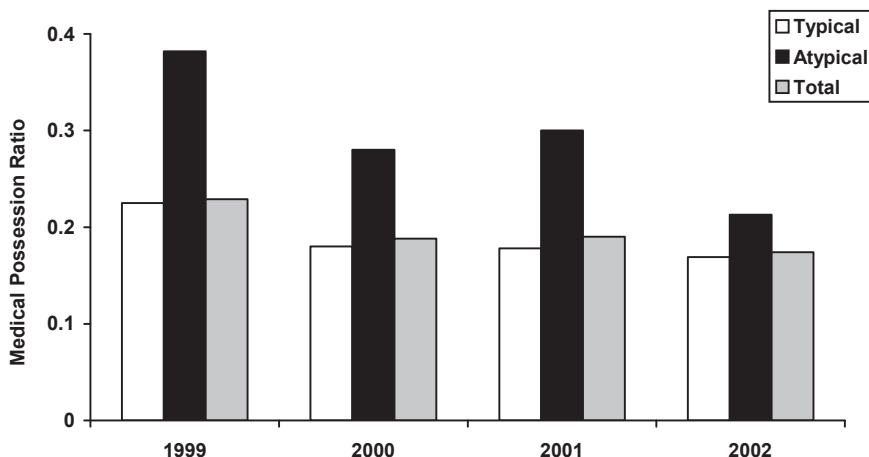


Persistence to antipsychotic treatment

The overall persistence to antipsychotic treatment (MPR: 0.174 in 2002) decreased over the years (Table 3). Such evidence might be partially due to the observed decreasing persistence for SGAs (0.382 in 1999 vs. 0.213 in 2002), although over the years it remained higher than typicals (0.225 in 1999 vs. 0.169 in 2002). Compared to the old ages, a higher MPR (average: 0.393) was reported in patients aged 15-49, commonly atypical users and patients with schizophrenia.

Adherence to indications of use reported on drug label

Typical users showed a higher adherence compared to the atypical group (80.8% vs. 36.3%, $P < 0.001$). No differences were reported by gender and age groups. The

Figure 3. Medical possession ratio of incident users, stratified by calendar year, and drug type.

main off-label use for the SGAs was senile dementia (29.8% of total cases of non-adherence), while the anxiety disorders not associated to any psychotic disorders was the most common off-label use related to the typical antipsychotics.

DISCUSSION

The results of the present study indicate that prevalence and incidence of antipsychotic treatments remain rather stable over the years 1999-2002. These data differ from a study performed in the UK [8] in the years 1991-2000, where it was reported an increasing prevalence of antipsychotic use with a relative reduction of the incidence rate.

Such discrepancy might be partially affected by the recent introduction in the drug market of SGAs. In our study an unchanged prevalence of typical users with a decreasing number of new users was shown. However, among atypical users the prevalence, but even the incidence, increased during the observed years. The DDD/1,000 inhabitants/day values for atypical drugs also showed a 4-fold increase from 1999 to 2002, while typical medications decreased of about one third over the years, thus confirming our hypothesis. This trend is also similar to that reported in a cross-sectional study conducted by Ashcroft et al [7], where atypical antipsychotics use resulted in a nearly 6-fold increase from 1997 to 2001 in UK, whilst use of conventional antipsychotics decreased by 24%. In the year 2002, olanzapine and risperidone became the most common used antipsychotic drugs, partially in contrast to studies conducted in the US, where starting from

1997 such drugs were the most widely prescribed [17]. Such evidence might be partially explained by the earlier launch of the above-mentioned medications in the US as compared to Italy.

Characteristics of antipsychotic drugs users

Women and patients >65 years old were more likely to receive an antipsychotic medication, particularly a traditional antipsychotic. According to the results from European Study of the Epidemiology of Mental Disorders (ESEMeD) Project [18], women would be twice as likely to suffer mood and anxiety disorders as men. Since one third of patients treated with conventional antipsychotics were affected by affective disorders, the discrepancy in the demographic characteristics among two antipsychotic groups, may be explained by the different diagnostic distribution. Nevertheless, demographics of antipsychotic drugs users changed over the study period, with antipsychotic use resulting continuously increased among males and younger people (14-29 years). Such variation might be partially due to the increasing use of atypical medications, since these agents are more likely to be prescribed to men and younger people than conventional antipsychotics [19]. However, among atypical users, it was reported a statistically significant increase of mean age during 4 years, attributable to the rapidly increasing number of older people affected by dementia (mean age: 81.1 ± 7.6).

Persistence to antipsychotic drugs treatment

A rather stable prevalence of antipsychotic use over the years with a decreasing incidence would suggest a slightly increasing average duration of antipsychotic treatment [8]. However, the study shows a decreasing trend of persistence to treatment over the study period. In our analysis the patients who received SGAs are more likely to receive continuous antipsychotic therapy than those on conventional antipsychotics. Such evidence has been confirmed in a study from Germany [5]. The higher percentage of continuous users with atypical drugs could be a proxy for a more favourable side effect profile. Another explanation may be correlated to the different distribution of diagnostic groups in the antipsychotic groups: SGAs are used to treat schizophrenia more than typical drugs, which, on the contrary, are mostly prescribed for acute psychosis associated to affective disorders or other psychiatric diseases, according to our study and to German one [5].

Adherence to indications reported on drug label

Typical drugs users appear to be more adherent to drug label indications, compared to the patients receiving SGAs. Such finding may be related to the fact that traditional medications have more indications reported on drug label with respect to the

atypical drugs. Surprisingly, among atypical users, the rate of elderly patients with dementia has been continuously increased along the study year, despite the recent debate on off-label use of SGAs. As previously mentioned, such patients should not be treated with these two agents not only because there is no specific indication, but also for a documented increased risk of cerebrovascular accidents [20].

Limitations of the study

The present study was performed using computerized medical records from general practice in Italy. According to Kaye et al [8], the observed changes may not pertain directly to patients treated in other settings (for example, psychiatric inpatients or individual in nursing homes). Furthermore some antipsychotic drugs might be subject to major distribution directly from local psychiatric services thus avoiding general practitioners. Nevertheless, because GPs in Italy initiate antipsychotic treatment for some patients and continue treatments begun by specialist for other patients, we believe that these data are likely to be more representative of national trends than those from psychiatric hospitals or clinics. Moreover, we did not perform an analysis aimed to evaluate antipsychotic drugs polytherapy, particularly the association between typical and atypical compounds, very common occurrence in daily clinical practice [21]. Therefore, further studies addressed to investigate antipsychotic drugs polytherapy in Italy are needed.

In conclusion, on the basis of the substantial increase of atypical antipsychotic drugs use in Italy from 1999 to 2002, and concerning the debate about the real safety profile and indication of use of the SGAs, we believe that effectiveness and tolerability as well as the prescribing appropriateness of atypical antipsychotics should be carefully monitored, particularly among older patients.

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2.2. Prescribing pattern of antipsychotic drugs in Italian general population: focus on elderly with dementia during the years 2000-2005

Submitted for publication

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ABSTRACT

Introduction: Since 2004, safety alerts have been issued by European regulatory agencies regarding the risk of off-label use of atypical antipsychotics in elderly demented persons. We evaluated the antipsychotic drug prescribing pattern in the Italian general population and elderly demented outpatients, before and after the safety warnings.

Methods: A cohort study was conducted using the electronic medical records of the Italian general practice database “Health Search/Thales” with information on about 1 million of subjects. One-year prevalence and incidence estimates were calculated for atypical and typical antipsychotic use. The monthly prevalence of both antipsychotic classes was also calculated in elderly demented patients.

Results: In the study population of 648,857 persons, 27,252 (4.2%) patients received at least one antipsychotic drug prescription. The prevalence of atypical antipsychotic use increased 3-times from 2000 to 2003 in the general population, remaining stable thereafter (3.4 per 1,000 in 2005). Use of typical antipsychotics decreased about one third in the same period, although it was still 3-times higher than atypicals in 2005 (10.9 per 1,000). Similar annual trends were observed in elderly patients, where use of atypical antipsychotics was more frequently for dementia than use of typicals (40.8% vs 23.7% in 2005).

Conclusion: In the last years, the prescribing pattern of antipsychotics changed in the Italian adult and elderly population. Compared to atypical antipsychotics, however, use of typical antipsychotics it is still three-times higher. The safety warnings seem to have partly influenced the trend in the use of both typical and atypical antipsychotics in elderly dementia outpatients.

INTRODUCTION

Antipsychotic drugs are commonly prescribed for the treatment of chronic mental illnesses and acute psychotic disorders associated to other psychiatric diseases, such as dementia, drug or alcohol abuse, depression or anxiety [1]. During the last two decades the marketing of the newer class of atypical antipsychotics changed the prescribing pattern of antipsychotics in general practice markedly, as reported in several US and European investigations [2-5]. Due to a supposed better safety profile, atypical antipsychotics, such as risperidone, olanzapine and quetiapine, have been increasingly prescribed in the treatment of psychiatric diseases. These diseases included dementia and related psychotic disturbances, where the atypical replaced the typical antipsychotics, such as phenothiazines (e.g. thioridazine and chlorpromazine) and butyrophenones (e.g. haloperidol) [2-5].

Ashcroft et al reported a nearly six-fold increase in the use of atypical antipsychotics in the UK between 1997 and 2001, whilst the use of conventional antipsychotics decreased by 24% [3]. In the US, two atypical agents, olanzapine and risperidone, are the most widely prescribed antipsychotics since 1997 [4]. A previous Italian investigation reported a 5-fold increase in use of atypical antipsychotic medications for the treatment of behavioral and psychotic symptoms of dementia (BPSD) in primary care during 1999-2002, despite the off-label status of this indication [5]. In the last years, however, the safety profile of atypical and typical antipsychotics was questioned by the scientific community and regulatory agencies. In March 2004, the European Committee on Safety of Medicines (CSM) recommended avoiding or switching the use of atypical antipsychotics in elderly with dementia, due to a 3-fold increased risk of cerebrovascular events [6]. On April 11, 2005, the Food and Drug Administration (FDA) warned healthcare providers about the increased all-cause mortality risk in elderly demented patients receiving atypical antipsychotics. This warning was thereafter extended to typical antipsychotics as well [7-8]. So far, only one Canadian study was performed to evaluate the effect of these safety warnings on the antipsychotic prescribing pattern [9]. This study demonstrated that the warnings had slowed down the increase in prescription of atypical antipsychotic drugs in patients with dementia but it had not changed the overall prescription rate of antipsychotics.

The aim of this drug utilization study was to evaluate how antipsychotic drug use changed in the general population, elderly and in elderly demented outpatients in the last years, after the issuing of the safety alerts.

METHODS

Data source

For this study, the electronic medical records as kept in the Health Search/Thales Database (HSD) were used. HSD was set up by the Italian College of General Practitioners (SIMG) in 1998 and currently captures data on more than 1 million patients from 800 general practitioners who are spread over the country. Characteristics of the database have been described in previous studies [5, 10, 11]. Briefly, HSD contains information about patient demographics, medical diagnoses either coded according to the ninth edition of International Classification of Diseases-Clinical Modification (ICD9-CM) or registered as clinical notes in free text, drug prescriptions coded according to the Anatomical Therapeutic Chemical (ATC) classification system, hospital referrals, and diagnostic investigations.

HSD is subject to a range of quality checks, particularly aimed at assessing the completeness of all collected information. Physicians who fail to meet standard quality criteria are not considered for epidemiological studies [12].

Study population

For this study, we selected all the patients registered in the lists of 400 GPs who met the standard quality criteria. These GPs are homogeneously distributed throughout Italy, so to include a number of patients that is proportional (about 1%) to the size of their respective population. Patients needed to be registered at least one year with the GP and be older than 15 since family pediatricians care for children until the age of 14 in Italy. Within the study sample, we identified all the patients receiving a first antipsychotic prescription (index date) during the years 2000–2005 (no prescription in year prior). For each patient, the following information was retrieved: age, gender, antipsychotic prescriptions, including brand name of the medication, ATC code, prescription date, and number of prescribed packages and indication of use.

Antipsychotic drugs

Antipsychotics were classified into the following groups: (1) atypicals, which consisted of clozapine, olanzapine, risperidone, quetiapine and aripiprazole (marketed in Italy since 2005), and (2) typicals, including the following subgroups: phenothiazines, butyrophenones, benzamides and other typical antipsychotics (thioxanthene, diphenylbutylpiperidine derivatives, and clotiapine) [5]. We included amisulpride among benzamides because it belongs to this chemical subgroup, although it is considered as atypical antipsychotic in Italy since 2002. However, until that date amisulpride was mainly used for treating dysthymia.

We also considered the long acting antipsychotics (haloperidol decanoate, fluphenazine decanoate, zuclopentixol decanoate, perphenazine enantate), separately. For each antipsychotic prescription, the coded indication of use directly linked to that prescription was identified. This indication of use was subsequently manually validated by two medical doctors through careful revision of all the clinical notes that were registered by GPs as free text. Finally, six diagnostic categories were created: 1) affective disorders with psychoses, 2) behavioral and psychotic disturbances of dementia, 3) schizophrenia, 4) anxiety disorders, 5) other psychotic disorders (i.e. delirium), and 6) not reported or not otherwise specified.

Data analysis

Patients who had at least one recorded antipsychotic prescription during the study period were classified as antipsychotic drug user. The annual prevalence of antipsychotic use was calculated by dividing the number of antipsychotic drug users per year by the number of subjects alive and registered in the GPs' list during the entire observation year. One-year prevalence rates of overall and type specific antipsychotic drug use were assessed, and the typical antipsychotic use was further stratified by different subgroups. All the rates were standardized for age according to the Italian population reported by Italian Office of National Statistics (ISTAT) in 2005. Prevalence of use was expressed as rates per 1,000/10,000 inhabitants together with 95% Confidence Interval, as needed. Age specific analyses were conducted for patients 65 years and older. In the elderly patients, the indication of use was further analysed. In demented elderly, we looked also at the yearly trend of antipsychotic drug use by single ingredient and the monthly trend in the prevalence of either atypical or typical antipsychotic use.

All the statistical analyses were conducted in SPSS/PC, version 13 (SPSS Inc, Chicago, Ill). The level of significance for all statistical tests was set at p-value below 0.05.

RESULTS

During the years 2000-2005, 27,252 (4.2%) persons received at least one antipsychotic (AP) drug prescription in the study population, which comprised a total of 648,857 persons. In this population, the annual prevalence of AP use increased from 2000 to 2001, and decreased in the years thereafter (in 2005: 13.3; 95% CI: 13.2-13.4 per 1,000 persons). In all the years, the prevalence of use of typical antipsychotics was much higher than that of atypicals. Time trends in user rates differed largely between atypical and typical antipsychotic drugs (**Table 1**).

Table 1. Prevalence of antipsychotic drug use (per 1,000 inhabitants per year) in the Italian general population during the years 2000-2005

Antipsychotic type	2000		2001		2002		2003		2004		2005	
	N. users	Prev.	N. users	Prev.	N. users	Prev.	N. users	Prev.	N. users	Prev.	N. users	Prev.
Atypicals	655	1.28	1,476	2.75	1,781	3.26	1,880	3.41	1,884	3.34	1,952	3.36
Typicals	7,643	14.93	8,411	15.65	7,934	14.53	6,283	11.4	6,180	10.97	6,356	10.94
Phenothiazines	1,933	3.78	2,092	3.89	1,910	3.50	1,843	3.34	1,993	3.54	2,038	3.51
Butyrophenones	1,511	2.95	1,725	3.21	1,866	3.42	1,887	3.42	2,074	3.68	2,299	3.96
Benzamides	4,414	8.62	4,827	8.98	4,291	7.86	2,579	4.68	2,197	3.90	2,105	3.62
Others	488	0.95	546	1.02	578	1.06	582	1.06	548	0.97	624	1.07
Total	8,036	15.70	9,363	17.42	9,151	16.76	7,607	13.8	7,527	13.36	7,749	13.34

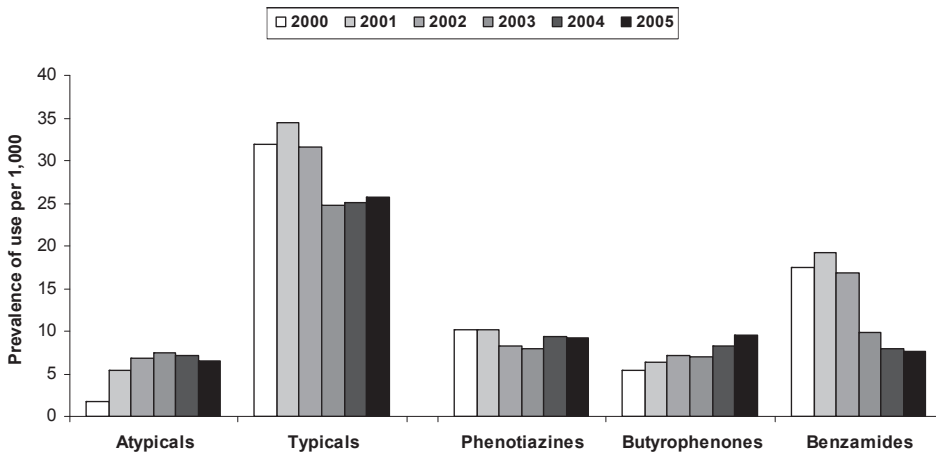
Use of atypical drugs increased almost three-fold from 2000 [1.28 (1.18-1.38) per 1,000] to 2003 [3.4 (3.3-3.6) per 1,000], but remained stable thereafter [in 2005: 3.4 (3.2-3.5) per 1,000]. Use of typical antipsychotics reduced three-fold during the study years, but, despite the decrease, it remained approximately three-times higher than that of atypical agents in 2005: 10.9 (10.7-11.2) per 1,000 (**Table 1**).

Among typical antipsychotics, phenothiazines, butyrophenones and benzamides showed a similar prevalence of use in 2005, but the trends were quite different over time. Use of butyrophenones progressively increased, use of benzamides strongly decreased, while use of phenothiazines did not substantially change during the study years. Long acting antipsychotics accounted for around 5% of total antipsychotic use during the whole period. No significant differences by gender in the observed trend between atypical and typical antipsychotics have been reported.

Elderly

Overall, 3,991 elderly patients (≥ 65 years) received at least one antipsychotic drug prescription in 2005, with a prevalence of use of 36.0 (34.0-38.0) per 1,000 persons per year, which is more than 3 times higher than in persons below 65 years.

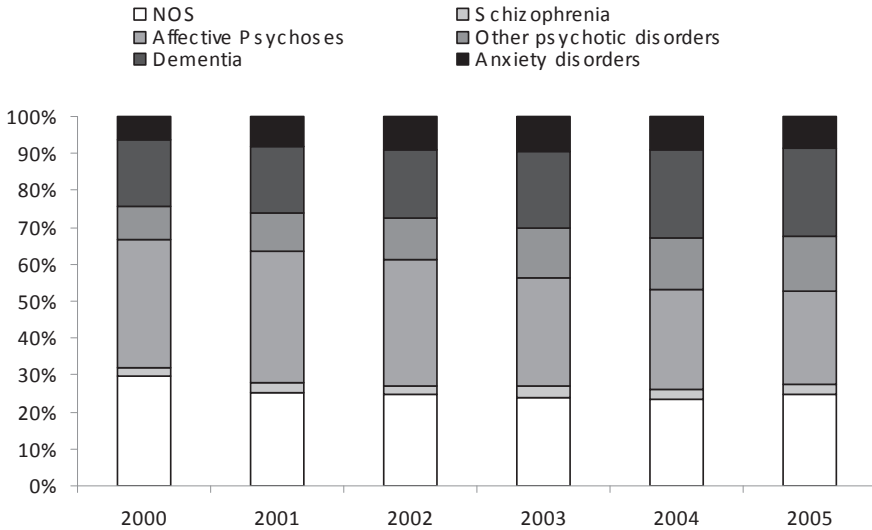
In line with overall trends, use of atypical antipsychotics increased from 2000 [1.8 (1.6-2.1) per 1,000] until 2003 [7.5 (7.0-8.0) per 1,000] in elderly, while the use of typical antipsychotics reduced by one third during the same period [31.9 (30.9-33.0) per 1,000 in 2000 vs 24.8 (23.9-25.7) per 1,000 in 2003]. In the years thereafter, the user rates of atypicals and typicals remained mostly constant (**Figure 1**). Within the group of typical agents, the prevalence of butyrophenones use almost doubled from 2000 to 2005, while use of phenothiazines and even more that of benzamides tended to decrease (**Figure 1**). The distribution of indications of use in elderly patients, who received either atypical or typical antipsychotics, is shown in **Figure 2a-b**. Typicals were mainly used in the treatment of psychoses associated with affective disorders (25.1% in 2005). On the other hand, the proportion of typical antipsychotic users with dementia has been increasing since

Figure 1. One-year prevalence of antipsychotic drug use (per 1,000 inhabitants) in community dwelling elderly during the years 2000-2005

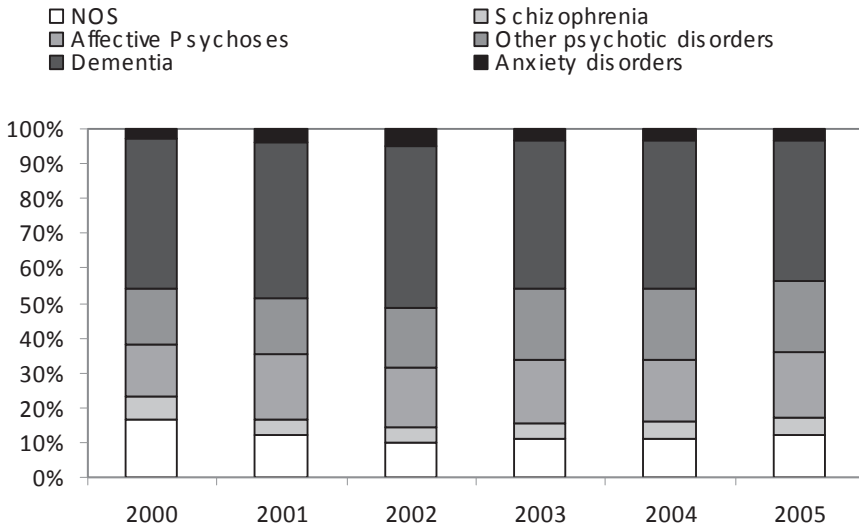
2003 (23.7% in 2005). Dementia and related disorders were the main indications of use for atypical antipsychotic users (40.8% in 2005), but this proportion has been declining starting from 2003. Some specific sub-analyses were conducted in elderly demented patients to take a better look on use of typical and atypical antipsychotics (**Figure 3-4**). The monthly trend in the use of atypical and typical antipsychotics in elderly persons with dementia is reported in **Figure 3**. The prevalence of use of atypical agents in demented patients progressively increased from January 2000 [0.2 (0.05-0.7) per 10,000 elderly persons] until the beginning of 2004 [9.7 (8.1-11.6) per 10,000], after which the increase slowed down. Conversely, the prevalence of use of typical antipsychotics decreased from 2001 [15.7 (13.5-18.2) per 10,000] until 2004 [10.7 (9.0-12.7) per 10,000], when its prevalence of use was almost overlapping that of atypical agents, then again slightly increasing in the following years, up to 12.1 (10.4-14.2) per 10,000 in December 2005. Analyses by active compound showed that haloperidol [27.8 (25.1-30.8) per 10,000 elderly persons], promazine [18.0 (15.8-20.4) per 10,000] and quetiapine [15.7 (13.7-18.0) per 10,000] were the most widely used antipsychotics in elderly patients for the treatment of behavioral and psychotic disorders of dementia in 2005 (**Figure 4**). The use of all of these medications for the treatment of dementia and related disorders shows an increasing yearly trend. Indeed, prevalence of use of haloperidol has been raising about 70% in elderly patients due to dementia, while promazine doubled in this patient group from 2000 to 2005. In the atypical antipsychotics, use of quetiapine increased dramatically in elderly patients for the treatment of dementia and related disorders, particularly after the safety alert issue in 2004, whereas use of risperidone and olanzapine reduced significantly in these patients from 2004.

Figure 2a-b. Distribution of indication of use in elderly patients receiving either atypical or typical antipsychotics

Typical antipsychotics



Atypical antipsychotics



NOS= not otherwise specified

DISCUSSION

To our knowledge this is the first European drug utilization study that explored the trend in the use of atypical and typical antipsychotic drugs in both general population and more specifically in elderly demented outpatients, before and after the safety warnings issued by European regulatory agencies in 2004 regarding atypical antipsychotics. Our population-based study documented an almost

Figure 3. Monthly trend in the prevalence of atypical and typical antipsychotic use in elderly outpatients because of dementia and related disorders

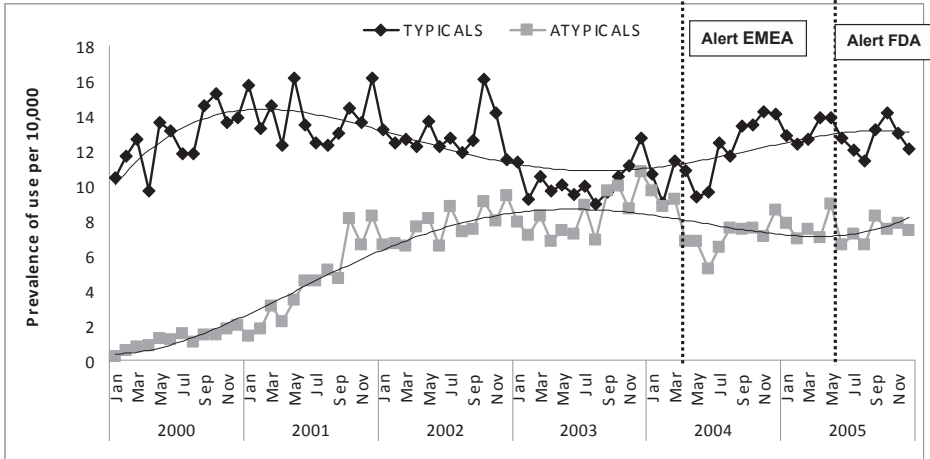
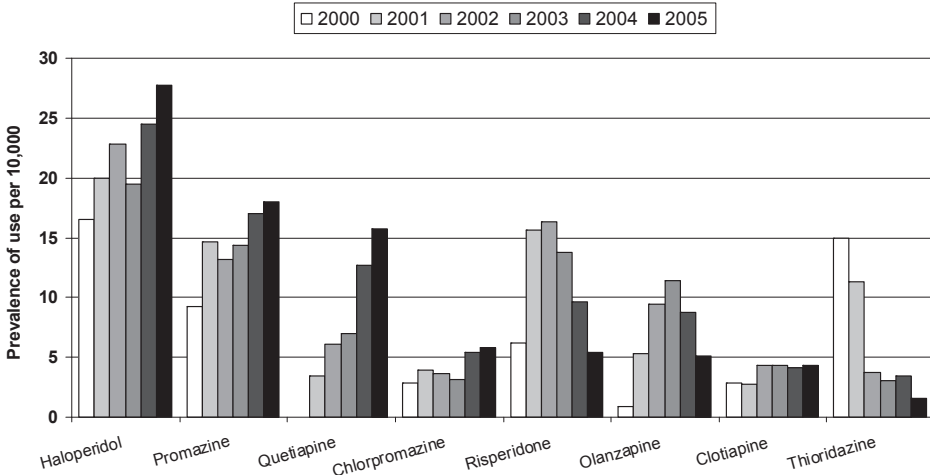


Figure 4. Annual trend in the prevalence of use of individual medications* in elderly patients



* Medications accounting for almost 90% of total antipsychotic drugs volume in elderly people.

three-fold increase in the use of atypical agents from 2000 to the end of 2003 in Italy, whilst this growth slowed down thereafter. The prevalence of use of typical antipsychotics reduced by one-third until 2003 and was stable during 2004-2005 years. This trend was similar in elderly. A dramatic increase in the use of atypical agents in the general population, and particularly in elderly demented outpatients, starting from their marketing until 2002 was previously reported in Italy [5, 13], as well as in UK and US [3-4]. In Italy, national statistics have shown that the increase in the use of atypicals slowed down after 2004, which is consistent with our findings. [14] The most likely explanation for the change in trend are the warnings

that were provided by the Italian Drug Agency, in line with other international agencies on the safety of atypical and typical antipsychotics in elderly demented patients [15]. However, despite these warnings more than 3% of Italian community dwelling elderly patients received at least one antipsychotic drug prescription in 2005, with a large proportion of those that were treated for dementia and related disorders. Use of antipsychotics in elderly is risky, as these psychotropics are often misused and overused in geriatric patient [16]. The actual safety profile of antipsychotic drugs in elderly patients has been questioned due to a number of warnings issued by regulatory agencies about the risks associated with atypical agents in elderly patients with dementia. These alerts have ignited a very animated and controversial debate in the scientific community and an impact on prescription rates of antipsychotic medications, not only among elderly patients with dementia, was expected [18]. Some health professionals were concerned that these warnings could be detrimental for older patients with dementia since atypical antipsychotic treatment could have been unnecessarily withheld, and clinicians would have adopted widespread use of conventional antipsychotic drugs [19]. Looking specifically at elderly demented persons, our study seems to support the idea that the safety warnings slowed the growth in the use of atypical antipsychotics. Due to substitution of conventional agents, this did not reduce the overall user prevalence of antipsychotics due to substitution by conventional agents. Fukuda et al also reported that the safety alerts launched by regulatory agencies could lead to the replacement of atypical with typical agents and, on the basis of the assessment of a small group of Japanese psychiatric inpatients, this switching would not result in better clinical outcomes both in terms of effectiveness and safety [20]. So far only one Canadian study had previously assessed the effect of these alerts on the antipsychotic prescribing pattern, but it only looked at the antipsychotic use in elderly demented patients [9]. The Canadian prevalence rates are higher than the ones we found which may be explained by geographical and health care differences. We may have a slight underestimation of antipsychotic use in our study as well, since a certain amount of antipsychotic drugs have been directly dispensed by psychiatric local services that are dedicated to the management of older patients with dementia in recent years, and these prescriptions would have been missing in the general practice database which was used in this study. In line with our study, however, the Canadians documented a significant decrease in the use of atypical agents in elderly patients with dementia after the safety alerts, while the overall prescription rate of antipsychotics was not reduced in these patients. Despite the decrease, however, about 40% of atypical antipsychotic users (compared to 25% typical antipsychotics users) were still treated because of dementia and related disorders in 2005, after regulatory agencies warned health professionals against

the off-label use of atypical agents for this indication. This is in line with the off-label use reported in nursing homes in the US [21]. Haloperidol was the most frequently prescribed antipsychotic to elderly patients because of dementia and related disorders. A recent Cochrane review of this typical antipsychotic has shown that haloperidol could be effective in the management of behavioural symptoms in dementia [22], while other reviews contrasted with these conclusions [23]. Risperidone and olanzapine showed a declining trend starting from 2004, in contrast to quetiapine whose utilization has been continuously increasing since its marketing in 2000. These observed trends, with a reduction in the use only for those atypical agents (risperidone and olanzapine) that were specifically mentioned in the safety alerts, would confirm an effect of these warnings on the antipsychotic drug use.

This study should be interpreted with caution since it was performed using electronic health records from general practice in Italy. Therefore, the observed changes in the prescribing pattern of antipsychotic drugs may not pertain directly to patients treated in other settings (e.g., psychiatric inpatients or elderly persons with mental illnesses that are residents in nursing homes) [24]. GPs in Italy initiate antipsychotic treatment for some patients and continue treatments begun by specialists for other patients. However, some antipsychotic drugs might have also been dispensed via direct distribution from local psychiatric services caring specifically patients with dementia, thus bypassing general practitioners and, as a consequence, potentially leading to an underestimation of prevalence of antipsychotic use in our study. Direct distribution of antipsychotic drugs may vary on regional level and over time in Italy and affects preferentially atypical antipsychotics. According to the Italian National report on dispensing of medicines, up to 50% of atypical antipsychotic prescriptions could be directly dispensed by psychiatric local services in the year 2005 [14]. Finally, indication of use was not reported and could not be identified for around 20% of antipsychotic users although it was manually validated through careful revision of the clinical diary by two medical doctors.

To conclude, this study shows that drug utilization studies can provide relevant information on the effect of safety warnings that are launched by regulatory agencies on the prescribing pattern of drugs. This study supports the view that antipsychotics are frequently used in older people with psychiatric disorders, in particular dementia, despite the ongoing debate about their risks. The safety warnings that have been recently issued by regulatory agencies contributed to slow down the increasing trend in the use of atypical antipsychotics in Italian general population and at larger extent in elderly outpatients with dementia with a marginal shift towards typical antipsychotics in the last years.

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2.3. Risk of stroke with typical and atypical anti-psychotics: a retrospective cohort study including unexposed subjects

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ABSTRACT

The purpose of the study was to investigate the risk of stroke with typical and atypical antipsychotics in elderly subjects, weighting for a number of known risk-factors, including dementia. Data were retrospectively drawn from the primary care setting from the Health Search Database, which stores information on about 1.5% of the total Italian population served by general practitioners. All elderly patients (65+ years) prescribed an antipsychotic in monotherapy from January 2000 to June 2003 were selected for the study. A cohort of patients not exposed to antipsychotics was taken from the same database. Subjects who had previously had a stroke were excluded. The main outcome measure was the incidence of first-ever stroke during exposure to an antipsychotic. The sample included non-users (69,939), users of atypicals (599), butyrophenones (749), phenotiazines (907), and substituted benzamides (1,968). The crude incidence of stroke in subjects not exposed to antipsychotics was 12.0/1000 person-years. Risk was significantly higher for those on butyrophenones (47.1/1000), phenotiazines (72.7/1000), and in the atypical antipsychotic group (47.4/1000). Substituted benzamides had an almost significant higher risk (25.0/1000). Cox regression modelling, weighting for demographic and clinical variables with non-users as the reference group, showed the risk for stroke was 5.79 times for phenotiazines, 3.55 times for butyrophenones, and 2.46 times for atypicals. Clinicians should be cautious in prescribing phenotiazines and butyrophenones in elderly patients, since the risk for stroke would seem comparable or even greater than with atypicals.

INTRODUCTION

A few years ago some double-blind trials in elderly patients with behavioural and psychological symptoms of dementia (BPSD) reported that individuals treated with risperidone or olanzapine were at higher risk for cerebrovascular events (CVEs) compared with subjects randomized to placebo (Street *et al.*, 2000; Brodaty *et al.*, 2003). Following on from these reports and reanalyses indicating that other atypicals were also associated with CVEs, some regulatory agencies issued specific warnings against the use of some (FDA, 2003; EMEA, 2004; Committee on Safety of Medicines, 2004) or all (FDA, 2005) atypical antipsychotics in dementia patients. In the meanwhile, research on antipsychotics and stroke has broadened to include also typical antipsychotics and elderly subjects without dementia. In particular, large database studies reported a similar risk for stroke for both novel and older antipsychotics, and failed to demonstrate a preferential association between stroke and a given atypical compound (Hermann *et al.*, 2004; Gill *et al.*, 2005; Liperoti *et al.*, 2005; Wang *et al.*, 2005). Consequently a major dilemma arose (Lawlor, 2004; Mowat *et al.*, 2004; Nelson, 2005; Shah and Shu, 2005; Carson *et al.*, 2006) about which was the best antipsychotic treatment for BPSD patients; those who stopped taking a novel antipsychotic may nevertheless be in need of another treatment, because the course of the disorder may be less benign than previously thought (Raju *et al.*, 2005). Furthermore, evidence from the recent literature is often flawed by a number of factors. Typical antipsychotics in general were grouped into a unitary broad class, irrespective from their belonging to different chemical groups (Hermann *et al.*, 2004; Gill *et al.*, 2005; Liperoti *et al.*, 2005). Furthermore, the class of substituted benzamides was never evaluated, though these antipsychotics are widely prescribed in various, especially European Countries. Furthermore, no recent studies have considered comparable unexposed subjects with details of other medical risk factors, or have excluded patients with a previous stroke (Hermann *et al.*, 2004; Gill *et al.*, 2005; Liperoti *et al.*, 2005; Finkel *et al.*, 2005; Formiga *et al.*, 2005; Layton *et al.*, 2005; Percudani *et al.*, 2005).

Following on from these observations we investigated the risk for first-ever stroke in a general population of elderly patients, in cohorts exposed to butyrophenones, phenothiazines, and substituted benzamides. Risk ratios were compared with unexposed subjects and patients exposed to atypical antipsychotics.

METHODS AND MATERIALS

Setting

The study included subjects from the Health Search Database (HSD), a computerized system set up in the mid-1990s to collect data taken from the daily clinical activities of general practitioners (GPs). The characteristics of the database have been described in previous studies (Filippi et al., 2003a,b; Sacchetti et al., 2005; Trifirò et al, 2005). Currently, the database contains information from 550 GPs from all over Italy with a total of about 800,000 patients, i.e. 1.5% of the Italian population. After extensive training on software use, GPs store data in real time and send them to a central server based in Florence, where a GPs association, the Società Italiana dei Medici di Medicina Generale, processes the data for research purposes. To ensure quality, every 3 months all the information collected in the database undergoes extensive monitoring with a scheduled feedback from administrators to users. Physicians who failed to meet standard quality criteria were not considered for this research, in agreement with the criteria set by Lawrenson et al. (1999). A unique identification number links all data to an individual patient who remains anonymous and no identifying details are available. Written informed consent to the processing of data was given by each patient to the treating physician. Information collected include patient demographics, medical diagnoses coded according to the ninth edition of International Classification of Diseases (ICD-9), drug prescriptions coded according to the Anatomical Chemical Classification system (ATC), hospital referrals and results of diagnostic investigations. In the case of the death of a patient, a diagnosis is coded as the most reasonable cause of death. The HSD also generates a Chronic Disease Score (Von Korff *et al.*, 1992), that gives a total score according to the number of medication classes given to a patient.

Exposure definition

The study period spanned from January 1st, 2000 to June 30th 2003. Data were extracted in July 2003, and the GPs selected for this study (320) were those who had reported complete data at the end of the study period. Subjects were enrolled in the study when they were first prescribed an antipsychotic, and censoring (end of follow-up) was performed at the end of the study period, occurrence of the outcome (stroke, as defined below), discontinuation of antipsychotic therapy, when the patient moved away from the GP practice, or death, whichever came first. For each prescription, the time of exposure was computed according to the criteria set by Strauss *et al.* (2004), adding an extra 30 days of carryover to the time covered by the daily prescription dose. After this time, individuals who did not

receive another antipsychotic prescription were censored. Patients were grouped into the following cohorts on the basis of exposure to antipsychotic medications during follow-up: (a) “non-users”, i.e. individuals who were never treated with antipsychotics throughout the time of their monitoring in the database; (b) users of atypical antipsychotics in monotherapy: olanzapine, risperidone, quetiapine, and clozapine (switchers with overlapping prescriptions were not included); (c) users of typical antipsychotics in monotherapy (both depot and non-depot formulations); (d) users of substituted benzamides (sulpiride, amisulpride). Aripiprazole was not licensed during the years under scrutiny, and ziprasidone is currently under registration in Italy: therefore these antipsychotics were not considered in the study. Inclusion criteria were the following: (i) age greater than 64 years; (ii) no antipsychotics prescribed in the 3 months before study entry; (iii) no prescriptions of other antipsychotics during the observation period; (iv) more than 1 year of valid clinical history registered in the HSD. Exclusion criteria were: (i) previous cerebrovascular events (ICD9 codes: 430-8); (ii) cerebral tumours (191, 225, 239.6); (iii) coagulopathy (284, 286-7); (iv) a diagnosis of stroke recorded the same day as the first antipsychotic prescription. Subjects were selected irrespective of a diagnosis of dementia.

Outcome definition

The primary outcome was a diagnosis of stroke recorded during the study period. Cases were identified through ICD9 codes (434.9, 438.0, 342, 342.0, 342.1 and 342.9) or encoded medical problems described as “stroke,” “hemiparesis,” or “hemiplegia” registered in the HSD during the follow up. Validation studies have established an accuracy rate of 90% for the diagnosis of stroke based on these codes (Mayo *et al.*, 1994; Filippi *et al.*, 2003a; Leone *et al.*, 2004).

Statistical analysis

Standard descriptive statistics were used to assess any possible clinical and demographic difference among exposure groups. Crude incidence rates of stroke were calculated for each study cohort by dividing the number of cases by the cumulative drug exposure, expressed as person-years.

To examine the independent effect of the use of antipsychotics on the risk for stroke, a multivariate Cox proportional regression analysis was performed. The main advantages of Cox analysis are that it can weight for the effects of covariates, other than exposure to an antipsychotic, and it can be applied when variable lengths of time of observation are produced by each subject. All analyses were performed with STATA 7.0 (STATA Corporation, Texas USA).

RESULTS

The total sample consisted of 74,162 subjects, 69,939 non-users, 599 on atypicals, 749 on butyrophenones, 907 on phenotiazines, and 1968 on substituted benzamides. The key sociodemographic and clinical features of the five cohorts are reported in Table 1, together with details of significant differences. Overall, the most frequent diseases were hypertension, diagnosed in more than half of the subjects, and diabetes, dyslipidemia, obesity, COPD, diagnosed in about one-sixth of the sample.

Dementia was diagnosed in 17.5% of those on antipsychotics. The more common specific psychiatric diagnoses were 'other' psychotic disorders (36.1%) and affective disorders (13.3%), while schizophrenia was diagnosed only in 0.9% of those prescribed an antipsychotic. The crude incidence of stroke in subjects not exposed to antipsychotics was 12.0/1000 person-years (CI 11.5-12.5). When compared to this estimate, risk was significantly higher in those on butyrophenones (47.1/1000; CI 22.1-88.8), phenotiazines (72.7/1000; CI 43.3-107.7), and in the atypical antipsychotic group (47.4/1000; CI 23.4-86.5). Substituted benzamides had an almost significant higher risk (25.0/1000; CI 12.0-34.1) (Table 2). The mean interval from first prescription to new-onset stroke was 103.3 days (SD 112.7) in atypicals, 57.5 (SD 22.2) in butyrophenones, 21.3 (SD 18.8) in phenotiazines, and 120.5 (SD 119.6) in substituted benzamides ($F=0.30$, $p=n.s.$).

At univariate analysis stroke was associated with some of the sociodemographic and clinical variables: higher age, male sex, a Chronic Disease Score higher than 5, a diagnosis of Parkinson disease, and the use of anticoagulants (Table 3). Dementia, per se, had only a weak effect on stroke risk, and also affective disorders were not associated to the risk.

In order to weight for the effect of those variables who had a differential distribution in the cohorts all variables in Table 1 were entered in the Cox analysis (including dementia and psychiatric indication of use).

Two multivariate models were applied. In the first model the reference group was made up of subjects not exposed to antipsychotics (default risk=1). The risk of stroke was again higher for the group of phenotiazines (5.79 times; CI 3.07-10.9), butyrophenones (3.55; CI 1.56-8.07), and atypicals (2.46; CI 1.07-5.65) when compared to unexposed subjects. The group of substituted benzamides had an almost significantly higher risk (2.2; CI 0.98-4.90). The second model took atypical users as the reference group (default risk=1), and allowed us to compare typical vs. atypical antipsychotic drugs, while weighing for the same covariates entered in the previous model. Phenotiazines had a significantly higher risk (2.34) for stroke

Table 1. Demographic and clinical characteristics of different exposure cohorts

Variable	Non-Users N=69,939 (%)	Butyrophenones N=749 (%)	Phenothiazines N=907 (%)	Subst. Benzamides N=1,968 (%)	Atypicals N=599 (%)	p
Mean age (SD)	75.7 (7.9)	81.9 (8.7)	82.6 (8.9)	75.4 (7.2)	79.8 (7.9)	** a
Females	40,220 (57.5)	484 (64.6)	547 (60.3)	1,466 (74.5)	371 (61.9)	** b
Chronic Disease Score						
1-5	40,816 (58.4)	585 (78.1)	685 (75.5)	1,556 (79.1)	452 (75.5)	** b
> 5	29,123 (41.6)	164 (21.9)	222 (24.5)	412 (20.9)	147 (24.5)	
Diseases affecting risk of stroke						
Hypertension	40,624 (58.1)	407 (54.3)	503 (55.5)	1,208 (61.4)	337 (56.3)	n.s.
History of coronary Heart Diseases	6,469 (9.2)	84 (11.2)	127 (14.0)	167 (8.5)	75 (12.5)	** b
Heart failure	2,512 (3.6)	51 (6.8)	59 (6.5)	52 (2.6)	31 (5.2)	** b
Atrial Fibrillation	3,983 (5.7)	56 (7.5)	65 (7.2)	89 (4.5)	33 (5.5)	** b
Other arrhythmias	3,213 (4.6)	33 (4.4)	39 (4.3)	79 (4.0)	30 (5.0)	n.s.
Diabetes mellitus	10,913 (15.6)	116 (15.5)	154 (17.0)	250 (12.7)	97 (16.2)	** b
Dyslipidemia	14,198 (20.3)	77 (10.3)	94 (10.4)	387 (19.7)	79 (13.2)	** b
COPD	10,340 (14.8)	126 (16.8)	168 (18.5)	270 (13.7)	105 (17.5)	** b
Pneumonia	3,506 (5.0)	30 (4.0)	44 (4.9)	70 (3.6)	46 (7.7)	** b
Dementia	1,215 (1.7)	211 (28.2)	227 (25.0)	64 (3.3)	235 (39.2)	** b
Parkinson's disease	1,503 (2.1)	97 (13.0)	83 (9.2)	57 (2.9)	118 (19.7)	** b
Malignant neoplasm	3,361 (4.8)	26 (3.5)	27 (3.0)	40 (2.0)	14 (2.3)	** b
Obesity	9,711 (13.9)	80 (10.7)	85 (9.4)	286 (14.5)	69 (11.5)	** b
Concurrent use of medications						
Anticoagulants	23,376 (33.4)	161 (21.5)	205 (22.6)	405 (20.6)	160 (26.7)	** b
Diuretics	19,371 (27.7)	154 (20.6)	210 (23.2)	287 (14.6)	90 (15.0)	** b
Beta-blockers	10,283 (14.7)	19 (2.5)	41 (4.5)	187 (9.5)	28 (4.7)	** b
ACE-inhibitors	25,061 (35.8)	167 (22.3)	199 (21.9)	507 (25.8)	151 (25.2)	** b
Calcium-channel blockers	18,541 (26.5)	91 (12.1)	135 (14.9)	331 (16.8)	77 (12.9)	** b
Angiotensin receptor blockers	5,562 (8.0)	14 (1.9)	27 (3.0)	86 (4.4)	17 (2.8)	** b
Benzodiazepines	12,382 (17.7)	159 (21.2)	188 (20.7)	542 (27.5)	148 (24.7)	** b
Sympathomimetic drugs	8,345 (11.9)	33 (4.4)	35 (3.9)	89 (4.5)	24 (4.0)	** b
Psychiatric indication of use						
Schizophrenia		14 (1.9)	6 (0.7)	2 (0.1)	18 (3.0)	** c
Other Psychotic Disorders		401 (53.5)	431 (47.5)	334 (17.0)	359 (59.9)	** c
Affective Disorders		56 (7.5)	46 (5.1)	386 (19.6)	74 (12.5)	** c
Other or no diagnosis		278 (37.1)	423 (46.6)	1,239 (63.0)	148 (24.7)	** c

* p<0.05; ** p<0.01

a F, 5,74162 d.f.;

b Chi2, 4 d.f.

c Chi2, 3 d.f.

n.s. = not significant

Table 2. Incidence of stroke among persons taking antipsychotic medications and unexposed subjects

Treatment group	Mean days of follow-up (SD)	Cases of stroke	Years of follow-up (per 1,000)	Crude incidence per 1000 PY (95% CI)
UNEXPOSED	1,069 (327)	2,459	205.0	12.0 (11.5-12.5)
BUTYROPHENONES	87 (87)	8	0.17	47.1 (22.1-88.8)
PHENOTHIAZINES	82 (47)	16	0.22	72.7 (43.3-107.7)
OTHER TYPICALS ^a	106 (119)	1	0.04	25.0 (2.3-116.6)
SUBSTITUTED BENZAMIDES ^b	124 (121)	14	0.67	20.9 (12.0-34.1)
ATYPICALS	117 (112)	9	0.19	47.4 (23.4-86.5)

^a thioxanthenes, diphenylbutylpiperidine derivative, dibenzothiazepine;

^b sulpiride, amisulpride.

Table 3. Sociodemographic variables, illnesses and treatments associated with stroke

Variables	Crude incidence per 1,000 PY (95% CI)	p value ^a
AGE GROUPS		< 0.001
65-80	9.8 (9.3-10.3)	
≥ 80	19.6 (18.4-20.8)	
GENDER		< 0.001
Males	13.6 (12.8-14.4)	
Females	11.2 (10.6-11.8)	
CHRONIC DISEASE SCORE		< 0.001
1-5	10.1 (9.5-10.6)	
> 5	14.9 (14.1-15.7)	
CO-MORBIDITIES		
Parkinson's disease	24.3 (20.0-29.3)	< 0.001
CONCURRENT MEDICATIONS		
Anticoagulants	20.4 (19.4-21.5)	<0.001

^a Chi square, 1 d.f.

when compared to atypical antipsychotics. No significant interactions between antipsychotic class and other variables were found.

DISCUSSION

The main findings of this study can be summarised as follows. When compared to antipsychotic-free controls, elderly patients taking antipsychotics in monotherapy were at higher risk for first-ever stroke. The increased incidence of stroke involved all the chemical families of antipsychotics we tested, although the association was only near to significance for substituted benzamides. Among the users of antipsychotics, the unadjusted and adjusted stroke risk of patients treated with phenothiazines exceeded that found in subjects exposed to atypical antipsychotics. The increased risk of stroke associated with antipsychotic medications was not

Table 4. Risk of stroke in different treatment groups

	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio ^a (95% CI)
Model I		
Unexposed subjects as the reference group		
NON-USE	1:00	1.0
BUTYROPHENONES	3.32 (1.64-6.70)	3.55 (1.56-8.07)
PHENOTHIAZINES	5.26 (3.26-8.89)	5.79 (3.07-10.90)
ATYPICAL ANTIPSYCHOTICS	2.07 (1.07-3.99)	2.46 (1.07-5.65)
SUBSTITUTED BENZAMIDES	1.58 (0.92-2.69)	2.20 (0.98-4.90)
Model II		
Subjects exposed to atypicals as the reference group		
ATYPICAL ANTIPSYCHOTICS	1:00	
NON-USERS	0.65 (0.33-1.26)	0.40 (0.17-0.92)
BUTYROPHENONES	1.55 (0.60-4.04)	1.44 (0.55-3.76)
PHENOTHIAZINES	2.57 (1.13-5.84)	2.34 (1.01-5.41)
SUBSTITUTED BENZAMIDES	1.08 (0.47-2.52)	0.89 (0.33-2.38)

^a Cox proportional hazard regression analysis adjusted for age, gender, Chronic Disease Score, medical illnesses (dementia, Parkinson's disease, hypertension, ischemic heart diseases, heart failure, atrial fibrillation, diabetes, dyslipidemia, COPD, recent history of pneumonia, malignant neoplasm, obesity), psychiatric indication of use for an antipsychotic, use of drugs during follow-up (benzodiazepines, diuretics, CCBs, ACE-inhibitors, beta-blockers, anticoagulants, angiotensin receptor blockers, sympathicomimetic drugs).

confined to patients with dementia but was present in all the cohorts that were prescribed these drugs: antipsychotic users remained at higher risk for stroke even after controlling for dementia and other relevant confounders. This rather generalised association between the use of antipsychotic drugs and stroke was not unexpected on the basis of the pre-existing literature involving non demented patients treated with these compounds. For example, schizophrenia patients were reported to have an abnormally high prevalence of transient cerebral ischemia (Curkendall *et al.*, 2004), their actual and 10-year risk of stroke (McCreadie, 2003; Curkendall *et al.*, 2004) was almost two-fold that of the general population, and they presented an excess of cerebrovascular mortality (Brook, 1985; Allebech, 1986; Osby *et al.*, 2000; Joukamaa *et al.*, 2001). In turn, patients with depression or bipolar disorder were found to have abnormally high risk of dying from cerebrovascular accidents (Schwalb, 1987; Zhenge *et al.*, 1997; Schwalb and Schwalb; Osby *et al.*, 2001; Angst *et al.*, 2002).

These results substantially agree with other observational studies which have generally failed to find a difference in the risk of stroke when users of atypical antipsychotics are compared to users of typicals (Hermann *et al.*, 2004; Gill *et al.*, 2005; Layton *et al.*, 2005). However, in our sample the majority of patients were treated with typical antipsychotics; in previous reports (Hermann *et al.*, 2004; Gill *et al.*, 2005; Liperoti *et al.*, 2005; Formiga *et al.*, 2005) the majority of the patients were treated with atypical compounds. The low number of subjects (or person-years) in our atypical cohort is explained by the restrictions placed by the Italian

legislation on the prescription of atypical antipsychotics by general practitioners. Indeed, only after the indication of a psychiatrist working in the public mental health service can a novel antipsychotic be prescribed by a primary care doctor.

Some strengths and weaknesses of our study must be discussed. This is the first study that reports estimates of stroke on a general elderly population unexposed to antipsychotics, taken from the same general practitioners database as the patients exposed to these drugs. Some recent studies on the general population have investigated the crude annual incidence rate of first-ever stroke. This was reported to be 1.74/1000 in a German study (Kolominsky-Rabas *et al.*, 1988), 1.79/1000 in a south-Italian study (Di Carlo *et al.*, 2003), and 2.8/1000 in a Scottish study (Syme *et al.*, 2005). All these studies were based on the total population, including newborns. Since our study investigated only elderly patients, we re-ran the selection on the total population served by general practitioners (i.e. subjects aged 14 or more) and found an annual crude incidence rate of 2.77/1000 person-years which compares well with that found by other studies based on case register data. A second novelty of the study is the independent evaluation of the two most prescribed classes of typical antipsychotics, namely phenothiazines and butyrophenones: no other studies have so far performed this dissection although renewed interest in the use of older antipsychotics has emerged after recommendations from the regulatory agencies (FDA, 2003; EMEA, 2004; Committee on Safety of Medicines, 2004; FDA, 2005). Furthermore, the investigation of an association between substituted benzamides and stroke was definitely original. Data on substituted benzamides should however not only require replication, but also possible specific subanalyses. Although sulpiride and amisulpride belong to the same chemical group and share a selective antagonist activity on dopamine receptors, it cannot be indeed completely dismissed that these two substituted benzamides differ in their clinical profile: the label of atypical antipsychotic appears fully justified for amisulpride (Leucht *et al.*, 2002; Mota Neto *et al.*, 2007), but questionable for sulpiride (Soares *et al.*, 2007), as the superiority of this last compound on first-generation antipsychotics is actually evidence-based for movement disorders and only anecdotal for negative symptoms. Thanks to the many variables coded in the general practitioners database we could adjust the estimated risks for many, possibly confounding variables. This is now highly advisable, given the evidence emerging from the re-analysis of randomised controlled trials that identified pre-existing vascular risk factors in subjects who developed stroke while in therapy (Smith and Beier, 2004; De Deyn *et al.*, 2005). In particular, in our study the estimates of risk were weighted for thirteen diseases (including dementia) and eight types of treatment (including antihypertensives and anticoagulants). The majority of these variables constitute well-established risk factors for stroke (Elkind and

Sacco, 1988; Sacco *et al.*, 1997; Davis *et al.*, 1998; Goldstein, 2000; Lindsberger and Grau, 2003; Humphries and Morgan, 2004). We dealt with differences between cohorts by adjusting in the Cox analysis for potential confounders, as was done in some other studies on stroke and antipsychotics (Hermann *et al.*, 2004; Gill *et al.*, 2005). Another statistical approach could have been the propensity score matching, but we relied on Cox regression modelling for the real advantages of the propensity score matching is still debated and it seems to give results similar to conventional multivariate methods (Sturmer *et al.*, 2006; Shah *et al.*, 2005). We excluded subjects with a previous stroke in order to focus on true incidence and not recurrent stroke, thus contributing new data on first-ever stroke. The adoption of these strict exclusion criteria is both a strength and a weakness of the study: the risk estimate was undoubtedly associated with antipsychotic exposure but it did not allow analysis of subjects with prior cerebrovascular events. Some distortions in the identification of cases with stroke could also have occurred in the study as stroke leading to hospital admission might have been recorded in the database after actual occurrence. We believe, however, that such potential misclassification would be scarcely influential because there is no reason to assume a preferential concentration of patients with a delayed registration of the event in a given cohort. Although cerebrovascular adverse events reported in randomised controlled trials of atypical antipsychotics consisted of both transient ischemic attacks (TIA) and stroke, we focused exclusively on stroke, similar to other studies (Hermann *et al.*, 2004; Gill *et al.*, 2005). However, a recent study reported that about 70% of TIA episodes occur within a week prior to stroke, suggesting that a stroke diagnosis might capture previous TIAs (Johnstone *et al.*, 2000; Hill *et al.*, 2004; Rothwell and Warlow, 2005). Also, our study was a retrospective analysis of a very large clinical set, so that a chart diagnosis of stroke was the principal outcome measure. Although a previous reliability study has shown for this measure a 90% accuracy (Leone *et al.*, 2004), diagnoses were based only on the ICD-9 codes, and not on structured evaluations as in RCTs. Sub-analyses targeted to assess the possible effects of the dose and duration of antipsychotic treatment on stroke incidence were not addressed; the influence of these putative sources of variation seems dubious, however, as the increased risk for cerebrovascular events reported in BPSD clinical trials did not appear associated with dose and duration of olanzapine or risperidone treatment (Street *et al.*, 2000; Brodaty *et al.*, 2003). The sample study included a relatively small proportion of patients with dementia. Patients with this diagnosis represented from 3.3% to 39.2 % of antipsychotic users and only 1.7% of non users. Given the low number of incident cases, a stratified analysis for this variable was not performed. Anyway, dementia was entered in the Cox regression, so that risk ratios were weighted for this variable. No data were

available on other factors known to be associated with stroke such as smoking habits, bad diet, and physical exercise, but these data are probably out of the reach of very large databases in the primary care setting, and this information was not present in all the major studies published recently. Waiting for specific research aimed at resolving the complex interplay of factors contributing to stroke, it remains that the increased risk for stroke in patients receiving antipsychotic medication should not be ascribed solely to antipsychotic drugs. For instance, it may simply be that those prescribed drugs are predisposed to stroke because of unhealthy lifestyles, difficulties to look for health care, inadequate management of predisposing morbidities, and inability to cope with protective health behaviours, all of which are often present in the clinical conditions treated with an antipsychotic. Also, the possibility of a diathesis facilitating stroke shared by patients with dementia, schizophrenia or mood disorders cannot be dismissed: reports (Wada-Isoe *et al.*, 2004, Zhang *et al.*, 2002, Garver *et al.*, 2003, O'Brien *et al.*, 2004) of abnormal interleukin 6 levels in all these groups could support this hypothesis, given the possible association of this pro-inflammatory cytokine with stroke (Chamorro, 2004, Dziedzic *et al.*, 2004). In the meanwhile, clinicians should systematically identify the presence of cerebrovascular predisposing factors whenever they are planning a treatment with antipsychotics irrespective of the specific diagnosis. Subsequently, the physician should carefully evaluate alternative treatment strategies for high-risk patients. For individuals with a recognised cerebrovascular vulnerability who need treatment with antipsychotics, the choice of drug should consider the global aspects of efficacy and tolerability; sufficient evidence to favour some compounds over others on the potential for stroke or related accidents is still not available. Our data would suggest special caution with phenothiazines, while the risk associated with substituted benzamides should be further investigated.

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2.4. All-cause mortality associated with atypical and typical antipsychotics in demented outpatients

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ABSTRACT

Purpose: To estimate the association between use of typical and atypical antipsychotics and all-cause mortality in a population of demented outpatients.

Methods: The study cohort comprised all demented patients older than 65 years and registered in the Integrated Primary Care Information (IPCI) database, during 1996-2004. First, mortality rates were calculated during use of atypical and typical antipsychotics. Second, we assessed the association between use of atypical and typical antipsychotics and all-cause mortality through a nested case-control study in the cohort of demented patients. Each case was matched to all eligible controls at the date of death by age and duration of dementia. Odds ratios were estimated through conditional logistic regression analyses.

Results: The crude mortality rate was 30.1 (95% CI: 18.2-47.1) and 25.2 (21.0-29.8) per 100 person-years during use of atypical and typical antipsychotics, respectively. No significant difference in risk of death was observed between current users of atypical and typical antipsychotics (OR= 1.3; 95% CI: 0.7-2.4). Both types of antipsychotics were associated with a significantly increased risk of death as compared to non-users (OR= 2.2, 1.2-3.9 for atypical antipsychotics; OR=1.7, 1.3-2.2 for typical antipsychotics).

Conclusions: Conventional antipsychotic drug should be included in the FDA's Public Health advisory, which currently warns only of the increased risk of death with the use of atypical antipsychotics in elderly demented persons.

INTRODUCTION

In the treatment of behavioral and psychotic symptoms in demented patients (BPSD), atypical antipsychotics have tended to replace typical antipsychotics, despite their off-label use for this indication.¹⁻² Atypical antipsychotics are supposed to have a better safety profile than typical antipsychotics, especially with regards to extrapyramidal symptoms³. However, recently, concern has been raised about the safety of atypical antipsychotics in older demented adults. Pooled data from several clinical trials showed a 3-fold increase in risk of cerebrovascular events (CVEs) in patients with BPSD, who were treated with olanzapine or risperidone, compared to placebo⁴⁻⁵. In addition, a 2-fold increase in all-cause mortality was observed in demented patients who were treated with olanzapine⁶. As a consequence, the Committee on Safety of Medicines (CSM) has recommended avoiding the use of atypical antipsychotics in elderly with BPSD in March 2004⁶. On April 11, 2005, the Food and Drug Administration (FDA) has issued another public health advisory to warn healthcare providers against the off-label use of atypical antipsychotic medications in elderly with BPSD because of an increased mortality risk⁷. No warning was issued for the typical antipsychotics, although the FDA is now considering it, since some data would suggest a similar increase in mortality risk also for these drugs⁷.

To date, several articles have been published on predictors of mortality in patients with dementia⁸⁻¹⁰. However, only one observational study has been performed to specifically explore the association between antipsychotic use and risk of all-cause mortality in elderly persons, but this was not limited to demented patients.¹¹

In light of the warnings expressed by FDA and CSM regarding atypical antipsychotics, we aimed to compare the risk of all-cause mortality between users of typical and atypical antipsychotics by means of a nested case control study in a cohort of demented patients.

METHODS

Setting

In the Netherlands, all persons have their own general practitioner who files all relevant medical details on their patients from primary care visits, hospital admissions and visits to outpatient clinics. For this study, data were retrieved from the Integrated Primary Care Information (IPCI) database, a longitudinal general practice research database set up in 1992 and containing data from electronic medical records from a group of 150 general practitioners (GPs) in the Netherlands. Details of the database have been previously described¹²⁻¹³. Briefly, the database contains

the complete medical records of approximately 500,000 patients with an age and gender distribution representative of the Netherlands. The electronic records contain coded and anonymous data on patient demographics, reasons for visits (in free text), signs and symptoms, diagnoses (using the International Classification for Primary Care ¹⁴ and free text) from general practitioners and specialists, referrals, hospitalizations, as well as drug prescriptions, including product name + anatomical therapeutic chemical classification (ATC code), dispensed quantity, dosage regimen and indication. To maximize completeness of the data, general practitioners participating in the IPCI project are not allowed to maintain a system of paper-based records, aside from the electronic medical records. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research ¹². The Scientific and Ethical Advisory Board of the IPCI project approved the study.

Study cohort

The study cohort comprised all patients 65 years or older, who were affected by dementia and had at least 1 year of medical history recorded in the database, during the study period (1996-2004). Subjects were followed from the latest of the following dates: one year of valid database history, age 65 year or diagnosis of dementia until the earliest of the following censoring dates: death, latest availability of data, transferring out of the General Practitioner (GP) practice or end of study period.

Cases and controls

The primary study outcome was all-cause mortality. All potential deaths were reviewed by two medically trained persons, blinded to exposure and unaware of the study objective, in order to assess the date of death (index date).

For the nested case control study, we matched to each case all eligible controls in the study cohort on year of birth, duration of dementia and index date.

Exposure definition

For each antipsychotic drug prescription, we calculated the prescription length by dividing the total number of prescribed units (capsules/tablets) by the prescribed number of units per day. For calculation of mortality rates during treatment with antipsychotic drugs, we used days of exposure plus a carry-over of 60 days, as denominator. Exposure days were calculated separately for atypical antipsychotics, typical antipsychotics and combinations (overlapping use). Carry-over was considered only if there were gaps between consecutive prescriptions or if there was no subsequent prescription.

For nested case-control analysis, exposure at the index date was classified, according to antipsychotic use, in one of the following mutually exclusive groups: current use, past use and non-use. A patient was classified as a current user if the index date fell during the duration of antipsychotic treatment or within a maximum of 60 days after the end of the last prescription¹⁵. A person was classified as past user if the antipsychotic treatment was discontinued more than 60 days before the index date. If patients had no prescription for an antipsychotic drug prior to the index date during the study period, they were classified as nonusers. If persons had used more than one type of antipsychotic, they were classified as combined current users if both types of antipsychotics were currently used, otherwise current exposure of one class overruled past exposure. In a sub-analysis, switchers from atypical to typical or vice versa were studied separately. Among current users of both antipsychotic types the effect of daily dose ($<$ or \geq than 0.5 defined daily dose (DDD) equivalents¹⁶ was evaluated. The DDD is the recommended average maintenance dosage of a drug for an adult for the main indication, as defined by the World Health Organization.

Other Covariates

There are many potential risk factors for death in demented patients. We considered as potential confounders: history of cardio- and cerebrovascular diseases (angina pectoris, myocardial infarction, heart failure, atrial fibrillation, peripheral arterial disease, stroke and transient ischemic attack), pneumonia, chronic obstructive pulmonary diseases (COPD), diabetes mellitus, cancer and Parkinson's disease or parkinsonism, home-bound lifestyle, and concomitant use at the index date of antibiotics, corticosteroids, sympathicomimetics, cardiovascular drugs (digoxin, diuretics, calcium channel-blockers, beta-blockers, ACE inhibitors, angiotensin receptor blockers, anticoagulants, lipid lowering drugs) and psychotropic medications (SSRI and Tricyclic antidepressants, lithium, opioids, benzodiazepines).

Statistical analysis

As a first step, we calculated the crude mortality rates for each type of antipsychotic by dividing the number of deaths by the accumulated amount of drug exposure. In the case-control analysis, the univariate association between each risk factor and death was estimated through conditional logistic regression. All covariates that were significantly ($p < 0.05$) associated with mortality were evaluated as potential confounders in the final analyses.

In order to evaluate the association between use of typical and atypical antipsychotics and all-cause mortality, a conditional logistic regression analysis was conducted using two different reference categories: non-use of antipsychotics

and current use of typical antipsychotics. As confounders, we retained all risk factors that were significantly associated with death and changed the risk estimate for current use of any antipsychotic type more than 5%¹⁷. Effect modification was explored by stratifying for age, gender and type of dementia although it was anticipated that the study had not enough power.

RESULTS

Cohort

The study cohort comprised 2,385 elderly patients with dementia: 772 (32.4%) with Alzheimer's disease, 320 (13.4%) with vascular dementia and 1,293 (54.2%) with mixed or unspecified dementia. Of these, 680 (28.5%) and 78 (3.3%) had received prescriptions for typical and atypical antipsychotics after dementia diagnosis, respectively, and 63 (2.6%) had received both types of drugs, 39 of those started with typical antipsychotics and switched to atypical drugs, mostly because of extrapyramidal symptoms.

The amount of accumulated exposure was of 56.5 person-years (PY) for use of atypical antipsychotics, 500.8 PY for typical antipsychotics and 12.1 PY for combined use. During follow-up, 407 persons died. The crude mortality rates during current use of atypical, typical and overlapping use of atypical and typical antipsychotics were 30.1 (18.2-47.1), 25.2 (21.0-29.8) and 16.5 (3.3-53.0) per 100 PY, respectively.

Nested case-control study

Of the 407 deaths that occurred during follow-up, 398 (97.8%) could be matched on year of birth, duration of dementia and index date to one or more controls. Male gender and advanced age (>85 years) were positively associated with death as well as a variety of cardiovascular diseases (Table 1). Recent history of pneumonia, current use of antibiotics and opioids were factors strongly associated with death. Baseline characteristics of controls that were currently exposed to atypical or typical antipsychotics were compared to assess differences between these treatment groups. Patients treated with typical antipsychotics were more likely to be affected by heart failure and chronic obstructive pulmonary diseases, and to have suffered prior events of stroke and myocardial infarction in comparison to users of atypical antipsychotic. On the other hand, users of atypical antipsychotics were more often treated with other psychotropic medications (benzodiazepines and antidepressants) than users of typical antipsychotics (data not shown). Table 2 shows the association between use of antipsychotics and all-cause mortality. With reference to non-use, current use of both atypical (OR_{adj} : 2.2, 95% CI: 1.2-3.9)

Table 1. Characteristics of cases and controls

Covariate	Cases N=398 (%)	Controls N=4,023 (%)	Unadjusted Matched Odds Ratio (95% CI)
Mean Age (SD), years	85.3 (6.5)	84.5 (5.0)	-
Age groups, years			Matched
65-75	32 (8.0)	167 (4.2)	
76-85	162 (40.7)	2,145 (53.3)	
> 85	204 (51.3)	1,711 (42.5)	
Gender (male)	145 (36.4)	1,073 (26.7)	1.7 (1.3 – 2.1)
Smoking	39 (9.8)	381 (9.5)	1.1 (0.8 – 1.6)
<i>Cardiovascular diseases</i>			
Hypertension	249 (62.6)	2,543 (63.2)	1.1 (0.9 – 1.3)
Angina	61 (15.3)	533 (13.2)	1.2 (0.9 – 1.6)
Myocardial Infarction	45 (11.3)	251 (6.2)	2.1 (1.5 – 2.9)
TIA	59 (14.8)	311 (7.7)	2.1 (1.5 – 2.8)
Stroke	60 (15.1)	360 (8.9)	1.8 (1.3 – 2.5)
Heart Failure	128 (32.2)	673 (16.7)	2.3 (1.8 – 2.9)
Atrial Fibrillation	46 (11.6)	400 (9.9)	1.3 (0.9 – 1.8)
Peripheral Arterial Disease	22 (5.5)	157 (3.9)	1.5 (0.9 – 2.4)
<i>Other diseases</i>			
Pneumonia (one year prior)	23 (5.8)	43 (1.1)	5.3 (3.1 – 9.1)
COPD	70 (17.6)	449 (11.2)	1.8 (1.3 – 2.4)
Parkinson(ism)	52 (13.1)	316 (7.9)	1.9 (1.4 – 2.6)
Diabetes Mellitus	84 (21.1)	749 (18.6)	1.3 (1.0-1.6)
Cancer	66 (16.6)	468 (11.6)	1.6 (1.2 – 2.1)
<i>Concomitant medications</i>			
Diuretics	144 (36.2)	1,189 (29.6)	1.4 (1.1 – 1.7)
Digoxin	61 (15.3)	447 (11.1)	1.5 (1.1 – 2.1)
CCB	22 (5.5)	326 (8.1)	0.7 (0.4 – 1.1)
Beta-blockers	44 (11.1)	531 (13.2)	0.8 (0.6 – 1.2)
Angiotensin Receptor Blockers	12 (3.0)	94 (2.3)	1.2 (0.7 – 2.3)
Ace-inhibitors	63 (15.8)	575 (14.3)	1.2 (0.9 – 1.6)
Anticoagulants	135 (33.9)	1,394 (34.7)	1.0 (0.8 – 1.3)
Lipid lowering drugs	4 (1.0)	91 (2.3)	0.5 (0.2 – 1.3)
SSRI	18 (4.5)	302 (7.5)	0.7 (0.4 – 1.1)
Tricyclic antidepressant	11 (2.8)	133 (3.3)	0.9 (0.5 – 1.7)
Opioids	75 (18.8)	71 (1.8)	11.1 (7.7 – 16.0)
Benzodiazepines	113 (28.4)	1,012 (25.2)	1.2 (1.0 – 1.5)
Corticosteroids	33 (8.3)	148 (3.7)	2.4 (1.6 – 3.6)
Antibiotics	81 (20.4)	295 (7.3)	3.1 (2.3 – 4.1)

Values are numbers (percentages) unless stated otherwise.

Legend: TIA= Transient Ischemic Attack; PAD= Peripheral Arterial Disease; COPD= Chronic Obstructive Pulmonary Disease; CCB= Calcium Channel Blocker; SSRI= Selective Serotonin Re-uptake Inhibitor.

and typical antipsychotic drugs (1.7, 1.3-2.2) were associated with a significantly increased risk of death. In comparison to current use of typical antipsychotics, the risk of death was similar in current users of atypical antipsychotics (1.3, 0.7-2.4).

Among current users of both atypical and typical antipsychotics, we observed a strong effect of dose on the association with death. Concerning atypical antipsychotics, the risk of death increased also with increasing duration of use (data not shown). An analysis on the individual atypical antipsychotics showed some heterogeneity among them, with the strongest for olanzapine but we had limited power to assess differences (Table 2).

Sub-analyses targeted to explore whether the association between use of atypical antipsychotics and death differed by gender, age, type of dementia and switching from one antipsychotic type to another one are shown in table 3. Gender (females) and advanced age (≥ 80 years old) seemed to modify the risk of death for current users of atypical antipsychotics, as compared to use of typical antipsychotics, but none of these interactions was significant. The risk of death associated with use of atypical antipsychotics, as compared to typical antipsychotics, was higher in patients starting directly on atypical medications (1.7, 0.8-3.3) than in patients who switched from typical medications to atypical ones (0.8, 0.1-8.2).

Table 2. Association between antipsychotic drug use and death in persons with dementia.

Antipsychotic use	Cases N= 398 (%)	Controls N= 4,023 (%)	OR unadjusted (95% CI)	OR adjusted[^] (95% CI)
<i>Non-use</i>	214 (53.8)	2,721 (67.6)	1.0 (ref)	1.0 (ref)
<i>Atypical antipsychotic use</i>				
Current*	18 (4.5)	99 (2.5)	2.2 (1.3-3.7)	2.2 (1.2-3.9)
Olanzapine	3 (0.8)	5 (0.1)	6.0 (1.3-27.0)	6.7 (1.4-32.1)
Risperidone	13 (3.3)	89 (2.2)	1.8 (1.0-3.3)	1.7 (0.9-3.4)
Clozapine	2 (0.5)	7 (0.2)	2.5 (0.4-14.7)	1.8 (0.3-11.2)
Quetiapine	1 (0.3)	0	No data	No data
Past	3 (0.8)	38 (0.9)	1.2 (0.4-4.1)	1.4 (0.4-5.2)
<i>Typical antipsychotic use</i>				
Current	110 (27.6)	732 (18.2)	1.8 (1.4-2.3)	1.7 (1.3-2.2)
Past	46 (11.6)	402 (10.0)	1.4 (1.0-2.0)	1.4 (0.9-2.0)
<i>Combined antipsychotic use</i>				
Current	2 (0.5)	14 (0.3)	1.8 (0.4-8.5)	1.8 (0.4-8.7)
Past	5 (1.3)	17 (0.4)	2.9 (1.0-8.3)	3.0 (0.9-9.9)
Current typical use	110 (27.6)	732 (18.2)	1.0 (ref)	1.0 (ref)
Current atypical use	18 (4.5)	99 (2.5)	1.2 (0.7-2.1)	1.3 (0.7-2.4)

Legend: CI= confidence interval; OR= odds ratio.

[^]OR matched and additionally adjusted for gender and factors changing the risk estimate for antipsychotic users by more than 5% (Heart failure, COPD, Parkinson(ism), home-bound lifestyle, benzodiazepines, antibiotics). *Current use of different atypical antipsychotics is not mutually exclusive.

Table 3. Risk of death in subgroups of current users of atypical and typical antipsychotics.

Variables	Current use of antipsychotic drug	Cases N= 398 (%*)	Controls N=4,023 (%*)	OR adjusted [^] (95% CI)
Males	atypical	3 (0.8)	24 (0.6)	0.4 (0.1-2.8)
	typical	35 (8.8)	179 (4.4)	1.0 (ref)
Females	atypical	15 (3.8)	75 (1.9)	1.6 (0.7-3.3)
	typical	75 (18.8)	553 (13.7)	1.0 (ref)
65-79 years old	atypical	5 (1.3)	21 (0.5)	0.8 (0.2-2.9)
	typical	18 (4.5)	83 (2.1)	1.0 (ref)
≥80 years old	atypical	13 (3.3)	78 (1.9)	1.4 (0.7-2.7)
	typical	92 (23.1)	649 (16.1)	1.0 (ref)
Alzheimer's disease	atypical	4 (1.0)	28 (0.7)	0.9 (0.2-4.4)
	typical	41 (10.3)	302 (7.5)	1.0 (ref)
Vascular dementia	atypical	3 (0.8)	23 (0.6)	0.6 (0.1-10.2)
	typical	17 (4.3)	106 (2.6)	1.0 (ref)
Mixed/unspecified dementia	atypical	11 (2.8)	48 (1.2)	1.7 (0.8-4.1)
	typical	52 (13.1)	324 (8.1)	1.0 (ref)
Switchers	atypical	2 (0.5)	29 (0.7)	0.8 (0.1-8.2)
	typical	2 (0.5)	12 (0.3)	1.0 (ref)
Non-switchers	atypical	16 (4.0)	70 (1.7)	1.7 (0.8-3.3)
	typical	108 (27.1)	720 (17.9)	1.0 (ref)

[^]OR adjusted for gender, Parkinson(ism), heart failure, COPD, home-bound lifestyle, concomitant use of benzodiazepines and antibiotics.

*Percentage based on total cases and controls, including those not exposed to antipsychotics, past users of any antipsychotic type and users of combination.

DISCUSSION

In this study, we found no difference in the risk of death between atypical and typical antipsychotic use in elderly outpatients with dementia. The use of atypical and typical antipsychotics was similarly associated with a significant and dose-related increase in risk of all-cause mortality compared to non-users. Our finding on atypical antipsychotics is consistent with the public health advisory that was recently issued by FDA ⁷. Health care providers were informed about the results of a pooled analysis of seventeen placebo-controlled studies that showed a 1.7 fold increased risk of death during use of atypical antipsychotics. Data on typical antipsychotics from clinical trials for this indication are limited but are consistent with a similar increase in the risk of death ⁷. Our study results underline that the risk of death is similarly elevated in users of typical antipsychotics. The FDA did not mention effects of dose and duration. In our study, the risk of death increased with increasing daily dose for both antipsychotic types and with increasing duration of use for atypical antipsychotics. In general, a positive dose-response supports a causal effect. A recently published meta-analysis of randomized placebo-controlled trials of atypical antipsychotics in patients with dementia ¹⁸ highlighted that use of these newer antipsychotics for relatively brief periods (8-12 weeks) may be associ-

ated with a small increased risk of death as compared with placebo. In line with our results, it is also highlighted that this effect may not be limited to atypical drugs and may be associated also with haloperidol and other antipsychotics that have not been tested for this indication of use¹⁸. Prior to our investigation, only one US observational study¹¹ had explored the association between antipsychotic medication use and risk of all-cause death in elderly patients, independent of the presence of dementia. The results from that study also suggest that conventional antipsychotic medications are at least as likely as atypical agents to increase the risk of death among elderly persons. In light of previous alerts⁴⁻⁵ and scientific evidences from other observational studies¹⁹⁻²², however, further evaluations should be performed to more precisely establish whether differences in the risk of well-defined fatal event, such as stroke or arrhythmias, may be reported between users of atypical and typical antipsychotics. Although exploratory and underpowered, our sub-analyses suggested that certain subgroups of atypical and typical antipsychotic users would have different risks of death related to antipsychotic drug use. In particular, the risk of death was higher in females than males for atypical antipsychotics, compared to users of typical antipsychotics. Gender as a risk factor of death in demented patients is controversial^{9,23-24}. Patients starting directly with atypical antipsychotics were at higher risk of death compared to those switching from typical to atypical antipsychotics. Future studies should provide also more data on the differential risk in users of antipsychotics who are switchers and non-switchers.

To our knowledge, this is the first observational study specifically comparing the effect of atypical and typical antipsychotic drugs on all-cause mortality in a cohort of elderly patients who have been diagnosed with dementia. The strength of this study is the information on many confounders, dementia, dose and duration of antipsychotic drug use and the possibility to review reason for switching. However, several limitations of our study warrant caution. In any observational study, selection bias, information bias and residual confounding should be considered as alternative explanations for the study finding. Selection bias was minimal as all data were obtained from prospectively collected medical records that are maintained for patient care purposes. Information bias by misclassification of the outcome will be minimal since death is consistently registered by GPs¹⁵. A previous study on the IPCI database has shown that the incidence of sudden cardiac death is in line with estimates from other sources²⁵. Studies on mortality and influenza vaccination in the IPCI database additionally underlined the validity of the data on mortality²⁶. Misclassification of exposure may have occurred since we used outpatient prescription data and had no information whether the antipsychotic drug prescriptions were actually filled and taken. It is likely, however, that such

exposure misclassification will be evenly distributed among cases and controls and, therefore, the actual risk may be underestimated. To limit exposure misclassification due to inpatient prescriptions, we excluded all patients who transferred out of the GP practice (e.g. to a nursing home or long-term care facility). Many risk factors for death were considered in our study, even though residual confounding due to unmeasured confounders or severity of disease cannot be excluded. Opioids are often given in the end-stage of life to alleviate pain in terminally ill patients. Since this variable can be considered a proxy of death rather than a confounder of the association between use of antipsychotics and death, we did not include use of opioids in the multivariate analysis. Inclusion of opioids in the model did not change the association between atypicals and typicals and risk of death.

To summarize, our study shows that both types of antipsychotic drugs are associated with an increased and dose-related risk of death in elderly demented persons, which is consistent with results from placebo-controlled trials. Since behavioral and psychotic symptoms requiring antipsychotic treatment may themselves be predictors of mortality within older demented patients²⁷, however, confounding by indication may explain at least part of that association. On the other hand, the main study finding is that patients with dementia who are currently treated with typical antipsychotics in an outpatient setting have a similar risk of death as users of atypical antipsychotics.

Therefore, our data supports the fact that conventional antipsychotic drugs should be included in the FDA's Public Health advisory, which currently warns only of the increased risk of death with the use of atypical antipsychotics in elderly demented persons.

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2.5. Fatal and non fatal community acquired pneumonia associated with antipsychotic drug use in elderly patients

Submitted for publication

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ABSTRACT

Context: Recently, the Food and Drug Administration highlighted that mortality is increased during use of antipsychotics in elderly dementia patients and pneumonia is one of the most frequently reported causes of death. The alert regarded atypical antipsychotics but was recently extended also to typical antipsychotics.

Objective: To evaluate whether use of typical or atypical antipsychotics is associated with fatal/non-fatal pneumonia in elderly patients.

Design, Setting and Participants: A population based nested case-control study was conducted in a cohort of antipsychotic (AP) drug users who were 65 years or older during the years 1996-2006 in the Dutch Integrated Primary Care Information (IPCI) medical record database. Cases were all patients with an incident fatal or non-fatal community-acquired pneumonia. Up to 20 controls were matched to each case on age, gender and index date. Exposure to AP was categorized by type, recency and daily dose of use and the association with pneumonia was assessed using conditional logistic regression.

Main outcome measure: Association between fatal/non-fatal community acquired pneumonia and antipsychotic use.

Results: 258 incident cases of pneumonia were matched to 1,686 controls. Sixty-four (24.8%) of the cases died within 30 days and were considered fatal cases. Current use of either atypical (OR: 2.64; 95% CI: 1.51-4.61) or typical (OR: 1.74; 95% CI: 1.22-2.49) antipsychotics was associated with a increase in the risk of pneumonia compared to past use of any antipsychotic. The linear trend of dosage was significant for both current users of atypical and typical antipsychotics. Only atypical antipsychotics were associated with a significant increase in the risk of fatal pneumonia (OR: 5.5, 95% CI: 1.5-20.6).

Conclusion: The use of either atypical or typical antipsychotics in elderly patients appears to be associated in a dose-dependent fashion with the development of community-acquired pneumonia.

INTRODUCTION

Antipsychotic (AP) drugs, which are generally distinguished in typical (conventional) and atypical (newer) agents, are widely used in geriatric psychiatric disorders, such as affective psychoses, agitation and behavioral and psychological symptoms of dementia [1-2]. Although antipsychotics are effective for some indications, they are often over- and misused in elderly patients and recently their safety profile was questioned by the Food and Drug Administration (FDA) [1]. In 2005 the FDA informed health professionals about the results of a pooled analysis of placebo-controlled clinical trials, reporting a 70% increased risk in all-cause mortality in elderly demented patients who were treated with atypical antipsychotics [3]. According to the FDA alert, pneumonia was one of the most frequently reported causes of death [3]. Although the warning focused on atypical antipsychotics, the FDA underlined that a similar increased risk could not be excluded for the typical antipsychotics. Subsequent observational studies confirmed this suspicion since they found that mortality was elevated in elderly patients receiving either atypical or typical antipsychotic drugs [4-6]. In June 2008, the FDA extended the warning about the increased risk of all-cause mortality also to the typical antipsychotics, when used off-label in elderly dementia patients [7].

The mechanism behind the demonstrated increase in mortality is not clear and the question remains whether antipsychotics may increase the risk of pneumonia and thereby mortality. This is not easy to assess since the baseline risk of fatal pneumonia is already high in elderly patients with psychiatric diseases [8].

To our knowledge, two studies (one in the Netherlands and one in US) have evaluated the association between antipsychotic drug use and pneumonia, but both studies captured only hospitalized pneumonia [9-10]. Compared to non-users, the Dutch study showed a 3-fold increased risk of pneumonia in atypical users and a 60% increase in users of typical antipsychotics [9]. The U.S. study that included a cohort of patients hospitalized for pneumonia found that use of typical antipsychotics was associated with a 50% increased risk of mortality in inpatients with pneumonia [10].

To further explore the association between atypical and typical antipsychotic drug use and the risk of fatal/non-fatal community-acquired pneumonia we conducted a case control study nested in a cohort of elderly outpatients receiving antipsychotic drugs.

METHODS

Setting

For this study, data were retrieved from the Integrated Primary Care Information (IPCI) database, a longitudinal general practice research database set up in 1992 and containing data from electronic medical records from a group of 200 general practitioners (GPs) in the Netherlands. All Dutch inhabitants are registered with their own GP. The GP is the gatekeeper to all further care and files all relevant medical details from primary care visits, hospital admissions and visits to outpatient clinics. Details of the IPCI database have been previously described [11]. Briefly, the database contains the complete medical records of approximately 800,000 patients. The age and gender distribution of the IPCI population is representative of the whole country. The electronic records contain anonymous data on patient demographics, reasons for visits (in free text), signs and symptoms, diagnoses (using the International Classification for Primary Care and free text) [12] from the GPs and the specialists, along with referrals, hospitalizations, as well as drug prescriptions, including product name + anatomical therapeutic chemical classification (ATC code), dispensed quantity, dosage regimen and indication of use [13]. To maximize completeness of the data, GPs participating in the IPCI project are not allowed to maintain any paper-based records. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmacoepidemiological research [14]. The Scientific and Ethical Advisory Board of the IPCI project approved the study (Study Protocol N. 07/05).

Study cohort

The source population comprised all patients who were registered in the IPCI database and were 65 years or older during the study period (January 1, 1996 - December 31, 2006). The study cohort included all elderly patients that received a first antipsychotic drug prescription during the study years. Cohort members were followed from the cohort entry date until the earliest of the following events: pneumonia, death, moving out of the practice area or end of the study period. Persons, who were diagnosed with lung cancer, either before or during the observation period, were excluded.

Identification and Ascertainment of Pneumonia

Cases were all persons with a first ascertained community-acquired pneumonia during follow-up. Pneumonia was identified through searches of coded diagnoses and narratives in the electronic medical record [15]. The electronic medical records

of all potential patients were reviewed manually by two medically trained researchers (E.F.S, G.T.) who were blinded towards the exposure. Cases were classified as certain (either confirmed by a specialist or diagnosed by chest X-ray) or possible (diagnosed by GPs on the basis of respiratory sign/symptoms). For unresolved cases, a third medical doctor arbitrated. All of the remaining potential cases were excluded. The date of first specific symptoms related to pneumonia (i.e. fever, respiratory signs/symptoms) was defined as the index date (ID). Pneumonia was considered fatal if the person died within 30 days after ID [16].

Controls

By using incidence density sampling, up to 20 controls (individuals alive and disease-free at index date) from the cohort of new users of antipsychotic drugs were matched to each case on the year of birth, gender and index date.

Exposure definition

For the estimate of the association between antipsychotic drugs and pneumonia, we created exposure categories based on drug type, timing, dose and duration of use. Antipsychotic drug use was obtained from the prescription files and the length of treatment was calculated based on the dispensed number of units and the dosing regimen. In detail, we calculated the duration as the total number of units per prescription divided by the prescribed daily number of these units. Antipsychotic drugs were grouped in: 1) Atypical antipsychotics: clozapine, olanzapine, risperidone, quetiapine; 2) Typical antipsychotics, divided in Butyrophenones, Phenothiazines, and Others (Benzamides, Thioxanthene and Diphenylbutylpiperidine derivatives); 3) Combination of atypical and typical antipsychotics, in case of concomitant use. Exposure to antipsychotic drug types was categorized by time since last use. Drug use was defined as current if the prescription duration covered the index date or ended 30 days or less (carry-over effect) prior to that, as recent if the end of the last prescription was between 30 and 180 days prior to the index date, and as past if the last prescription ended more than 180 days before ID. If patients had used more than one type of antipsychotic drug, current exposure of one class overruled past exposure of the other, unless they were concomitantly used. Among current users of antipsychotic drugs, we studied the risk of fatal and non-fatal pneumonia for the most widely prescribed compounds, by daily dosage (\leq or $>$ median DDD) and by different durations of use (≤ 7 , ≤ 30 and ≤ 60 days).

Covariates

As covariates, we considered age, gender, calendar time (matching variables), indication of use of antipsychotic drugs (behavioral and psychological symptoms of dementia, psychoses associated to affective disorders, anxiety disorders, including agitation and sleep disorders, and other psychotic disturbances) as obtained from the electronic medical record, smoking, home bound lifestyle (defined as receiving at least 2 visits from GP at home within 1 month prior to index date), cardiovascular diseases (heart failure, hypertension, angina, history of myocardial infarction, cardiac arrhythmias), history of cerebrovascular disorders, Parkinson's disease (identified as diagnosis and/or anti-Parkinson drug use), chronic obstructive pulmonary disease (COPD), diabetes mellitus, chronic renal disease, chronic liver disease, cancer (except for lung cancer). With respect to medications, we looked at any prior use of cardiovascular drugs (diuretics, digoxin, ACE-inhibitors, sartanes, calcium-channel blockers, beta-blockers, lipid-lowering drugs, aspirin and other antiplatelet drugs, anticoagulants), gastric acid-suppressive drugs, and concomitant use (within 3 months prior to the index date) of antibiotics, systemic corticosteroids, respiratory drugs (nasal and throat preparations, drugs for obstructive airway diseases, cough and cold preparations, antihistamines for systemic use and other respiratory system products), and psychotropic drugs (benzodiazepines, tricyclic antidepressants, selective serotonin reuptake inhibitors, opioids and anticonvulsants).

Data Analysis

To reduce confounding by indication a nested case control analysis was conducted in a cohort of new users of antipsychotic drugs. We selected new users of antipsychotics for two reasons: 1) to calculate crude incidence rates of pneumonia in users of atypical and typical antipsychotics; 2) to avoid bias due to depletion of susceptible patients: if the risk of pneumonia changes over time bias is introduced by prevalent users since not all of their time at risk is observed [9]. Crude incidence rates of pneumonia in users of atypical and typical antipsychotics were calculated by dividing the number of cases by the corresponding persons-months of exposure (PMs). Relative risks of community acquired pneumonia were estimated as odds ratio (OR) by using conditional logistic regression analysis, while adjusting for all covariates that were significantly ($p < .05$) associated with pneumonia in the univariate analysis. Relative risks (plus 95% confidence intervals [CIs]) were calculated for typical and atypical antipsychotics by comparing current use to past use of any antipsychotics; in current users, the effects of the most commonly prescribed individual medications, and the effect of dose (in defined daily dose equivalents) and duration of use were estimated. Moreover, a linear trend across the dosage

strata was tested including dosage as ordinal variable in the conditional logistic regression model. In order to directly compare the effect of atypical and typical antipsychotics, an analysis was conducted that assessed the effects of current use of atypicals by using current use of typical agents as reference group. Since one of the potential explanations of a differential effect on pneumonia between the antipsychotic classes could be the differences in anti-histaminergic effects, a post-hoc analysis was conducted that used current use of butyrophenones as reference group since these antipsychotics have the lowest affinity for the anti-histaminergic receptor H¹ (see Table 5). To evaluate the association between use of antipsychotics and fatal pneumonia, all the above mentioned analyses were repeated in a dataset that comprised only the fatal cases of pneumonia (defined as those events leading to death within 30 days from the onset) and their matched controls. A sensitivity analysis was conducted that defined fatal pneumonia as death occurring within 7 days after the onset of pneumonia. Moreover, to compare our findings with those from previous publications that included only hospitalized pneumonia, we performed a sensitivity analysis restricted to pneumonia cases requiring hospitalization and their matched controls. Several sensitivity analyses were also conducted in order to rule out the impact of potential protopathic and information biases. Severe pneumonia may induce delirium and trigger subsequent antipsychotic drug use in elderly patients [17]. If the date of onset of pneumonia is not defined with certainty that might result in a protopathic bias, i.e. a drug which is used to treat prodromic symptoms of the outcome may falsely be considered to actually cause the outcome [18]. To explore whether the association between antipsychotic drugs and pneumonia was distorted due to protopathic bias, we performed an analysis that excluded all patients who began the treatment within 7 days prior to the index date. To rule out possible outcome misclassification and inspect ascertainment bias a sensitivity analysis was conducted excluding all pneumonia cases that were judged to be only possible.

The number of pneumonia cases attributable to use of atypical and typical antipsychotics was calculated by multiplying the adjusted attributable risk percentage $((OR-1)/OR)$ with the incidence rate (in Person-Months) and the average duration of use in months [15].

All conditional logistic regression analyses were conducted in SPSS/PC, version 13 (SPSS Inc, Chicago, Ill). The level of significance for all statistical tests was set at p-value below 0.05.

RESULTS

The study cohort comprised 2,560 elderly patients who received a first antipsychotic medication prescription during the follow-up period (Figure 1). Among those, 2,263 (88.4%) started with typical antipsychotics, 277 (10.8%) with atypicals (20 patients received a combination of atypical and typical antipsychotics). The mean duration of use was 154 and 128 days for atypical and typical antipsychotics, respectively. After cohort entry 264 patients suffered a first pneumonia. The incidence rates of pneumonia were 1.12 and 0.78 cases per 100 person-months (PMs) among current users of atypical and typical antipsychotics, respectively (Table 1).

Figure 1. Selection of incident cases of community acquired pneumonia and matched controls by using Integrated Primary Care Information (IPCI) database.

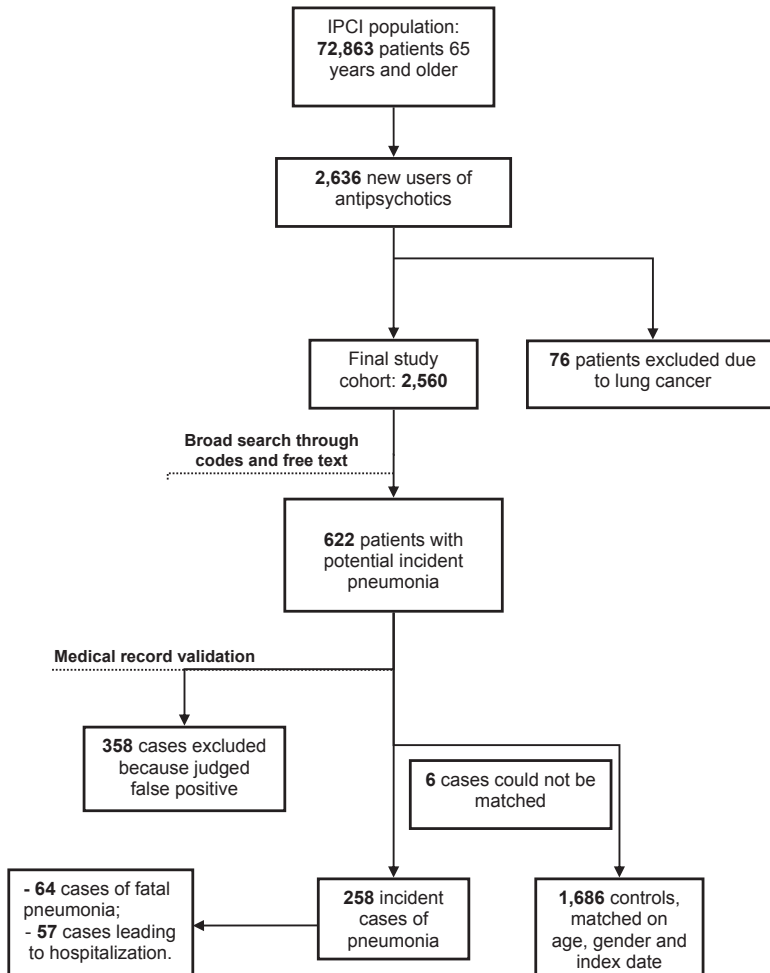


Table 1. Incidence rate (IR) of pneumonia by exposure to antipsychotic drugs.

Antipsychotic exposure	Cases of pneumonia	Person months (PM) exposure	IR (per 100 PM)
Atypical antipsychotics (N=277)			
Current use	22	1,967	1.12
Recent use	15	1,649	0.91
Past use	8	1,829	0.44
Typical antipsychotics (N=2,263)			
Current use	76	9,689	0.78
Recent use	79	10,461	0.76
Past use	62	15,001	0.41
Combination of both types (N=20)			
Current use	1	131	0.76
Recent use	1	94	1.06
Past use	-	162	-

Pneumonia rates were comparable between past use of atypical and typical antipsychotic drugs. Of the 264 cases, 258 could be matched to 1,686 controls on age, gender and index date. Fifty-seven cases (22.1%) were hospitalized for pneumonia and 64 (24.8%) were considered fatal (Figure 1). Cases were more likely to be home bound and to be diagnosed with chronic obstructive pulmonary diseases, diabetes mellitus and arrhythmias (Table 2). Chronic use of anticoagulants and concomitant use of antibiotics, corticosteroids, tricyclic antidepressants and opioids were also risk factors for pneumonia in this cohort. The indications for antipsychotic drug use were not associated with pneumonia. Current use of atypical (OR: 2.64; 95% CI: 1.51-4.61) and typical (OR: 1.74; 95% CI: 1.22-2.49) antipsychotics was associated with an increased risk of pneumonia when compared to past use (Table 3). The increased risk disappeared after stopping medication as recent use of antipsychotics was not associated with an increased risk of pneumonia anymore. Current use of atypical antipsychotics was associated with a non-significant 50% higher risk of pneumonia compared to current use of typical antipsychotics (OR: 1.52, 95% CI: 0.87-2.64). Analyses of chemical subgroups of typical antipsychotics showed some heterogeneity. Use of butyrophenones was associated with only a slightly increased risk of pneumonia (OR: 1.56; 95% CI: 1.07-2.29) while the use of phenothiazines was associated with a four-fold increased risk (OR: 4.32, 95% CI: 1.57-11.87) (Table 3). Adjustment for frequency of use of different subtypes in determining the class effect for typical antipsychotics showed that the overall class effect remained approximately the same (OR: 2.03; 95% CI: 1.20-3.45). Analysis of individual drugs showed that risperidone (OR: 3.30; 95% CI: 1.84-5.93) was associated with the highest risk of pneumonia (Table 4). The daily dosage of either atypical or typical antipsychotics was generally very low in current users (median: 0.15 DDD). Patients receiving higher doses (above median) of either atypical or

Table 2. Characteristics of cases and controls.

Covariates	Cases N=258 (%)	Controls N= 1,686 (%)	Odds Ratio (95% CI)	P-value
<i>Gender</i>			Matching factor	
Males	116 (45.0)	457 (27.1)		
<i>Mean Age (SD)</i>	83.7 (7.5)	83.2 (5.9)	Matching factor	
Smoking	38 (14.7)	193 (11.4)	1.24 (0.82-1.88)	.13
Home bound lifestyle	38 (14.7)	107 (6.3)	2.11 (1.35-3.29)	< .001
<i>Cardiovascular diseases</i>				
Angina	49 (19.0)	355 (21.1)	0.79 (0.55-1.14)	.45
History of myocardial infarction	5 (1.9)	37 (2.2)	0.72 (0.28-1.87)	.79
History of cerebrovascular events	45 (17.4)	233 (13.8)	1.26 (0.92-1.72)	.11
Heart Failure	56 (21.7)	269 (16.0)	1.24 (0.87-1.78)	.05
Arrhythmias	36 (14.0)	165 (9.8)	1.54 (1.03-2.31)	.04
Hypertension	45 (17.4)	381 (22.6)	0.79 (0.55-1.13)	.06
<i>Other diseases potentially related to pneumonia</i>				
Swallowing problems	7 (2.7)	47 (2.8)	0.81 (0.33-2.00)	.95
COPD	49 (19.0)	190 (11.3)	1.62 (1.12-2.36)	< .001
Diabetes Mellitus	58 (22.5)	282 (16.7)	1.52 (1.08-2.15)	.02
Chronic renal disease	7 (2.7)	38 (2.3)	1.07 (0.46-2.47)	.65
Chronic hepatic diseases	10 (3.9)	52 (3.1)	1.30 (0.61-2.76)	.50
Cancer (except for lung cancer)	36 (14.0)	188 (11.2)	1.23 (0.81-1.87)	.20
Parkinson's disease	30 (11.6)	135 (8.0)	1.45 (0.92-2.30)	.05
<i>Indication for antipsychotic drug use</i>				.001
BPSD	80 (31.0)	607 (36.0)	0.84 (0.59-1.19)	
Affective psychoses	11 (4.3)	136 (8.1)	0.55 (0.28-1.09)	
Anxiety disorders*	75 (29.1)	347 (20.6)	1.34 (0.93-1.91)	
Other psychotic disorders	87 (33.7)	509 (30.2)	1.00	
Not reported	5 (1.9)	87 (5.2)	0.40 (0.16-1.02)	
<i>Use of cardiovascular drugs</i>				
Antihypertensive drugs	141 (54.7)	936 (55.5)	1.00 (0.76-1.33)	.80
Digoxin	26 (10.1)	132 (7.8)	1.44 (0.90-2.29)	.22
Antiplatelet drugs	79 (30.6)	459 (27.2)	1.22 (0.89-1.66)	.26
Anticoagulants	42 (16.3)	171 (10.1)	2.19 (1.48-3.24)	.003
Lipid lowering drugs	15 (5.8)	86 (5.1)	1.34 (0.75-2.40)	.63
Use of gastric acid suppressive drugs	45 (17.4)	244 (14.5)	1.26 (0.87-1.82)	.21
<i>Concomitant use of:</i>				
Respiratory drugs	31 (12.0)	158 (9.4)	1.27 (0.82-1.97)	.18
Corticosteroids	17 (6.6)	43 (2.6)	2.75 (1.48-5.11)	< .001
Antibiotics	52 (20.2)	219 (13.0)	1.66 (1.16-2.38)	.002
<i>Psychotropic drugs</i>				
Opioids	20 (7.8)	61 (3.6)	2.41 (1.35-4.31)	.002
Benzodiazepines	57 (22.1)	335 (19.9)	1.23 (0.88-1.72)	.41
Anticonvulsants	1 (0.4)	32 (1.9)	0.17 (0.03-1.30)	.19
TCA	15 (5.8)	43 (2.6)	2.40 (1.27-4.51)	.003
SSRI	12 (4.7)	69 (4.1)	1.30 (0.68-2.48)	.82

Legend: COPD=Chronic Obstructive Pulmonary Disease; BPSD= Behavioural and Psychological Symptoms of Dementia; Respiratory drugs= Cough and cold preparation, Antihistamines for systemic use, Nasal and throat preparations, Drugs for obstructive airways diseases and other respiratory system products; TCA= Tricyclic antidepressant; SSRI= Selective Serotonin Reuptake Inhibitor.*including sleep disorders and agitation.

Table 3. Association between use of antipsychotic drugs and pneumonia in the cohort of new users of antipsychotic drugs.

Antipsychotic exposure	Fatal and non-fatal pneumonia				Fatal pneumonia			
	Cases N=258 (%)	Controls N=1,686 (%)	Matched OR (95% CI)	Adj [^] OR (95% CI)	Cases N=64 (%)	Controls N=401 (%)	Matched OR (95% CI)	Adj [^] OR (95% CI)
Current use								
Atypical	28 (10.9)	100 (5.9)	2.99 (1.76-5.09)	2.64 (1.51-4.61)	7 (10.9)	19 (4.7)	3.78 (1.19-11.98)	5.46 (1.45-20.56)
Typical	105 (40.7)	517 (30.7)	1.90 (1.34-2.70)	1.74 (1.22-2.49)	26 (40.6)	139 (34.7)	1.83 (0.88-3.77)	1.61 (0.72-3.56)
Butyrophenones	77 (29.8)	429 (25.4)	1.62 (1.11-2.36)	1.56 (1.07-2.29)	21 (32.8)	117 (29.2)	1.80 (0.85-3.82)	1.42 (0.61-3.27)
Phenothiazines	9 (3.5)	13 (0.8)	4.00 (1.44-11.14)	4.32 (1.57-11.9)	1 (1.6)	2 (0.5)	-	-
Others*	19 (7.4)	75 (4.4)	2.24 (1.20-4.16)	2.12 (1.14-3.98)	4 (6.3)	20 (5.0)	1.77 (0.51-6.20)	2.36 (0.62-8.97)
Combination of atypical and typical	4 (1.6)	8 (0.5)	4.52 (1.12-18.21)	5.35 (1.33-21.5)	-	2 (0.5)	-	-
Recent Use								
Atypical	5 (1.9)	39 (2.3)	1.41 (0.48-4.17)	1.33 (0.44-4.03)	-	5 (1.2)	-	-
Typical	46 (17.8)	279 (16.5)	1.56 (1.02-2.39)	1.28 (0.82-2.00)	17 (26.6)	82 (20.4)	1.82 (0.81-4.09)	1.36 (0.56-3.33)
Combination of atypical and typical	1 (0.4)	2 (0.1)	-	-	-	-	-	-
Past Use of any AP	69 (26.7)	741 (44.0)	Reference Group	Reference Group	14 (21.9)	154 (38.4)	Reference Group	Reference Group

[^]Adjusted for diabetes mellitus, COPD, arrhythmias, home bound lifestyle, indication of use of antipsychotics and any prior use of anticoagulants and concomitant use of corticosteroids, antibiotics, TCA and opioids; * Thioxanthene, Diphenylbutylpiperidine and Benzamides derivatives.

typical antipsychotics were those with the highest risk of pneumonia (Table 4). The linear trend of dosage was significant for both current users of atypical ($p < .005$) and typical antipsychotics ($p < .001$). There was no clear pattern of the duration of use, however, the highest risk was observed during the first week of treatment (Table 4). There was no significant effect modification by presence of behavioral and psychological symptoms of dementia (BPSD) or concomitant use of benzodiazepines, SSRIs or TCAs. Exclusion of patients with BPSD did not remove the association between current use of atypical (OR: 3.33; 95% CI: 1.37-8.08) or typical antipsychotics (OR: 1.85; 95% CI: 1.17-2.93) and pneumonia. Use of atypical but not that of typical antipsychotics was associated with fatal pneumonia (OR: 5.5; 95% CI: 1.5-20.6) (Table 3). If a fatal event was defined as death occurring within 7 days rather than within 30 days, the risk estimate for atypical antipsychotics was 3.8 (95% CI: 0.67-21.0). If cases were limited to pneumonia requiring hospitalization, only the use of atypical antipsychotics was associated with pneumonia (OR: 6.3, 95% CI: 2.0-19.5). Various sensitivity analyses were

Table 4. Dose, duration and individual drug response analysis for the association between current use of antipsychotics and the risk of pneumonia*.

	Cases N= 258 (%)	Controls N=1,686 (%)	Crude OR (95% CI)	Adjusted [^] OR (95% CI)
By dosage#				
<i>Current use of Atypical APs</i>				
≤ 0.15 DDD	6 (2.3)	30 (1.8)	1.88 (0.71-4.98)	1.42 (0.48-4.17)
> 0.15 DDD	22 (8.5)	70 (4.2)	3.55 (1.97-6.38)	3.31 (1.80-6.11)
<i>Current use of Typical APs</i>				
≤ 0.15 DDD	60 (23.3)	329 (19.5)	1.72 (1.15-2.55)	1.53 (1.02-2.29)
> 0.15 DDD	45 (17.4)	188 (11.2)	2.20 (1.40-3.45)	2.12 (1.33-3.49)
By duration of use				
<i>Current use of Atypical APs</i>				
≤ 7 days	13 (5.0)	33 (2.0)	4.62 (2.18-9.74)	3.89 (1.75-8.64)
≤ 30 days	23 (8.9)	64 (3.8)	3.68 (2.07-6.54)	3.22 (1.75-5.93)
≤ 60 days	26 (10.1)	86 (5.1)	3.29 (1.91-5.69)	2.96 (1.66-5.25)
<i>Current use of Typical APs</i>				
≤ 7 days	49 (19.0)	170 (10.1)	2.63 (1.70-4.06)	2.29 (1.46-3.60)
≤ 30 days	80 (31.0)	319 (18.9)	2.20 (1.52-3.21)	2.01 (1.36-2.95)
≤ 60 days	90 (34.9)	403 (23.9)	2.02 (1.41-2.90)	1.85 (1.27-2.68)
By active compound**				
<i>Current use of:</i>				
Risperidone	26 (10.1)	71 (4.2)	3.63 (2.09-6.32)	3.30 (1.84-5.93)
Olanzapine	5 (1.9)	23 (1.4)	2.41 (0.83-7.00)	2.08 (0.69-6.24)
Pipamperon	46 (17.8)	276 (16.4)	1.55 (1.01-2.38)	1.50 (0.97-2.33)
Haloperidol	40 (15.5)	161 (9.5)	2.43 (1.53-3.86)	2.03 (1.25-3.28)
Zuclophenthixol	11 (4.3)	39 (2.3)	2.19 (0.99-4.85)	2.00 (0.88-4.51)

*Past use of any antipsychotic drugs was the reference category; [^]Adjusted for diabetes mellitus, COPD, arrhythmias, home bound lifestyle, indication of use of antipsychotics and any prior use of anticoagulants and concomitant use of corticosteroids, antibiotics, TCA and opioids; # linear trend across the 3 dosage strata is significant for both current users of atypical ($p < .005$) and typical antipsychotics ($p < .001$), ** Only the drugs with more than 3 users for each cell in two by two tables have been considered. The use of individual drugs was not mutually exclusive.

conducted to estimate the effect size of possible misclassification of exposure or outcome. Varying the current use window by diminishing the carry-over period from 30 to 20, 10 or 0 days resulted in a slightly reduced risk for current users of atypical antipsychotics (OR from 2.64 to 2.24 in 0 days carry-over), while no changes were observed for current users of typical antipsychotics. Exclusion of cases in which pneumonia was classified only as possible (diagnosis from GP based on signs/symptoms consistent with pneumonia, without further ascertainment) slightly reduced the effect estimates, particularly for typical antipsychotics [OR: 2.13 (95% CI: 1.96-3.92) and 1.36 (95% CI: 0.92-2.00) for current users of atypical and typical antipsychotics, respectively]. To verify the existence of protopathic bias, we performed a sensitivity analysis excluding all patients who started antipsychotic therapy within 7 days prior to the pneumonia onset but the risk estimates did not change substantially [OR: 2.50 (95% CI: 1.37-4.54) and 1.49 (95% CI: 1.02-2.18) for current users of atypical and typical antipsychotics, respectively]. In the elderly patients using antipsychotics in this study, the adjusted attributable risk is 62% for

Table 5. Affinity values (pKi) of different antipsychotics for H₁, histaminergic (H₁) and cholinergic receptors, based on literature search [31-36][^]

Atypical antipsychotic	H₁	MUSC	M₁	M₂	M₃
Clozapine	8.70±0.53	7.61±0.40	8.22±0.61	7.08±0.44	7.59±0.30
Olanzapine	8.85±0.73	7.75±0.54	8.15±0.38	7.32±0.34	7.36±0.43
Quetiapine	7.89±0.71	6.03±0.68	6.86±0.06	6.20±0.00	5.40±0.50
Risperidone	7.86±0.81	4.94±0.46	5.18±0.52	5.21±0.42	5.07±0.52
Typical antipsychotic					
Phenothiazines					
Chlorpromazine	8.10±0.50	7.01±0.68	7.21±0.35	6.56±0.35	7.22±0.09
Fluphenazine	7.68±0.59	5.72±0.60	5.49±0.28	5.66±0.66	5.84±0.11
Perphenazine	8.10±0.60	5.70±0.79	5.77	5.54	5.73
Prochlorperazine	7.72±0.51	6.04±0.34	6.11	5.85	
Thioridazine	7.77±0.42	7.79±0.26	8.19±0.41	7.58±0.71	7.61±0.26
Trifluoperazine	7.20±0.20	5.89±0.06	5.89	5.66	6.00
Mesoridazine	8.74	7.22±0.00	7.80±0.24	7.17±0.64	7.55
Levomepromazine	8.69		7.37	6.58	7.41
Periciazine	7.16*	6.09*			
Butyrophenones					
Bromperidol	6.01±0.12	5.36±0.49	5.12	5.74	5.15
Haloperidol	6.07±0.45	5.15±0.45	5.51±0.53	5.28±0.38	5.15±0.53
Benperidol	6.69*	6.30*			
Droperidol	5.60*				
Others					
Pimozide	6.45	5.86			
Sulpiride	4.14	4.37			
Flupenthixol	9.06*	5.32*			
Zuclopenthixol	7.40*	6.10*			
Tiapride	8.00*	4.50*			
Penfluridol	5.47*				

Legend: H₁=histamine-1 receptor subtype; MUSC=muscarinic non-selective; M₁=muscarinic-1 receptor subtype; M₂=muscarinic-2 receptor subtype; M₃=muscarinic-3 receptor subtype.

[^] When more than one data was available mean ± SD was reported, while the cell was left empty when no data were available. Values labeled with * are referred to affinity values at rat receptors.

atypical and 43% for typical antipsychotics. Therefore, 0.69 pneumonia cases per 100 person-months of atypical antipsychotic exposure can be directly attributed to the medication, while the figure is 0.33 pneumonia cases per 100 person-months for typical antipsychotics. Since the average duration of use was 5.1 person-months for atypical and 4.2 person-months for typical antipsychotics, this translates into the following number needed to harm (NNH): 29 for atypical antipsychotics and 73 for typical antipsychotics. NNH represents the number of patients that should be treated with either atypical or typical antipsychotics to observe 1 case of pneumonia. Table 5 shows the affinity of different antipsychotics for H¹ histaminergic (H¹) and cholinergic receptors. Overall, affinity to H¹ histaminergic receptor of antipsychotics is higher than affinity to cholinergic receptors. In particular, looking at mean values of all the compounds included in each subgroup, atypical

antipsychotics, similarly to phenothiazines, have the highest affinity to H¹ receptor while butyrophenones have the lowest affinity. When compared to current use of butyrophenones (lowest H¹ affinity), a non-statistically significant increase in the risk of pneumonia was observed in antipsychotic groups with the highest H¹ affinity: atypical antipsychotics (OR: 1.74; 95% CI: 0.99-3.07) and phenothiazines (OR: 2.60; 95% CI: 0.92-7.33). Moreover, combining atypical antipsychotics and phenothiazines, which have similar H¹ -receptor affinity, showed a significantly increased association with pneumonia for these drugs as compared to butyrophenones (OR: 1.90, 95% CI: 1.13-3.21).

DISCUSSION

This study shows that the use of either atypical or typical antipsychotics in community-dwelling elderly is associated with the development of community acquired pneumonia. Exposure to antipsychotic drugs is associated with an increased risk of fatal/non-fatal pneumonia in a dose-dependent fashion; the risk is high early after the beginning of the treatment but it rapidly disappears upon withdrawal of medication. Atypical antipsychotics are also associated with fatal pneumonia and hospitalized pneumonia. Although our design was different, the conclusion of this study are in line with those of a previous Dutch investigation which reported an increased risk of hospitalized pneumonia shortly after the initiation of antipsychotic drugs, especially with atypical agents (adj. OR: 3.1, 95% CI: 1.9–5.1; comparator=non use) [9]. Partly in contrast, a small incompletely reported U.S. study including data Medicaid patients found no significant difference in the risk of hospitalized pneumonia between the two classes of antipsychotics (after 30 days therapy, typical versus atypical antipsychotics: OR=1.11; 95% CI: 0.76-1.63) [19]. However, in this study published as letter to editor, hospitalized pneumonia was not the main outcome. The possible mechanisms by which exposure to antipsychotics could be associated with the development of pneumonia remain speculative. Use of typical antipsychotics may be a risk factor for aspiration pneumonia, as a result of extrapyramidal effects, such as akinesia [20]. On the contrary, atypical antipsychotics are markedly less likely to cause extrapyramidal adverse events, including akinesia, particularly when used at the low dosages, as reported in this study [21-22]. In light of the observed increased risk of pneumonia in both atypical and typical antipsychotics, therefore mechanisms other than extrapyramidal adverse events may play a role in the antipsychotic-induced pneumonia. The histamine-1 receptor blocking effect and the anticholinergic action of antipsychotics have been proposed as alternative explanations for the occurrence of

pneumonia [9]. The anticholinergic effect of antipsychotics can induce dryness of the mouth, possibly leading to impaired oro-pharyngeal bolus transport and thereby to aspiration pneumonia. This hypothesis could also explain why the use of tricyclic antidepressants (agents with marked anticholinergic effects) was a strong risk factor for pneumonia in our study. On the other hand, excessive sedation as a result of histamine-1 receptor blocking in the central nervous system is a well-known cause of swallowing problems, which could facilitate aspiration pneumonia [23]. In line with this hypothesis, our study showed a higher risk of pneumonia for atypical antipsychotics and phenothiazines compared to butyrophenones, with the latter ones being the antipsychotics with the lowest affinity for antihistaminergic receptor H¹. Moreover, some antipsychotics are known to have direct or indirect effects on the immune system [24]. Most specifically, clozapine has been proven to induce neutropenia in up to 3% of patients and agranulocytosis in approximately 1% of patients, thus increasing the risk for infections, such as pneumonia [25]. Although less well-evidenced, leukopenia and neutropenia have also been associated with use of the atypical antipsychotics, such as risperidone and olanzapine, as well as with typical antipsychotics [26-27].

Another important finding of this study was the high fatality rate and the strong association between atypical antipsychotic use and fatal community-acquired pneumonia [14]. Yet, the presence of neuropsychiatric disease is a strong risk factor for mortality among patients with pneumonia [28]. Likewise pneumonia is an independent predictor of death in very old patients with neuropsychiatric conditions (mean age of our study sample: 83 years) [29]. With regard to the association between fatal pneumonia and antipsychotics, Barnett et al reported higher fatality rates in users of typical antipsychotics, in contrast to our study [10]. Since that study was not nested in an antipsychotic drug user cohort, but in a cohort of inpatients with pneumonia, the results are difficult to compare and may be subject to confounding by severity, illness or co-morbidity, as the authors acknowledged.

Strength and limitations

The strength of this study is the availability of information on many potential confounders, indication of use, dose and duration of antipsychotic drug use. Moreover, we studied pneumonia resulting in hospitalization as well as those cared for in outpatient setting. However, several limitations of our study merit consideration. As in any observational study, selection bias, information bias and residual confounding should be considered as alternative explanations for the findings. Selection bias was unlikely as all the data were obtained from prospectively collected medical records that are maintained for patient care purposes.

Information bias by misclassification of the outcome is similarly unlikely since all pneumonia cases were retrieved from the medical records and reviewed by medically trained researchers blinded towards the exposure. Exclusion of those cases for which pneumonia was considered only possible (those cases diagnosed by GPs based on symptoms but no objective assessment) similarly reduced the effect estimate by 20% both for atypical as well as typical antipsychotics. Ascertainment of disease was associated with antipsychotic drug use (being lower in users since aspiration pneumonia is a known side effect), but not differential between atypical and typical antipsychotics. Misclassification of exposure may have occurred since we used outpatient prescription data and had no information about actual filling and use of the medications. However, due to the way data were collected it is very unlikely that such a misclassification would have been differential between cases and controls and, therefore, the actual risk may have possibly been underestimated. Confounding was addressed in the design and analysis phases. In order to minimize the effect of confounding by indication, the whole study was conducted in a cohort of new users of antipsychotic drugs and past use was chosen as reference category. To explore the effect of confounding by dementia severity we conducted a sensitivity analysis which excluded BPSD patients, and this did not yield different effect estimates. The incidence rates of pneumonia were similar during past use of atypical and typical antipsychotics, which supports the notion that confounding by indication between two classes was minimal. Many risk factors for pneumonia were considered in our study. Nevertheless, residual confounding due to unmeasured covariates or severity of disease can never be excluded. However, only strong and highly prevalent risk factors would be able to explain the study findings and it is unlikely that these covariates have been omitted. Despite the fact that the mechanisms by which antipsychotics may cause pneumonia are unlikely to differ in different settings we should warn against generalization of these results to patients living in nursing homes or long term care facilities since these were not included in this study.

In conclusion, our study shows that the use of either atypical or typical antipsychotics in elderly outpatients is associated with the development of community-acquired pneumonia in a dose-dependent fashion and early after the beginning of treatment in elderly outpatients. Use of atypical antipsychotics appears also to be associated with fatal cases of pneumonia. These study findings should be observed also in light of the ongoing discussion about the effectiveness of antipsychotics in elderly patients. In particular, The Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) showed that antipsychotics may be effective for some symptoms included in the BPSD, but would not improve the quality of life in patients with Alzheimer's disease [30].

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2.6. Safety of antipsychotics in elderly patients with dementia: atypical and conventional agents have the same risks?

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ABSTRACT

With the progressive aging of the population in Western Countries, the number of patients affected by dementia is rapidly increasing. Treatment of dementia addresses two main clinical manifestations: cognitive deterioration and “behavioral and psychological symptoms of dementia” (BPSD). What should be considered the most appropriate pharmacological treatment for BPSD has remained questionable due to the availability of only a limited number of trials that have evaluated comparatively effectiveness and safety of different treatments. Despite this lack of information, antipsychotic drugs, especially atypical agents, have been increasingly utilized in clinical practice in the last decade. This article reviews all the evidences concerning the safety of both atypical and conventional antipsychotics used in the treatment of BPSD in elderly patients with dementia. As regard new safety issues, results from meta-analyses of clinical trials and observational studies report overall a similarly increased risk in all-cause mortality and cerebrovascular adverse events in users of both atypical and conventional antipsychotics. On the other hand, safety issues specifically related to antipsychotic types consist of cardiotoxicity, namely proarrhythmic activity, and extrapyramidal symptoms for conventional antipsychotics, and metabolic effects (i.e. increased risk of diabetes and obesity) for atypical antipsychotics, as largely described in both clinical trials and thereafter observational investigations.

INTRODUCTION

Epidemiology of Dementia

The progressive aging of the population is associated with an increase of patients affected by dementia. At present time, in the United States, the prevalence of dementia is estimated to be around 20-30% among community dwelling individuals over 80 years, and up to 60-80% among elderly in nursing homes. This translates in about 4 millions of individuals currently affected by Alzheimer's disease only in the United States with a new case diagnosed every 72 seconds [1]. Dementia is growingly becoming a critical issue for any health care system, especially in western countries. Indeed, dementia causes progressive disability and it is an independent predictor of mortality. The expected lifetime for dementia patients is estimated to be between 5 and 12 years after initial diagnosis [1]. Treatment addresses two main clinical manifestations: cognitive deterioration and "behavioral and psychological symptoms of dementia" (BPSD). BPSD is a complex of symptoms – sometime clustered – and main clinical features include hallucinations, delusions, agitation, wandering and aggression or abuse. Virtually all patients with dementia will develop changes in behaviour and personality [2]. The nature and frequency of these symptoms might vary over the course of the illness, and the relation to the severity of the disease is not univocal. BPSD are generally more troubling and challenging than cognitive decline since they result in an increased caregiver burden, an accelerated cognitive deterioration, earlier institutionalization and excess mortality [3].

Management of BPSD

Treatment of BPSD should initially consider all of non pharmacological means. Should this approach be unsuccessful, physicians should rely upon the use of medications. The only class of drugs with some evidence of efficacy is that of antipsychotics. These medications are generally classified as either conventional or atypical antipsychotics [4]. The latter were introduced in the '90s and were called atypical because supposedly devoid of extrapyramidal side effects. Indeed, atypical antipsychotics present with a receptor binding profile that is extremely more complex and diversified than conventional agents. In 2006, Ballard and Waite [5] completed a review for the Cochrane Collaboration concluding that risperidone and olanzapine have a modest efficacy in reducing aggression and psychosis but neither should be routinely used because of their serious adverse events. Increasingly, safety concerns have ignited a controversial debate about the risk-benefit ratio of these agents. More recently, a meta-analysis of 7 studies on atypical antipsychotics (risperidone, olanzapine or quetiapine) for the treatment of BPSD was published [6]. It documented no statistically or clinically significant

differences in effectiveness between atypical antipsychotics and placebo. This finding was confirmed by the CATIE-AD investigators who also reported that the placebo group had significantly lower health costs than patients on either risperidone, olanzapine or quetiapine [7]. Likewise, there is insufficient evidence to suggest that psychotropic medications other than antipsychotics represent an overall effective and safer treatment alternative for BPSD [8].

Off-label use of antipsychotics

Either conventional or atypical antipsychotics are not approved for the treatment of BPSD with the only exception of haloperidol. So, the use of these agents for this indication should be considered off-label, despite being endorsed by institution like the American Academy of Neurology. Accordingly, risperidone is currently approved for the treatment of one or more symptoms of BPSD in over 30 countries [9]. Certainly, recent years have witnessed an increased utilization of antipsychotics and in particular of atypical agents in view of a supposed better risk profile and tolerability relative to conventional agents. Studies from United Kingdom and Canada have reported an increase in overall antipsychotic prescribing to older patients in long term care facilities [10-12]. Other investigations have shown that atypical antipsychotics have become the agents more commonly prescribed [13]. In Italy, a drug utilization study has documented a 5-fold increased use of atypical agents for the treatment of BPSD between 1999 and 2004 [14].

Warnings and safety alerts

The trend toward a rapidly increasing utilization of atypical antipsychotics has been paralleled by the release of several warnings and safety alerts concerning the risks associated with their off-label use in elderly with BPSD. With an unprecedented move, the manufacturer of risperidone in October 2002 notified all Canadian healthcare professionals that an increased rate of cerebrovascular events among risperidone users relative to placebo was becoming evident in drug-sponsored clinical trials [15]. In March 2004, the UK Committee on Safety of Medicines (CSM) through a Dear Doctor Letter [16] has recommended avoiding atypical antipsychotic administration to elderly demented individuals with behavioural disturbances, particularly in patients with a high baseline risk of stroke. Information about harm was available for olanzapine and risperidone. However, a similar warning has been recently issued also by the manufacturer of aripiprazole [17]. On April 2005, an official warning was issued by the Food and Drug Administration (FDA)[18] to inform health professionals about the results of a pooled analysis of 17 RCTs reporting a 1.7 times increased risk of all-cause mortality associated with atypical antipsychotic use in elderly with BPSD, compared to placebo with an

increased risk evident in 15 of 17 trials analyzed. FDA has documented a similar increased risk of death with conventional antipsychotics use but has refrained from adding a warning in the Summary of Product Characteristics because data about conventional antipsychotics were based on only one trial with haloperidol. These alerts have ignited a very animated debate in the scientific community. Some authors judge the warnings on atypical antipsychotics as unnecessarily alarming and potentially detrimental for patients with dementia [19]. They reason that avoidance of these pharmacological agents could lead to a more widespread use of conventional antipsychotics. Other researchers instead are concerned that there is no clear evidence to support a greater benefits with atypical relative to conventional antipsychotics [20]. This review will thoroughly evaluate the currently available data on the potential risks associated with the use of antipsychotics. We will review as separate issues: all-cause mortality, cerebrovascular events, cardiac effects, vascular effects, metabolic abnormalities, extrapyramidal symptoms and hyperprolactinemia.

ALL-CAUSE MORTALITY

In April 2005, the results of a meta-analysis including 17 placebo-controlled studies of four drugs (olanzapine, risperidone, quetiapine and aripiprazole) were made available [18]. The studies were, on average, 10 weeks in duration and enrolled a combined 5,106 elderly patients with dementia. The findings revealed a 4.5% mortality rate among patients who had been treated with atypical antipsychotics, compared with 2.6% among patients on placebo. It is noteworthy that already in 2004, based on a pooled analysis of randomized clinical trials (RCTs) the European Medicines Agency (EMA) had issued a warning about a two-fold increased risk of all-cause mortality associated with olanzapine. The exact mechanism for the increased risk has yet to be identified. However, despite a substantial variability, causes of death were primarily cardiac (i.e. heart failure or sudden death) or infectious (i.e. pneumonia). A recent re-analysis of olanzapine trial data found no significant differences in mortality between olanzapine and conventional agents [22]. Likewise, FDA claimed that a similar increased risk of death could also be reported for conventional antipsychotics, although limited availability of RCTs could not allow a precise risk estimate. In fact, a new meta-analysis of RCTs [23] found that a conventional antipsychotic, haloperidol, for which comparable data could be accrued was associated with about two-fold increased mortality versus placebo, a risk even higher than that associated with the use of atypical agents. In light of the uncertainty about the actual risk of all-cause mortality associated

with either atypical or conventional antipsychotics, and in consideration of substantial limits of the trials, a number of observational studies [9, 24-32] have been completed in the last few years. A US retrospective cohort study [24] based on a health insurance database found that conventional antipsychotics were associated with a significantly higher risk of mortality than were atypical antipsychotics at all intervals studied (≤ 180 days: RR=1.37; 95% CI: 1.27-1.49; < 40 days: RR=1.56; 1.37-1.78; 40-79 days: RR=1.37; 1.19-1.59; and 80-180 days: RR=1.27; 1.14-1.41) and in all subgroups defined according to the presence or absence of dementia or nursing home residency. The greatest increase in risk occurred soon after therapy was initiated and with higher dosages of conventional antipsychotics. Such finding was confirmed by a population-based, retrospective cohort study carried out using the administrative health care database in Ontario [25]. Authors reported that relative to atypical antipsychotic use, conventional antipsychotic use was associated with a higher risk for death in both short and long term treatment of community-dwelling elderly with dementia. Similarly, Liperoti et al. [32] has documented that among residents of nursing homes in 5 US states, conventional antipsychotics were associated with a 22% increased risk of all-cause mortality relative to atypical agents. Not all of the observational studies have supported these conclusions. A case control study nested in a cohort of elderly outpatients with dementia was conducted using data from Dutch general practice database [26]. This investigation reported no statistically significant differences in the risk of all-cause mortality between users of atypical and conventional antipsychotics, while both antipsychotic classes were associated with a significantly higher and dose-dependent risk of dying, compared to placebo. Another study reported that the adjusted mortality risk for atypicals was similar to that for conventional antipsychotics [28]. In general, it remains controversial whether data available should be interpreted as describing a class effect, as claimed by FDA, or the risk of death may vary across different ingredients [29]. However, not an enough number of patients have been studied in RCTs to adequately explore the risk of death associated with individual antipsychotics use, nor observational studies could fill the gap. The only exception is for risperidone for which a meta-analysis of 6 RCTs (N=1,721), was carried out [9]. The pooled analysis found a not significant and dose-independent increase in mortality compared to placebo (mortality rate: 4.0% vs. 3.1%; RR=1.21, 0.76-2.06). More recently, Liperoti et al. [32] using the SAGE (Systematic Assessment of Geriatric drugs use via Epidemiology) database have completed a study comparing each atypical antipsychotics to haloperidol and to other conventional agents. Relative to risperidone users, risk of all cause mortality was not differential among other atypicals users while was higher for haloperidol users [32].

To summarize, observational studies carried out after the warnings launched by regulatory agencies confirmed that an increased risk of all-cause mortality is associated with antipsychotic use in elderly with dementia, compared to non users. Conventional antipsychotics have a similar, if not higher risk of death than atypical agents (Table 1). Risk of death is increased early after beginning of treatment and seems explained by an excess mortality from cardiovascular causes and pneumonia.

CEREBROVASCULAR EVENTS

A pooled analysis of RCTs has documented an increased risk for transient ischemic attacks (TIA) and stroke of about 3-fold with risperidone and olanzapine, compared to placebo [33-35]. Despite a substantial uncertainty about the diagnostic accuracy of either TIA or stroke in the trials considered, a warning was issued and extended to all atypical antipsychotics. In the scientific community, some authors judged this alert as inappropriate because no comparative data between atypical and conventional was available. Moreover, the causal relation appeared to be extremely difficult to establish in most cases. Nevertheless, a number of potential mechanisms have been postulated to explain a possible increased incidence of stroke with the use of atypical antipsychotics in elderly persons with dementia [36, 37]. Atypical antipsychotics could induce orthostatic hypotension, as a result of antagonism at alpha-adrenergic receptors. Elderly with a pre-existing cerebrovascular disease might experience a TIA or CVAE as a consequence of hypotension aggravating the deficit in cerebral perfusion. Alternatively, after an episode of orthostatic hypotension, there could be a rebound excess of catecholamines with vasoconstriction and aggravation of cerebral vascular insufficiency. Other putative mechanisms proposed include hyperprolactinemia and thromboembolism. Beyond the biological plausibility, several recently published observational studies [38-45] have explored the comparative risk of stroke associated with both atypical and conventional antipsychotics (Table 2). These population-based, observational studies were performed through administrative databases [38-41, 43, 44], general practice database [45], or through prescription event monitoring methodology [42]. Most of these studies selected elderly patients [38, 43, 45] eventually living in nursing home [39], while only Gill et al. [40] and Barnett et al. [44] looked specifically at older adults with a diagnosis of dementia. In all of the studies, outcome was any case of CVAEs, including both transient ischemic attack and stroke, resulting in hospital admission (all, except for Sacchetti et al. [45] and Layton et al. [42]), or as collected in general practitioners' records [45] or through

Table 1. List of post-marketing studies on the risk of death associated to antipsychotic drugs that have been published so far.

Author (Ref)	Study Design - Population	Outcome	Exposure	Main findings
<i>Meta-analysis</i>				
Schneider et al. [29]	Meta-analysis of 15 published/unpublished randomized, placebo-controlled, parallel group clinical trials of atypical antipsychotic drugs – 5,110 elderly dementia patients	All-cause mortality	Aripiprazole (3 trials, 10 weeks duration), olanzapine (5 trials, 6-26 weeks duration), risperidone (5 trials, 8-12 weeks duration), and quetiapine (3 trials, 10-26 weeks duration) vs placebo (in 1 trial vs haloperidol).	a) Mortality rate: - any antipsychotic drug: 3.5%; - placebo: 2.3%. b) Overall OR for death in antipsychotic users versus placebo: 1.54 (1.06-2.23); c) No differential risk for individual drugs
Haupt et al. [7]	Meta-analysis of 6 phase 2/3 double blind randomized placebo-controlled trials of risperidone – 1,721 elderly dementia patients (mean age 82.3)	All-cause mortality	Risperidone (0.5, 1,2 mg/die) and placebo	a) Mortality rate: - Risperidone: 4.0%; - Placebo: 3.1%; b) RR: 1.21 (0.71-2.06) c) No increased risk with increased risperidone dose
<i>Observational studies</i>				
Wang et al. [30]	Retrospective cohort study – 22,890 patients 65 years of age or older from Pennsylvania Medicare	All-cause mortality	Incident use of atypical and typical antipsychotics	a) Adjusted relative risk of death (typical vs atypical): - within 180 days: 1.37 (1.27-1.49); - within 40 days: 1.56 (1.37-1.78); - 40-79 days: 1.37 (1.19-1.59); - 80-180 days: 1.27 (1.14-1.41); b) the risk in conventional use increased with higher dosage.
Nonino et al. [31]	Cohort study – 2,314 patients older than 65 with diagnosis of dementia from the Dementia Registry of Local Health Care Unit of Modena	All-cause mortality	Incident use of atypical antipsychotics (AA) (at least 30 day therapy) versus non use of atypical antipsychotics (NAA)	a) Mortality rate: - AA: 0.52/1,000 PY; - NAA: 0.55/1,000PY; b) Risk difference: 0.047 (-0.251-0.2.86)
Trifiro et al. [32]	Nested case-control study – 2,385 elderly patients with dementia from the Dutch general practice database (GPC)	All-cause mortality	According to type of antipsychotic: - atypical - typical - combination - non use According to time of exposure: - current - past - never	a) current use of atypical vs current use of typical: OR= 1.3 (0.7-2.4); b) current use of atypical vs non use: OR= 2.2 (1.3-2.9); c) current use of typical vs non use: OR= 1.7 (1.3-2.2); d) Increase of risk of death in both atypical and typical antipsychotics was dose-dependent

Gill et al. [31]	Population based, retrospective cohort study – 27,259 propensity score matched pairs of older adults with dementia that were residents in Ontario	All cause mortality at 30, 60, 120 and 180 days after the initial dispensing of antipsychotic medication	Incident use of atypical and typical antipsychotics and non use, stratified in community dwelling (CD) and long term care (LTC) cohorts	a) Adjusted relative risk at 30 days of atypical versus non use: - CD: 1.31 (1.02-1.70); - LTC: 1.55 (1.15-2.07) b) similar relative risk was shown at 180 days; c) conventional antipsychotic use was associated with higher risk for death than atypicals at all time points
Schneeweiss et al. [33]	Retrospective cohort study – 37,241 elderly people who received antipsychotics and were British Columbia residents	180 day all-cause mortality	Incident use of atypical and typical antipsychotics	a) Mortality rate: - typical: 14.1% - atypical: 9.6% b) adjusted relative risk (risperidone as reference): - haloperidol: 2.14 (1.86-2.45) c) the greatest increase in mortality was associated at high dosage of typicals and during the first 40 days of therapy
Kales et al. [34]	Retrospective cohort study – 10,615 patients older than 65 year with diagnosis of dementia from US Department of Veteran Affairs registries	One year all-cause mortality from National Death Index	Incident use of atypical and typical antipsychotics, combination of both types, and other psychotropic drugs (antidepressant, anticonvulsants and hypnotic/anxiolytics	a) Mortality rate: - Atypical: 22.6% - Typical: 25.2% - Combination: 29.1% - Other psychotropic drugs: 14.6% b) Adjusted relative risk (typical as reference): - atypical: 0.93 (0.75- 1.16) - combination: 1.33 (0.94-1.86) - other psychotropic drugs: 0.56 (0.45-0.70)
Hollis et al. [35]	Retrospective Cohort study. 16,634 veterans and war widows 65 years and older from Australian Department of Veteran Affairs claims-based pharmaceutical database	All-cause mortality	Incident use of antipsychotics, carbamazepine and valproate	<i>Incident use of olanzapine as reference category.</i> Incident use of haloperidol: RR= 2.26 (95% CI:2.08-2.47); Incident use of chlorpromazine: RR= 1.39 (1.15-1.67); Incident use of risperidone: RR= 1.23 (1.07-1.40)
Raivio et al. [36]	Cohort study –254 very frail patients with dementia (mean age: 86 years) from 7 Finnish nursing homes and 2 hospitals	All cause mortality during a two-year follow-up	Incident/prevalent use of atypical and antipsychotics and non use	a) 2 years mortality rate: - atypical: 32.1% - conventional: 45.3% - non use: 49.6% b) relative risk (versus non use): - atypical: 0.49 (0.24-0.99) - conventional: 0.68 (0.46-1.03)

Table 2. List of observational studies on the risk of cerebrovascular adverse events associated to antipsychotic drugs that have been published so far.

Author [Ref]	Study Design - Population	Outcome	Exposure	Main findings
Herrmann et al. [45]	Population based retrospective cohort study – 11,400 subjects > 65 years from administrative healthcare database in Ontario	Hospital admission due to stroke	Use of risperidone, olanzapine and typical antipsychotics	a) Adjusted relative risk vs. conventional antipsychotic: -risperidone: 1.4 (0.7-2.8) -olanzapine: 1.1 (0.5-2.3)
Gill et al. [47]	Population based retrospective cohort study – 32,710 subjects ≥ 65 years with dementia from administrative healthcare database in Ontario	Hospital admission due to ischemic stroke	New users of atypical (risperidone, quetiapine and olanzapine) and typical antipsychotics	a) Adjusted relative risk of atypical vs typical: 1.01 (0.81-1.26); b) subanalyses for selected population confirmed this finding.
Liperoti et al. [46]	Case-control study- residents of nursing homes in 6 U.S. states (SAGE database) with dementia	Hospital admission for stroke or transient ischemic attack	Current use of atypical and conventional antipsychotics and non use	Adjusted odds ratio (vs non use): - risperidone: 0.87 (0.67-1.12) - olanzapine 1.32 (0.83-2.11) - other atypicals: 1.57 (0.65-3.82) - conventional: 1.24 (0.95-1.63).
Finkel et al. [48]	Retrospective cohort study- Medicaid data	New case of acute inpatient admission for cerebrovascular events	Incident use of atypical antipsychotics (risperidone, olanzapine, quetiapine and ziprasidone) and haloperidol	a) Adjusted relative risk vs. risperidone: -olanzapine: 1.05 (0.63-1.73) -quetiapine: 0.66 (0.23-1.87) -haloperidol: 1.91 (1.02-3.60)
Layton et al. [49]	Prescription event monitoring study through data from UK National Health Service	Any cerebrovascular events within first 180 days therapy	Incident use of risperidone, quetiapine and olanzapine	a) Adjusted relative risk vs. olanzapine: - risperidone: 1.2 (0.5-3.0) - quetiapine: 2.1 (0.6-7.7) b) dementia is strong risk factor
Percudani et al. [50]	Case control study – 35,604 patients ≥ 65 years from administrative healthcare database in Lombardy, Italy	Hospital admission due to any cerebrovascular events	Previous use (as monotherapy) of atypical (risperidone, olanzapine, quetiapine and clozapine) and typical antipsychotics	Adjusted OR of atypical vs conventional: - 1.42 (1.24-1.64)
Barnett et al. [51]	Retrospective cohort study- 14,029 subjects ≥ 65 years with dementia from Veteran Administration and Medicare database	Hospital admission due to any cerebrovascular events	Incident use of atypical and typical antipsychotic and non use	a) Adjusted relative risk vs. non use: - typical: 1.29 (0.48-3.47) - atypical: 1.20 (0.83-1.74)
Sacchetti et al. [52]	Retrospective cohort study- 74,162 elderly patients from Italian general practice database	First ever stroke	Incident use of atypical antipsychotics, butyrophenones, phetioazines, benzamides and non use	a) Adjusted relative risk vs. non use: -atypical: 2.46 (1.07-5.65) -butyrophenones: 3.55 (1.56-8.07) -phetioazines: 5.79 (3.07-10.9) -benzamides: 2.2 (0.98-4.90)

questionnaires [42]. In summary, these studies suggested no increased risk of stroke with atypicals compared to conventional antipsychotics. Indeed, data seem to suggest that CVAE risk might actually be even lower for atypical antipsychotics than for conventional agents [46]. Interestingly, differential risk was reported for subgroups of conventional antipsychotic like phenothiazines and butyrophenones. The latter agents would be linked to a higher risk of stroke compared to atypical antipsychotics and benzamides and other older antipsychotics, as reported in studies where data were analysed in a disaggregated fashion [45]. Concerning atypical antipsychotics, although only few observational investigations examined accurately the risk of CVAE associated to the individual ingredients, no significant differences would be highlighted. Unfortunately, observational investigations were not able to assess accurately the relation between dose and duration of use of antipsychotic drugs and the occurrence of stroke. Data from the trials showed that all of risperidone and olanzapine users who developed CVAE were affected by a number of vascular risk factors (atrial fibrillation, hypertension, diabetes and hyperlipidaemia) that were either poorly treated or untreated [37]. In general, an underlying condition of vascular dementia was associated with a greater likelihood of cerebrovascular adverse events. Vascular dementia and history of CVAE were strong risk factors, according to the results of sub-analyses performed in some observational studies [39, 44]. Another issue is that the higher CVAE risk in elderly with dementia who use both conventional and atypical antipsychotic compared with non users could be partly explained by confounding by indication. Indeed, cognitive impairment, regardless of underlying aetiology, has been demonstrated to be a strong predictor of ischemic stroke independent of vascular risk factors [47]. In addition, individuals with Alzheimer's disease seem to be more likely to die from cerebrovascular disease than normal elderly subjects thus supporting potential for confounding by indication [48].

CARDIAC EFFECTS

Atypical antipsychotics may cause cardiac adverse effects including sinus tachycardia, atrial and ventricular extrasystoles, QTc interval prolongation, T wave inversion, ST segment depression, and atrioventricular blocks [49]. One area of recent interest, concern, and controversy is the clinical effect and meaning of changes in the rate corrected QT interval [50]. The Pfizer/FDA study [51], was the most extensive cardiac safety study related to the QTc intervals of antipsychotics ever conducted. Most cardiologists think that a QTc reading of more than 500 milliseconds puts a patient at significant risk for torsade de pointes, ventricular

fibrillation, and sudden death [52-57]. In the Pfizer/FDA study, all the novel antipsychotics, when used alone, showed a QTc reading of less than 500 milliseconds (FDA) including ziprasidone [51]. The mean QTc increase from baseline with ziprasidone was significant (6-10 milliseconds throughout the dosing level) and greater than the other atypicals. From greatest to least risk of QTc prolongation, Pfizer/FDA showed that thioridazine had the greatest danger of prolonging the QTc, followed in descending order by ziprasidone, quetiapine, risperidone, olanzapine, and haloperidol. As a result of this study, thioridazine received a “black box” warning and ziprasidone was approved with a label warning of the potential risks for prolongation of the QTc interval [58,59]. Almost all of the data concerning the cardiac effects of atypical antipsychotics have been generated either in preclinical pharmacologic studies or in young-adult patients with psychiatric conditions. Deleterious cardiac effects of antipsychotic medications have been well described with older antipsychotic medications. Some (e.g., phenothiazines) have been associated with an increased risk of ventricular arrhythmias, cardiac arrest, and sudden death [58,59]. The literature includes several case series in schizophrenic patients treated with thioridazine hydrochloride [60-62], haloperidol [63], and other conventional antipsychotics [64]. More recently, epidemiologic studies [65, 66] have confirmed a direct relationship between conventional antipsychotics and the risk of sudden death and this has been attributed to the QT-prolonging properties of conventional antipsychotics [67, 68].

Experience with atypical antipsychotics is evolving but, in general, they appear to be more “cardiosafe” than conventional medications. Despite experimental evidence that some atypical antipsychotics can also prolong QT interval [64] only clozapine has been linked to serious cardiac problems [69]. A single epidemiologic study on schizophrenic patients has suggested an increased risk of ventricular arrhythmias and cardiac arrest associated with risperidone, a finding not endorsed by the authors of that study [65]. Indeed, risperidone has a minimal effect on QT interval [64] and the only reported case of sudden death was not due to ventricular arrhythmias [70]. It is important to consider the cardiovascular effects of antipsychotic medications also in older patients with dementia and cardiovascular comorbidities. Recently, Liperoti et al conducted a case control study among nursing home residents in 6 US states using the SAGE database [71]. The 649 cases included residents hospitalized for cardiac arrest (40.6%), paroxysmal ventricular tachycardia (34.5%), and ventricular flutter or fibrillation (24.9%). After control for potential confounders, users of conventional antipsychotics showed an 86% increase in the risk of hospitalization for ventricular arrhythmias or cardiac arrest (odds ratio, 1.86; 95% confidence interval, 1.27-2.74) relative to nonusers. Among residents receiving conventional antipsychotics, those with cardiac disease

were 3.27 times (95% confidence interval, 1.95-5.47) more likely to be hospitalized for ventricular arrhythmias and cardiac arrest, compared with nonusers without cardiac disease. There was no increased risk associated with the use of atypical antipsychotics (odds ratio, 0.87; 95% confidence interval, 0.58-1.32). There are other infrequent or rare cardiac events linked to the use of antipsychotics. Some of the atypicals report congestive heart failure as a direct cardiac effect. This effect has been reported infrequently (1/100-1/1000) with olanzapine and rarely (<1/1000) with clozapine and quetiapine [72]. The vasodilator effects of the atypicals may counteract any major hemodynamic deterioration. However, therapeutic doses of antipsychotics do not seem to have important effects on myocardial function.

VASCULAR EFFECTS

Hypotension is a major and frequent side effect encountered with atypicals. The atypicals that most commonly cause hypotension, from the greatest to the lowest frequency, include clozapine (9%), quetiapine (7%), risperidone (5%), and olanzapine (5%); the least hypotensive (1%) effects are reported with ziprasidone or haloperidol [72]. Likewise, some antipsychotics can cause or exacerbate hypertension. Atypical antipsychotic medications that cause hypertension, with greater to lower frequency, include clozapine (4%), olanzapine (2%), ziprasidone (1%); the lowest risk of hypertension (1%) is caused by risperidone and quetiapine [72]. A possible association between venous thromboembolism (VTE) and the use of antipsychotic agents was first suggested in the 1950s after the introduction of phenothiazines [73]. Since then, several case studies [74-76] have supported the notion of an increased risk of VTE with conventional antipsychotic agents. Recently, Zornberg and Jick [77] documented a 7-fold increase in the risk of idiopathic VTE among users of conventional antipsychotic agents who were younger than 60 years and free of major risk factors. A similar thromboembolic effect of conventional antipsychotic agents has been observed also among individuals with risk factors for VTE [78]. As for atypical antipsychotic agents, information on the risk of VTE has historically been limited to clozapine [79-81]. This association is primarily supported by results of a large record-linkage study in which a 5-fold increase in lethal pulmonary embolism was found [58]. More recently, 3 cases of VTE have been reported among elderly patients treated with olanzapine [82] and 1 case in a young man with a psychotic disorder [83]. Finally, a possible association between risperidone and massive pulmonary thromboembolism has been suggested from a review of autopsy records in a Japanese population [84]. Despite these suggestions, clear evidence of a possible thromboembolic effect of antipsychotic agents is lack-

ing. Most studies have been conducted on small samples with inadequate control for confounders. Moreover, elderly patients, who are among the most common recipients of antipsychotic medications, have been systematically excluded. A single study among adults 65 years and older compared the effect of antipsychotic agents on the risk of VTE relative to that of thyroid replacement therapy and found only a slightly increased risk with butyrophenones [85]. Recently, Liperoti et al. [86], conducted a retrospective cohort study to estimate the effect of atypical and conventional antipsychotic agents on the risk of hospitalization for VTE among elderly patients living in nursing homes in 5 US states. She identified 539 hospitalizations for VTE; venous thrombosis accounted for 77.6% and pulmonary embolism for 22.4%. The occurrence of VTE hospitalizations started early (30-60 days) and was distributed throughout the entire follow-up time. After adjusting for all potential confounders, the rate of hospitalization for VTE was increased for users of atypical antipsychotic agents, including risperidone (adjusted hazard ratio [HR], 1.98; 95% CI, 1.40-2.78), olanzapine (adjusted HR, 1.87; 95% CI, 1.06-3.27), and clozapine/quetiapine (adjusted HR, 2.68; 95% CI, 1.15-6.28). Instead, no increased rate of hospitalization for VTE was associated with phenothiazines (adjusted HR, 1.03; 95% CI, 0.60-1.77) or other conventional medications (adjusted HR, 0.98; 95% CI, 0.52-1.87). A much smaller case-control study in a cohort of patients 68 years of age has documented a similar point estimate for atypical antipsychotics but also an odds ratio of 4.1 for conventional agents [87]. The mechanisms by which antipsychotic medications may contribute to VTE remain to be established conclusively. Although conventional agents have been associated with enhanced aggregation of platelets [88], atypical antipsychotic agents have not been tested systematically. Recent *in vitro* data coming from the manufacturer do not support a direct effect of risperidone on human platelet function, plasma coagulation, and fibrinolysis [89]. However, atypical agents possess a high affinity for the serotonin receptor type 5HT_{2A}, and serotonin-induced platelet aggregation may be affected [90]. Evidence also exists that lupus anticoagulant and anticardiolipin antibody levels may be raised in patients taking conventional antipsychotic agents [91] and clozapine [92]. Venous stasis can be exacerbated by excessive sedation. Moreover, a recent meta-analysis has suggested a nearly 3-fold increased risk of peripheral edema associated with risperidone [93].

METABOLIC ABNORMALITIES

Weight gain

Significant weight gain is observed during treatment of schizophrenic patients with clozapine and olanzapine, with an increase in body fat being mainly responsible for olanzapine-induced weight gain [94-97]. In general, weight gain is observed during the first 4–12 weeks of treatment with most atypical antipsychotics. After this initial phase, weight gain continues at a lower level or even stabilizes. Clozapine and olanzapine cause weight gain that continues over a prolonged period [98]. Results of a meta-analysis showed a mean weight gain of 4.45 kg under treatment with clozapine, 4.15 kg for olanzapine, 2.10 kg for risperidone and 0.04 kg for ziprasidone respectively [99,100]. Increased food intake is partly being held responsible for the weight gain in psychotic patients and is possibly a consequence of the antipsychotic drug's interaction with neuronal dopamine-, serotonin- and histamine-receptors [101]. Antipsychotic agents block the 5-HT₂ receptor system resulting in a decreased serotonergic transmission and thereby causing obesity.

Changes of glucose homeostasis

A retrospective cohort study showed that among patients with schizophrenia the prevalence of type 2 diabetes mellitus (T₂DM) was over 20%, with no significant difference between atypical and conventional antipsychotics [102]. A more detailed analysis showed that during treatment with conventional antipsychotics the risk of diabetes was three times higher compared to the general population. Clozapine appears to be associated with a 1.4-fold higher prevalence than conventional antipsychotics and for olanzapine the factor is approximately 1.3. The relative risk of developing T₂DM seems to be slightly lower with quetiapine and risperidone. Since the introduction of atypical antipsychotics several case reports of new-onset diabetes and diabetic ketoacidosis have been published. In summary, 27 case reports of new-onset diabetes were found for clozapine, 39 for olanzapine, four for risperidone and three for quetiapine [103]. In most patients, the hyperglycaemia occurred within 6 weeks after start of treatment with the antipsychotic drug [103], in two patients, one with severe hyperglycaemia and one with ketoacidosis, within 1 week [104, 105]. Most cases of new-onset disturbances of the glucose homeostasis were reversible after discontinuation of the antipsychotic medication. Koller et al. [106] analysed 69 case reports of quetiapine-associated hyperglycaemia and T₂DM. In a large retrospective case–control study, patients taking olanzapine had a significant higher risk of developing T₂DM than patients without olanzapine (odds ratio 5.8) or patients treated with conventional antipsychotics (odds ratio 4.2) [107]. Possible mechanisms include weight gain, changes of insulin secretion,

development of peripheral insulin resistance and changes of cellular glucose uptake [108, 109]. Several authors suggest that the onset of diabetes during antipsychotic therapy is secondary to drug-induced weight gain [103], possibly both induced by histamine antagonism [110, 111]. However, the rapid onset of diabetes, the disappearance of hyperglycaemia after discontinuation of the drug and recurrence after reintroduction support the development of diabetes in patients on atypical antipsychotics being a drug-related effect, especially with regard to olanzapine and clozapine.

Disturbances of lipid metabolism

Additionally to weight gain and diabetes, some atypical antipsychotics cause hypertriglyceridaemia [112]. Increased adiposity can result in excess free fatty acids (FFA) release from hypertrophic adipocytes leading to higher FFA concentrations. These can induce muscle and hepatic insulin resistance, endothelial- and pancreatic-cell dysfunction and increased VLDL triglyceride production. A recent prospective study comparing the effects of clozapine, olanzapine, risperidone and sulpiride on glucose and lipid metabolism in first-episode schizophrenia at baseline and 8 weeks after inclusion showed that besides higher C-peptide, fasting insulin and insulin resistance index (IRI), cholesterol and triglyceride levels were significantly increased in the clozapine and olanzapine groups [113]. In a comparative study, treatment with various antipsychotics resulted in significantly elevated triglyceride levels in 56% of clozapine, 39% of olanzapine and 21% of risperidone-treated patients compared to none of haloperidol and 8% of fluphenazine-treated patients [114]. The same study showed a reduction of HDL cholesterol during treatment with clozapine and olanzapine, whereas total cholesterol levels were significantly lower in risperidone- and fluphenazine-treated patients. Koro et al. [115] observed a threefold higher risk of hyperlipidaemia for conventional antipsychotics when compared with a control population without antipsychotic exposure. Atypicals treatment associated odds varied: olanzapine use was associated with a nearly fivefold higher increase in the risk of developing hyperlipidaemia, whereas risperidone showed no significant difference [115]. A more recent study described a negative effect of olanzapine administration on total cholesterol and triglycerides, whereas favourable metabolic effects were observed in ziprasidone-treated patients with regard to total cholesterol, LDL and HDL [108]. These results were confirmed in another study with 1,493 patients [109]. An increase of serum lipid levels was already seen after 4 weeks of treatment with olanzapine or clozapine and was significantly correlated with increasing BMI. It is noteworthy that all of the information presented were gathered from studies in patients with either schizophrenia (the great majority) or bipolar disorder. Whether patients with BPSD receiving

antipsychotics develop similar disturbances is still debated. Indeed, only few and relatively small studies have been published. In 2006 Rondanelli et al. [116] have studied 36 AD patients who were residing in nursing homes and receiving either risperidone, olanzapine or quetiapine. The results of the study suggest that the treatment with low-dose of atypical antipsychotics is not associated with weight gain or increase the risk of developing type II diabetes or abnormalities of lipid metabolism. The CATIE-AD, instead, has highlighted a clear effect of all atypical antipsychotics under scrutiny to increase weight gain and BMI with olanzapine having the greatest effect followed by risperidone [117]. In contrast, there was no apparent effect on glucose levels, total cholesterol and triglycerides levels. Consistent results were reported by a post hoc analysis of 1,267 patients with BPSD receiving olanzapine (1-20 mg/day) [118]. The estimated probability of gaining more than 7% of initial body weight was significantly greater in patients treated with olanzapine versus placebo ($P < 0.001$). Weight gain in olanzapine-treated patients was significantly greater in individuals with a baseline body mass index of less than 25 kg/m². The same group of authors similarly concluded that as for the risk of diabetes, seven olanzapine clinical trials showed no statistically significant association with antipsychotic use [119]. Finally, a study on 95 patients with dementia receiving mostly olanzapine and risperidone showed no effect on any of the parameters of the metabolic syndrome based on the NCEP-ATPIII criteria [120].

EXTRAPYRAMIDAL EFFECTS

Conventional antipsychotics have been historically linked to a substantial incidence of extrapyramidal symptoms (EPS). The use of atypical antipsychotics is generally associated with a lower risk of EPS compared to conventional agents [121]. Different pharmacological mechanisms have been hypothesized including higher affinity for serotonin 5HT_{2A} than dopamine D₂ receptors, faster dissociation from D₂ receptors, selective affinity for mesolimbic rather than nigrostriatal D₂ receptors, partial agonism and intrinsic anticholinergic activity. Atypical antipsychotics differ in their relative risk of EPS, with risperidone associated with the highest risk and clozapine and quetiapine with the lowest [122]. With regard to acute EPS, such as acute dystonia, akathisia and parkinsonism, various meta-analyses have documented an advantage for atypical antipsychotics, although in most cases the comparator was the high-potency agent haloperidol [123, 124]. Differences in EPS risk were less marked when atypical antipsychotics were compared with low-potency conventional agents [125]. Concerning tardive dyskinesia, the limited

available evidence indicates that the use of atypical antipsychotics is associated with an incidence of 1% per year compared with 5% for conventional agents [126]. In this respect, a systematic review of 11 studies lasting 1 year or longer in patients with schizophrenia-spectrum disorders treated with atypical antipsychotics has clearly documented that these agents have a reduced risk for tardive dyskinesia [127]. As age is a risk factor for the development of tardive dyskinesia, older patients may be at even greater risk than the general adult population. In a study in patients highly vulnerable to tardive dyskinesia, including middle-aged and older adults, the use of atypical antipsychotics was associated with a significantly lower risk of developing tardive dyskinesia compared with conventional agents [128]. Although EPS with atypical antipsychotics may be less frequent and severe than with conventional agents, it should be acknowledged that most studies investigating this aspect focused on patients with psychiatric diagnoses other than dementia. The few randomized controlled studies evaluating the effect of newer antipsychotics in patients with dementia were too short (6 to 12 weeks) to provide any valuable information. A better understanding of the risk for EPS associated with various antipsychotics in patients with dementia has resulted from two retrospective cohort studies in elderly patients with dementia [129, 130]. In the first investigation, a dose-dependent increased risk of parkinsonism was documented among older adults with dementia prescribed atypical antipsychotics [129]. Interestingly, the risk of developing parkinsonism was similar among patients dispensed a high-dose atypical antipsychotics, usually risperidone, and those dispensed a higher potency conventional antipsychotic. Another cohort study investigated drug-induced movement disorders other than parkinsonism and found that the risk of developing tardive dyskinesia and other drug-induced movement disorders during treatment with an atypical antipsychotic was not statistically different from that with a conventional agent [130]. Few studies have approached the issue considering a surrogate end-point like falls, either cumulative or only those injurious ending into an hospitalization for femur fracture. A relatively small study of very short duration conducted among patients in residential care facilities in Australia has documented that despite fewer EPS, atypical antipsychotics were not associated with fewer falls relative to conventional agents [131]. A recent study from the SAGE study group would indicate that in a cohort of patients with Parkinson's disease, the use of risperidone and also clozapine are associated with an increased risk of falling similar to that of conventional antipsychotics [132]. These data are in agreement with the results of the study by Liperoti et al. on the risk of femur fracture [133]. After control for potential confounders the risk of hospitalization for femur fracture was equally increased for atypical (OR 1.37) and conventional antipsychotics (OR 1.35).

HYPERPROLACTINEMIA

Conventional antipsychotics may cause hyperprolactinemia by blocking dopamine D₂ receptors on pituitary lactotroph cells, thereby removing the tonic inhibition on prolactin release provided by dopamine secreted by the tuberoinfundibular neurons in the hypothalamus [134]. With exception of risperidone and amisulpride, newer antipsychotics have a weak potential to cause elevation of plasma prolactin levels. Plasma prolactin increase is generally dose related and is more common in women, while is independent of age [135]. Hyperprolactinemia may be asymptomatic or can cause a wide range of clinical symptoms. Resulting from either the direct effects of prolactin on body tissues (galactorrhea, gynecomastia) or endocrine-related secondary effects (sexual and reproductive dysfunction in the short-term and osteoporosis in the longer term) [136]. There are conflicting data on whether hyperprolactinemia is associated with an increased risk of breast cancer [134, 136]. As previously mentioned, hyperprolactinemia has been hypothesized as one of the possible mechanism for cerebrovascular effects induced by antipsychotics.

CONCLUSIONS

The burden of dementia in Western Countries has dramatically increased in recent years and will increase even further in the years to come. Despite the growing number of elderly patients who will be affected by cognitive deterioration and related psychotic/behavioral symptoms in the future, critical aspects of the management remain unsolved. Differences between two antipsychotic types and even among individual medications clearly exist in the risk of specific adverse events, such as extrapyramidal and metabolic effects. Clinicians should consider individual safety profile of different antipsychotic drugs whenever they decide to start a treatment. The lowest dosage and the shortest duration of use is recommended for both conventional and atypical antipsychotics in elderly subjects with dementia.

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CHAPTER 3

Antidepressant drugs in elderly: use and safety



3.1. Antidepressant drugs: prevalence, incidence and indication of use in general practice of Southern Italy during the years 2003-2004

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ABSTRACT

Purpose: To estimate one-year prevalence, one-year incidence and indication of use of AD drug treatment in general practice of Southern Italy during the years 2003-2004.

Methods: Among 142,346 individuals registered in the lists of 119 general practitioners of Southern Italy, we identified users of different AD types: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and other antidepressants. Annual prevalence of AD use was measured as the number of individuals receiving at least one AD prescription in the years 2003-2004, divided by the number of patients registered in the GP lists. One-year incidence of AD treatment was calculated as the number of new users of AD, divided by the number of total patients free from AD prescriptions in the previous year.

Results: Overall, one-year prevalence of AD use was 5.08 (95% Confidence Interval: 4.97-5.20) per 100 inhabitants in the year 2003, with a 20% increase in 2004 (6.00, 5.88-6.13). Prevalence of SSRI use markedly increased from 3.80 (3.73-3.90) in 2003 to 4.51 (4.40-4.61) in 2004. The incidence rates of SSRI, TCA and other antidepressant use were 2.11 (2.03-2.19), 0.38 (0.35-0.41) and 0.53 (0.49-0.57), respectively.

Depressive disorders were the main indication of use of any AD user (mostly for SSRI users), followed by anxious disturbances.

Conclusions: SSRIs, particularly those recently marketed, have been increasingly used during the last years, mainly to treat affective disorders.

INTRODUCTION

In Europe, according to a recent investigation¹ which estimated the prevalence of psychiatric diseases in the general population, a “lifetime” prevalence of affective disorders of 11.1% was reported. Primary care providers play a crucial role in the management of these disorders, as suggested by surveys²⁻³ showing that depressive symptoms are present in nearly 70% of patients who visit general practitioners. Antidepressant (AD) pharmacotherapy represents a key therapeutic strategy in the management of outpatients with major depression, and the introduction of selective serotonin reuptake inhibitors (SSRIs) into the market, since the late 80’s, has progressively changed AD prescribing patterns, both in Italy and in most Western Countries. According to a national Italian report on drug consumption⁴, SSRIs have been the most prescribed medications among neuropsychiatric drugs in the year 2004 (with a 18% increase with respect to the previous year). It is possible, however, that the wide and continuously increasing utilization of SSRIs might be partly related to the fact that these drugs are indicated not only in the treatment of major depression, but also in the treatment of a broad range of conditions, such as obsessive-compulsive disorders, panic attacks, generalised anxious disorders, eating disorders, somatoforms disorders, premenstrual syndrome disorders⁵. Although several investigations⁶⁻⁸ on AD prescribing patterns in primary care of Northern Italy have been previously carried out, these studies were limited by the lack of data on clinically relevant information, such as indication of use.

In order to fill this gap, the aims of this study were: a) to measure one-year prevalence, one-year incidence and distribution of AD use in general practice of Southern Italy; b) to characterise AD users, with particular regard to indication of use. Secondary objective of this investigation was to compare our data with national figures on drug consumption, in order to verify the reliability of this general practice database in performing drug-utilization studies.

METHODS

Data source

Data were extracted from the Arianna database during the years 2003-2004. Such a database, set up by the Health-Service Agency of the city of Caserta in the year 2000, currently contains information on a population of almost 300,000 individuals living in the catchments area of Caserta and registered in the lists of 225 general practitioners (GPs). Such a sample of physicians accounts for 73.7% (225/305) of total GPs who practice in the same area. Participating GPs record data

during their daily clinical practice through dedicated software, and, monthly, send complete and anonymous clinical data of their patients to the Arianna Database. Information collected include patient demographics, drug prescriptions that are coded according to the Anatomical Therapeutic Chemical classification system (ATC), and medical diagnoses coded by the ninth edition of International Classification of Diseases (ICD-9).

All participating GPs received extensive training in data collection techniques. Routine quality checks include the analysis of several parameters such as missing patient codes, the number of daily filled prescriptions and the proportion of prescriptions correctly linked to medical diagnoses, and monthly continuity of data submission. Any variations within defined ranges are investigated and back-submitted to each participating GP, in order to receive an immediate feedback about data quality and completeness. GPs failing to meet these standard quality criteria are not retained within the analyses, according to basic standards in the conduct of pharmacoepidemiological studies ⁹. So far, the Arianna database has been shown to provide accurate and reliable information. ¹⁰⁻¹¹

Study population

Overall, 119 GPs that continuously sent data to Arianna database during the years 2003-2004 were selected for this investigation. Among 142,346 individuals registered in their lists, users of ADs, defined as individuals receiving at least one AD (ATC: No6A) prescription during the observation years, were identified. Patients were included into the study irrespective of whether AD treatment was initiated by GPs or by specialists working in the public or private sector, in this case leading thereafter to GP prescriptions. In fact, in Italy the system works in such a way that outpatients receiving prescriptions in the public or private sector by specialists get the medicines free of charge through GP prescriptions. The following cohorts of AD users were identified according to the drug type being used: (1) tricyclic antidepressants (TCAs) (No6AA); (2) selective serotonin reuptake inhibitors (SSRIs) (No6AB); (3) other ADs: venlafaxine (No6AX16), reboxetine (No6AX18), mianserin (No6AX03), mirtazapine (No6AX11), trazodone (No6AX05) and nefazodone (No6AX06). Since February 2003, all antidepressant medications are totally reimbursed by Health National System in Italy. As a consequence, the study findings are free from the biases deriving from reimbursement restriction. After identification of AD users, the following information was retrieved using the Arianna database: patients' demographics, AD-related data (including product name, dispensed quantity and indication of use) recorded during the years 2003-4, concomitant medications prescribed at the first AD prescription date (index date), and concurrent diseases, for whom a drug prescription was issued prior to the index date.

One-year prevalence and incidence of antidepressant use

Annual prevalence of AD treatment was calculated as the number of AD drug users divided by the number of subjects alive and registered in the GPs' lists in the observation year. We defined "new user" as a patient receiving a first AD prescription during the year 2004, without any recorded AD prescription in the previous year. The incidence rate was measured as the number of "new users" divided by the number of subjects free from antidepressant drug use in the previous year. Both prevalence and incidence were expressed as rates per 100 inhabitants, together with 95% Confidence Interval (CI).

Statistical analysis

Chi-Square test for categorical variables and Student t-test for continuous variables, with a significance level of $P < 0.05$, were used for assessing the differences among users of various AD types. Statistical analyses were performed using STATA 6.0 (STATA Corporation, Texas, USA).

RESULTS

One-year prevalence of antidepressant medication use

Prevalence of AD use per 100 inhabitants, stratified by age groups and calendar years, is shown in **Figure 1**. On a total sample of 142,346 individuals registered in the lists of 119 GPs, prevalence of use was 5.08 (95% CI: 4.97-5.20) per 100

Figure 1. Prevalence of use of antidepressant medications during the years 2003-2004, stratified by age groups.

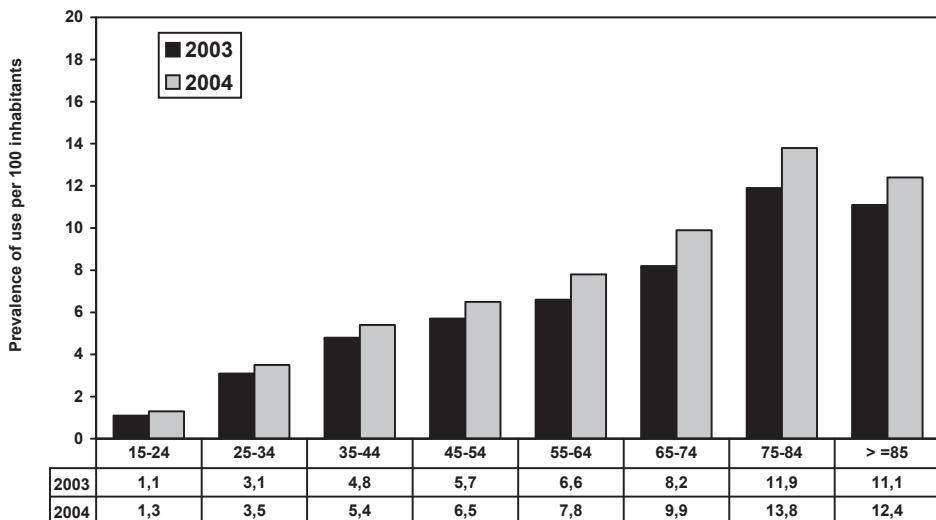
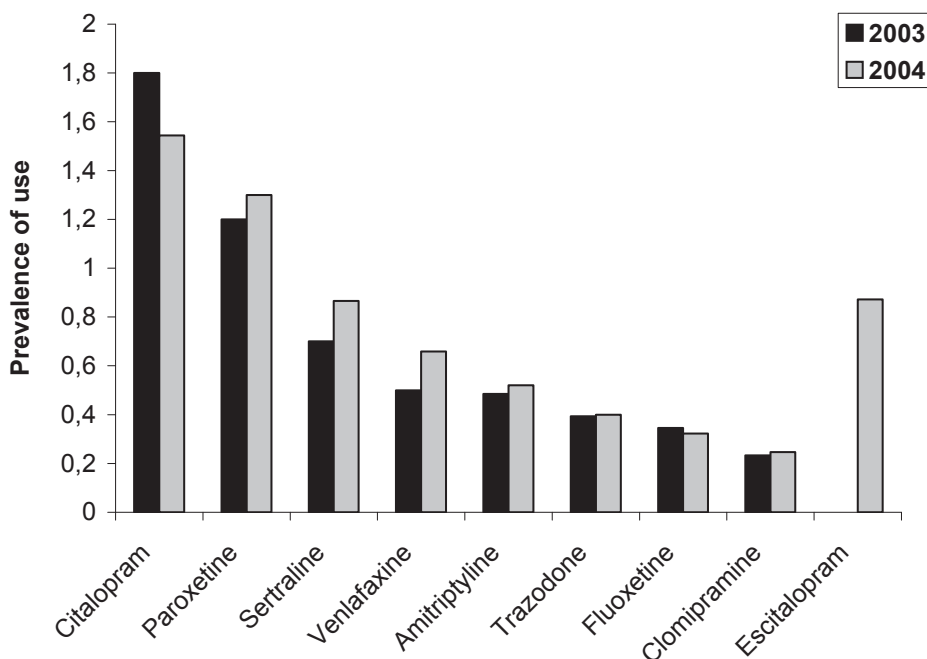
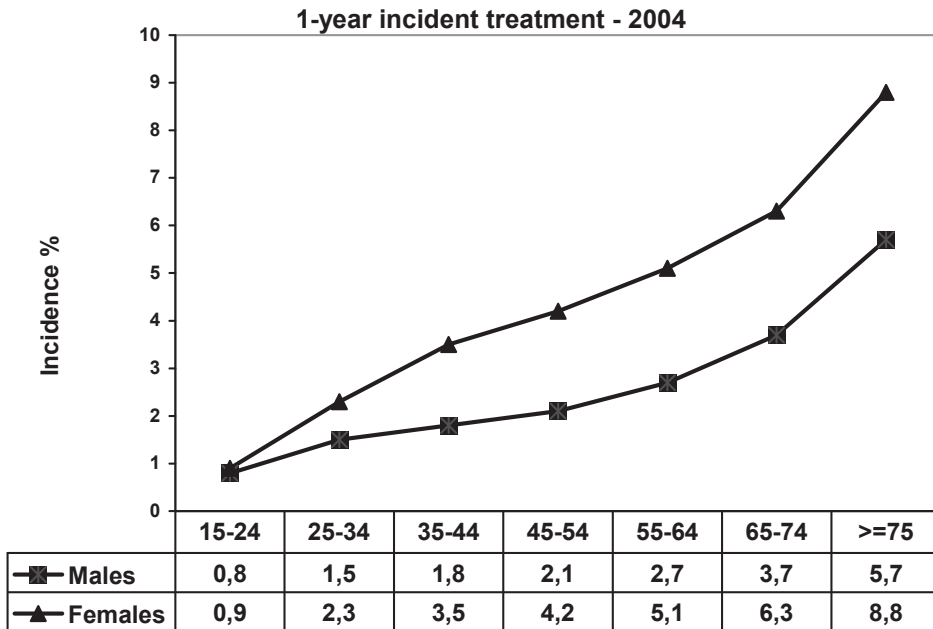


Figure 2. Prevalence of use (per 100 inhabitants) of mostly prescribed antidepressant medications* during the years 2003-04.

inhabitants in the year 2003, with a 20% increase in 2004 (6.00, 5.88-6.13). Prevalence was higher for females (2003: 6.64, 6.46-6.82; 2004: 7.82, 7.63- 8.01), and increased with increasing age in both years. Concerning different AD types, prevalence of SSRI use was higher than TCA use (2003: 0.80, 0.76-0.84; 2004: 0.89, 0.84-0.94) and other ADs (2003: 1.16, 1.11-1.21; 2004: 1.33, 1.28-1.40) and, differently from the other two groups, tended to dramatically increase during the two study years (2003: 3.80, 3.73-3.90; 2004: 4.51, 4.40-4.61). In **Figure 2**, the one-year prevalence of AD use for medications accounting for more than 90% of total AD prescriptions is shown. The three AD drugs with the highest prevalence of use in both years were SSRIs: citalopram (2003: 1.85, 1.78-1.92; 2004: 1.52, 1.46-1.59), paroxetine (2003: 1.15, 1.11-1.21; 2004: 1.35, 1.29-1.41) and sertraline (2003: 0.72, 0.68-0.77; 2004: 0.86, 0.81-0.90). Amitriptyline and venlafaxine were the most used medications among TCA and other ADs, respectively. The prevalence of first five medications appears to increase within the two study years, except for citalopram. The prevalence of escitalopram (0.86, 0.81-0.91), marketed in Italy since 2004, ranges in the third position among AD medications in this year. The 41% of escitalopram users switched to this drug after stopping other ADs in the previous year.

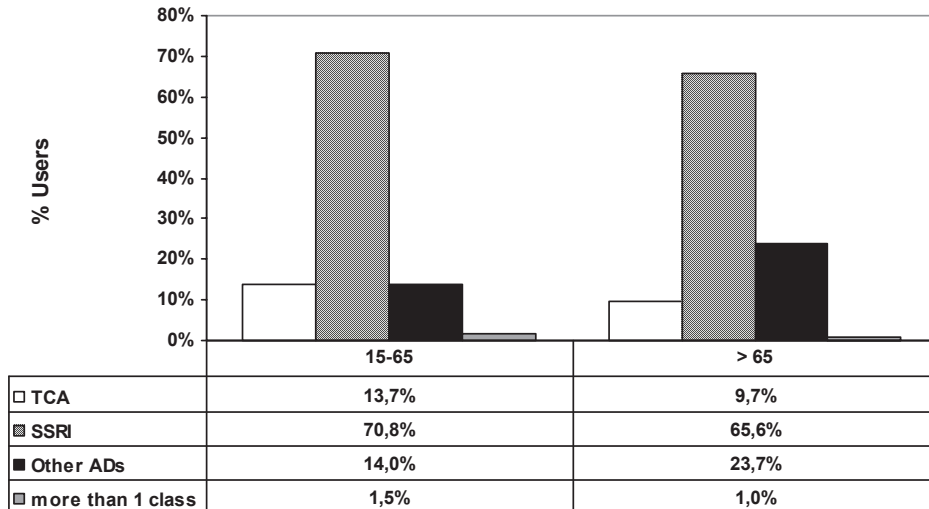
Figure 3. One-year incidence of antidepressant treatment in the year 2004, stratified by age groups and gender.

One-year incident treatment with antidepressant medications

Overall, one-year incidence rate of AD treatment was 3.06 (2.97-3.15) per 100 inhabitants during the year 2004 (**Figure 3**). The incidence rate was higher for females (3.93, 3.79-4.08) and, again, increased with increasing age. The incidence rates of SSRI, TCA and other AD use were respectively 2.11 (2.03-2.19), 0.38 (0.35-0.41) and 0.53 (0.49-0.57) per 100 inhabitants. **Figure 4** highlights the distribution of new treatments with different AD types. In general, SSRIs accounted for almost two thirds of total new treatments with ADs, while the remaining was equally distributed between TCA and other ADs. Compared to younger patients, however, a larger proportion of elderly people (23.7%) started a new treatment with AD, other than SSRI and TCA, and in particular with trazodone.

Clinical characteristics of antidepressant users

On a total sample of 142,346 subjects, 11,418 (8.0%) received at least one prescription of any AD medication during the study years: 8,671 received SSRI (75.9%), 1,869 TCA (16.4%) and 2,795 other AD prescription (24.5%), at least once. In **Table 1**, demographic and clinical characteristics of AD users, stratified by not mutually exclusive cohorts, are listed. Patients taking other ADs were significantly ($P < 0.05$) older than users of TCA and SSRI. In particular, 80% of other AD users older than 85 years received trazodone. A higher ($P < 0.05$) proportion of

Figure 4. Distribution of new treatments with antidepressant medications in 2004, stratified by age and drug type.

Legend: TCA= Tricyclic antidepressant; SSRI= Selective serotonin reuptake inhibitor; Other ADs= antidepressant medications, other than TCA and SSRI (venlafaxine, trazodone, reboxetine, mianserin, mirtazapine and nefazodone); More than 1 class= patient starting a treatment with more than 1 AD medication belonging to different classes. Categories are mutually exclusive.

Table 1. Demographic and clinical characteristics of antidepressant drug users* during the years 2003-2004, stratified by drug type.

Variables	TCA	95% CI	SSRI	95% CI	Other ADs	95% CI
	N=1,869 (%)		N=8,671 (%)		N=2,795 (%)	
<i>Mean age ± Standard Deviation, y</i>	53.6±17.2		54.1±18.2		59.0±18.6	
Gender						
Females	1,330 (71.2)	69.0-73.1	5,768 (66.5)	65.5-67.5	1,800 (64.4)	62.6-66.1
Males	539 (28.8)	26.8-30.9	2,903 (33.5)	32.4-34.4	995 (35.6)	33.8-37.3
<i>Indication of use**</i>						
Depressive disorders	937 (50.1)	47.8-52.3	5,831 (67.2)	66.2-68.2	1,789 (64.0)	62.2-65.7
Anxious disturbances	257 (13.8)	12.2-15.3	918 (10.6)	9.9-11.2	300 (10.7)	9.6-11.9
Bipolar disorders	159 (8.5)	7.3-9.8	795 (9.2)	8.5-9.7	219 (7.8)	6.8-8.8
Headache	150 (8.0)	6.8-9.3	95 (1.1)	0.8-1.3	13 (0.5)	0.2-0.7
Psychotic disorders	111 (5.9)	4.9-7.1	467 (5.4)	4.9-5.8	182 (6.5)	5.6-7.4
Psychiatric disturbances associated with somatic disorders	36 (1.9)	1.3-2.6	111 (1.3)	1.0-1.5	79 (2.8)	2.2-3.5
Dementia	17 (0.9)	0.5-1.4	112 (1.3)	1.0-1.5	84 (3.0)	2.4-3.7
Neuropathic pain	29 (1.6)	1.0-2.2	22 (0.3)	0.1-0.3	1 (0.04)	0.01-0.2
Not reported	173 (9.3)	8.0-10.6	320 (3.7)	3.3-4.1	128 (4.6)	3.8-5.4

Legend: TCA= Tricyclic antidepressant; SSRI= Selective serotonin reuptake inhibitor; Other ADs= antidepressant medications, other than TCA and SSRI (venlafaxine, trazodone, reboxetine, mianserin, mirtazapine and nefazodone).

*Patients receiving at least 1 antidepressant medication prescription during the years 2003-4. Antidepressant drug types are not mutually exclusives.

** Indication of use that was recorded at the first antidepressant prescription date, by drug type.

TCA users were females compared to SSRI users and other AD users. Depressive disorders, including neurotic depression, were the main indication of use of any AD, followed by anxious disturbances and bipolar disorders. Interestingly, patients affected by depressive disorders accounted for 67.2% of SSRI users, a proportion significantly ($P < 0.05$) higher than TCA users (50.1%). On the other hand, patients treated with TCA (8.0%) were significantly ($P < 0.05$) more affected by headache, mostly due to amitriptyline, than SSRI (1.1%) and other antidepressant users (0.5%).

DISCUSSION

One-year prevalence, incidence and distribution of antidepressants

The results of this study indicated a strikingly increasing prevalence of AD medication use in a general practice of Southern Italy during the years 2003-2004. This increase appears to be mostly related to SSRI.

Percudani et al⁶⁻⁷ reported a one-year prevalence of AD use of 4.43 per 100 inhabitants among 404,238 individuals living in Lombardy, a region of Northern Italy, during the year 2001. Since AD medication use has been progressively rising in the last years in Italy, due partly to SSRI reimbursement without restrictions, our results seem to be in line with this previous Italian investigation. In addition, our findings are comparable with Italian national data on drug consumption for 2004⁴. Similarly to our investigation, national data highlighted that citalopram, sertraline and paroxetine were the three most used ADs in Italy in 2004, with citalopram showing a 20% reduction compared to 2003.

On the other hand, our study shows the high prevalence of use of escitalopram that is the S-enantiomer of citalopram, marketed in Italy only at the beginning of 2004, thus confirming again data from Italian national report⁴. This finding confirms the trend of new marketed drugs to be widely prescribed in general practice, immediately after their introduction in drug market.¹² As expected, SSRIs accounted for almost two thirds of total one-year incident treatments with AD medications, with these agents mainly used in treating affective disorders. Although these figures seem in line with the background-frequency of psychiatric disorders that, theoretically, should be treated with AD agents, specific studies are warranted to precisely quantify the degree of coherence between the true frequency of these conditions and the frequency of AD use. Clearly, these analyses are complicated by the fact that not all these conditions are of sufficient severity to justify pharmacotherapy. According to our data, however, their wide range of indications of use might play only a minor role in choosing SSRI as antidepressant

therapy. Indeed, in line with previous European investigations, SSRI have been increasingly used to treat mainly affective disorders.^{5,13}

Interestingly, a lower proportion of people older than 65 years started a new AD therapy with SSRI or TCA, compared to younger patients. On the other hand, a relevant proportion of elderly people initiated a new AD treatment with trazodone, in line with another Italian study¹⁴, reporting a dramatically increased use of this drug in patients older than 85, in the year 2001. This large utilization of trazodone in elderly people might raise clinical issue, in view of the propensity of this antidepressant to cause orthostatic hypotension, and possibly thereby to increase the risk of falls and hip fractures, in these patients.¹⁵

Characteristics of antidepressant users

The main finding of our analysis is that the increase of SSRI use does not seem to be explained by a large number of prescriptions due to indications other than depression. Only 10% of SSRI users was treated because of anxious disturbances, and, in addition, a higher proportion of patients on SSRI were affected by depressive disorders compared to TCA users. Such data seem to be in contrast with Italian national data showing that 41.5% of SSRI prescriptions were related to neurotic disturbances. This disagreement, however, might be partly explained by different diagnostic categories being defined in our study and in that national report. This discrepancy highlights the need to adopt more efficient and internationally accepted tools and standards, targeted to better identify and code mental disorders in general practice setting. A number of previously published papers¹⁶⁻¹⁸ strongly supported the use of International Classification of Mental Disorders-Primary Health Care (ICD-10 PHC), a special edition of the ICD-10 that is addressed to general practitioners. Another study finding is the significantly higher proportion of TCA users who were treated because of headache, compared to users of SSRI and other ADs. This result is explained by the use of amitriptyline. According to Italian Summary of Product Characteristic of amitriptyline, “prophylaxis of migraine and chronic recurrent headaches” is listed among approved indications of use.

Strengths

To our knowledge, this is the first investigation targeted to assess the antidepressant medication use in general practice of Southern Italy.

The availability of clinical data in Caserta database allowed us to perform clinical characterisation of AD users in general practice, thus providing useful information on the indication of use of AD.

Limitations

This analysis was not aimed to evaluate any clinical outcome. In addition, such an investigation was performed using data concerning only two years, 2003 and 2004, collected from a restricted area of Southern Italy. It is therefore possible that these findings might not be fully generalized to the whole Italian general practice. However, the comparison with Italian national report on drug consumption supported the reliability of this database in providing information about AD drug utilization in Italy. We used outpatient prescription data and we had no information whether the antidepressant drug prescriptions were actually filled and taken. This limit should be taken into account since around half of the medicines prescribed for people with chronic conditions are not ultimately taken.¹⁹ Finally, this study was performed using computerized medical records from general practice. According to Kaye et al²⁰, the observed findings may not pertain directly to patients treated in other settings (e.g., psychiatric inpatients or individual in nursing homes). Since a relevant proportion of individuals living in residential settings receive AD drugs, the prevalence rates might have underestimated the use of these agents, especially in certain age groups, such as very old people, who are more likely to be admitted to these facilities.²¹ To avoid an additional underestimation, only GPs who continuously provided data to Arianna database during the whole observation period were included into the study. Sensitivity analysis did not show any significant difference in prescribing behaviour between GPs enrolled into the study and the others.

In conclusion, the AD use has been continuously increasing in general practice of Southern Italy in the last years, largely reflecting increasing use of newer agents, in particular SSRI. Nevertheless, such an increased use does not seem to be explained by large number of prescriptions due to indications other than depression. Indeed, affective disorders remain the main indication of use, particularly for SSRI.

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3.2. Risk of ischemic stroke associated with antidepressant drug use in elderly persons

Submitted for publication

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ABSTRACT

Background: Competing hypotheses have been formulated about a possible association between selective serotonin reuptake inhibitors (SSRIs) and ischemic stroke. However, the relationship between antidepressant drug use and ischemic stroke is still unclear. Aim of the study was to assess the association between use of different types of antidepressants and the risk of ischemic stroke in elderly outpatients.

Methods: A population-based, nested, case-control study was conducted in persons 65 years and older in the Integrated Primary Care Information (IPCI) database (1996-2005). Cases were all patients with a validated first ischemic stroke. Controls were matched on year of birth, sex and index date. Exposure to antidepressants was divided in current, past and non-use and further categorized by type (SSRI, tricyclic [TCA], other antidepressants), dose and duration. Conditional logistic regression was used to compare the risk of ischemic stroke between users of antidepressants and non-users.

Results: Overall, 996 incident ischemic strokes were identified. Current use of SSRIs was associated with a significantly increased risk as compared to non-use (OR: 1.55; 95% CI: 1.07-2.25) in elderly, particularly when used longer than 4 months. No associations were observed for current use of TCAs and other AD.

Conclusion: Compared to non use, only SSRI use appears to be associated with an increased risk of ischemic stroke in elderly patients, particularly as short term effect.

BACKGROUND

Antidepressant drugs (ADs) are widely used in elderly people for indications such as depressive symptoms, anxiety disorders and neuropathic pain [1-2].

The selective serotonin reuptake inhibitors (SSRIs) are considered the first-choice for the elderly with depressive symptoms, as these drugs are supposed to have similar efficacy to other antidepressants but better tolerability [3]. Recently, the effects of SSRIs on cerebral circulation have garnered attention after preliminary reports suggested an association between SSRI exposure and risk of abnormal bleeding, including hemorrhagic stroke [4-6]. SSRIs decrease the intracellular contents of serotonin in platelets by blocking serotonin transporter 5-HTT, thus inhibiting platelet function. This anti-platelet effect of SSRIs may ultimately increase the risk of hemorrhage, such as intracranial bleeding [7]. The same mechanism might theoretically protect against arterial thrombotic events, including ischemic stroke [7]. Previous investigations documented a significant reduction in the risk of myocardial infarction associated with SSRI use [8-9]. On the other hand, SSRIs may cause vasoconstriction in cerebral arteries as a result of serotonergic activation which may lead to ischemic stroke [10-11]. To date the net effect of SSRIs on the risk of ischemic and hemorrhagic stroke remains unclear.

Several studies explored the association between hemorrhagic stroke and SSRI and other antidepressant drug use but failed to show any significant associations [12-14]. Little is known about the risk of ischemic stroke in elderly persons using antidepressants, although approximately 80% of total strokes are ischemic ones in these patients [15]. An Italian study did not find an increased risk of cerebrovascular adverse effects in elderly patients who were treated with antidepressants, but did not differentiate between ischemic and hemorrhagic stroke [16]. Two studies did demonstrate an increased risk of ischemic stroke for SSRIs but did not consider the elderly specifically [17] or were limited to hospitalized stroke only and not considering other antidepressants and indication of use [18]. Altogether, the epidemiologic evidence about antidepressant use and risk of ischemic stroke is inconclusive.

Thus, the aim of this study was to assess the association between the use of various antidepressant drug types and the risk of a first-ever ischemic stroke in community-dwelling elderly persons.

METHODS

Setting

We employed a population-based, nested, case-control study. Data for this study were retrieved from the Integrated Primary Care Information (IPCI) database. The IPCI database is a longitudinal general practice research database set up in 1992 and containing data from electronic medical records from a group of 150 Dutch general practitioners' (GPs) practices. In the Netherlands, all persons have their own GP who serves as the gatekeeper to medical care and files all relevant medical details on their patients from primary care visits, hospital admissions and visits to outpatient clinics. A detailed description of the database has been previously reported [19]. Briefly, IPCI contains the medical records of approximately 800,000 patients with an age and gender distribution representative of the Netherlands. The electronic records contain coded and anonymous data on patient demographics, reasons for visits, signs, symptoms and medical diagnoses (using the International Classification for Primary Care [20]) from GPs and specialists, hospitalizations, as well as drug prescriptions. Drug prescriptions include product name, anatomical therapeutic chemical (ATC) classification, dispensed quantity, dosage regimen and coded indication. To maximize completeness of the data, GPs participating in the IPCI project are not allowed to maintain a system of paper-based records, aside from the electronic medical records. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research [21]. The Scientific and Ethical Advisory Board of the IPCI project approved the study.

Study population

The study started on January 1, 1996, and ended on December 31, 2005. The source population comprised all individuals 65 years and older with at least 1 year of data registered in the database. All individuals were followed from the study entry date until one of the following events, whichever came first: transient ischemic attack (TIA), stroke, death, moving out of the practice area, or end of the study period. Patients who had a recorded diagnosis of TIA or stroke in the medical history prior to the study entry were excluded. Patients with a diagnosis of cerebral tumor, either before or during the study period, were also excluded.

Case Identification and Ascertainment

Cases were all patients with a first-ever ischemic stroke that occurred during the study period. The case identification and ascertainment included two phases. First, we applied a broad search on patient clinical diary and summaries of specialist

letters, using coded diagnoses and key words for free text. Second, the electronic medical records of all potential cases of cerebrovascular accidents were manually reviewed by two medically trained researchers (G.T. and E.F.S), who were blinded to the exposure. Patients were classified as having a TIA, a hemorrhagic stroke, an undefined stroke, or an ischemic stroke. Ischemic stroke was considered if the diagnosis was confirmed by a CT-scan or explicitly mentioned by a consulting specialist or listed among discharge diagnoses. The date of initial symptoms (e.g. dizziness, unexplained falling, and headache) was considered as the index date. Only if a stroke was preceded by a TIA occurring less than one month before, TIA was taken as the index date. Otherwise, a TIA was not considered in order to avoid case misclassification. TIA, however, was used as a censoring point to avoid protopathic bias since some patients with TIA may receive treatment with antidepressants subsequently [22]. In case of disagreement between the two assessors in classifying the cases and identifying the index date, a consensus was found via discussion. For each case, all persons in follow-up at the time of the index date and of the same age and sex as the case served as a control in the statistical analyses.

Exposure definition

Information on antidepressant drug use was obtained from the prescription files. We created antidepressant exposure categories based on drug type, and recency, dose and duration of use. The legend duration was calculated as the total number of units per prescription divided by the prescribed daily number of these units. Antidepressant drugs were grouped according to the mechanism of action into: 1) Selective serotonin reuptake inhibitors (SSRIs): paroxetine, fluoxetine, citalopram, fluvoxamine and sertraline; 2) Tricyclic antidepressants (TCAs): clomipramine, amitriptyline, dothiepin, imipramine, trimipramine, lofepramine, maprotiline, doxepin, nortriptyline, desipramine, bupropion, moclobemide, opipramol, dosulepin and reboxetine; 3) Other antidepressants: venlafaxine, mirtazapine, mianserine, nefazodone and trazodone. A combination category was considered for concomitant use of more antidepressants belonging to different classes. We performed a secondary analysis in which we grouped antidepressant drugs based on the affinity to the serotonin transporter [14]: 1) high affinity (paroxetine, fluoxetine, sertraline, and clomipramine); 2) intermediate affinity (citalopram, fluvoxamine, amitriptyline, dothiepin, imipramine, and venlafaxine); 3) low affinity (trimipramine, lofepramine, maprotiline, doxepin, nortriptyline, desipramine, bupropion, moclobemide, opipramol, dosulepin, reboxetine, mirtazapine, mianserine, nefazodone and trazodone). Exposure to different types of antidepressants was further divided into current, past and never use. Drug use was defined as current if the prescription length covered the index date or ended less than 30 days

(carry-over effect) prior. Past use meant that the last prescription ended more than 30 days prior to the index date. Patients were defined as non users if antidepressant prescriptions were never recorded prior to the index date. To be able to study the dose-effect, we expressed daily dosing regimens as the prescribed number of defined daily dosages (DDD), as defined by the World Health Organization (see website: <http://www.whocc.no/atcddd/indexdatabase/>). Duration of antidepressant use was calculated as the cumulative number of prescription days during the follow-up period. The duration was divided into short term use if ≤ 180 days and long term use if > 180 days, as the median duration of any antidepressant use was 180 days.

Covariates

As potential confounders, we considered age, sex, and calendar time (matching factors), smoking cigarettes, presence of cardiovascular disease (heart failure, hypertension, angina, history of myocardial infarction, peripheral arterial disease, atrial fibrillation, phlebitis/thrombophlebitis), neuropsychiatric diseases (Parkinson's disease, dementia, and migraine), chronic obstructive pulmonary disease (COPD), diabetes mellitus, lipid metabolism disorders, coagulation/platelet abnormalities, malignant tumors, pneumonia (within 3 months prior to the index date). We also considered chronic use of diuretics, digoxin, ACE-inhibitors, angiotensin receptor blockers, calcium-channel blockers, beta-blockers, lipid-lowering drugs, vasodilators and concomitant use (within 3 months prior to index date) of low dose aspirin, anticoagulants, antibiotics, systemic corticosteroids, NSAIDs, benzodiazepines, antipsychotic drugs, and opioids. Depression itself may be a risk factor for stroke and therefore confounding by indication cannot be easily ruled out [23]. To address this issue, two medically trained researchers (G.T. and E.F.S.) manually assessed the indication of use of antidepressant drugs from the free text of the medical records. Reasons for use were classified as depression, anxiety, headache, neuropathic pain, and other/unspecified disorders. This approach was taken for all exposed cases and for a randomly selected sample of the exposed controls ($N=425$).

Data Analysis

Relative risks of ischemic stroke plus 95% confidence intervals [CIs] were estimated by calculating odds ratios by using conditional logistic regression analysis. We performed adjustment for all covariates that were associated with ischemic stroke at the univariate analyses. In these analyses current and past use of different types of antidepressants (SSRI, TCA and other antidepressants) were compared to non-use. To compare directly the risk for ischemic stroke among

different antidepressant types, we performed an additional analysis with current use of TCA as comparator. A secondary analysis was carried out considering as exposure categories antidepressants with high, intermediate and low affinity to the serotonin transporter. A linear trend across strata of increasing affinity to the serotonin transporter was tested by including affinity as an ordinal variable in the logistic regression model. A sensitivity analysis was conducted in which we removed the carry over effect of 30 days. Among current users of antidepressants, we further calculated odds ratios for the risk of ischemic stroke with individual medications, daily dosage (≤ 0.5 and > 0.5 DDD), and cumulative duration of use (≤ 180 days and >180 days). Stratified analyses were conducted to study age and history of ischemic vascular disease as effect modifiers. To evaluate the presence of confounding by indication we also performed an analysis according to the type of antidepressant and the indication of use.

Antidepressant drugs may be prescribed to treat symptoms of cerebral ischemic disorders occurring shortly before stroke, thus some cases of ischemic stroke could be mistakenly attributed to antidepressant exposure (i.e. protopathic bias). To further assess the possible effect of protopathic bias on the association between antidepressants and ischemic stroke, we performed sensitivity analyses in which all patients, who started antidepressant treatment within 30, 60 and 90 days before the index date, were excluded. All analyses were conducted in SPSS/PC, version 13 (SPSS Inc, Chicago, Ill). The level of significance for all statistical tests was 2-sided $P < 0.05$.

RESULTS

The source population for this study comprised 70,392 individuals of 65 years and older. Of them, 1,176 (1.7%) were excluded because of cerebral tumors ($n=138$) or history of cerebrovascular event ($n=1,038$) prior to the study entry. The final study population comprised 69,216 elderly persons (43% males, average age: 72.7 ± 7.6 years). Within this population, 1,354 (2.0%) persons experienced a first-ever stroke (ischemic, hemorrhagic and undefined subtypes) during the study period, of which 996 (74%) were classified as incident ischemic stroke. Per case there were on average 493 age and sex matched controls available as a comparator. Demographic and clinical characteristics of cases and controls are reported in **Table 1**. Co-morbidities like hypertension, coronary heart diseases, atrial fibrillation, coagulation abnormalities, diabetes mellitus, COPD, and dementia, and concomitant use of corticosteroids, anticoagulants and opioids were associated with ischemic stroke. Among cases, 151 (15.2%) received at least one antidepressant drug at any time

Table 1. Demographic and clinical characteristics of cases compared to age and sex matched non-cases.

Current Use	Cases N=996 (%)	Controls (%)	Crude OR* (95% CI)
<i>Age groups (years)</i>			
			Matching factor
65-74	321 (32.2)	233,006 (47.4)	
75-84	447 (44.9)	220,358 (44.9)	
≥ 85	228 (22.9)	37,912 (7.7)	
<i>Gender</i>			
			Matching factor
Males	416 (41.8)	187,250 (38.1)	
Females	580 (58.2)	304,026 (61.8)	
Smoking cigarettes	55 (5.5)	27,274 (5.6)	1.19 (0.90-1.58)
<i>Cardiovascular diseases</i>			
Hypertension	386 (38.8)	143,231 (29.1)	1.56 (1.37-1.77)
Angina	141 (14.2)	51,312 (10.4)	1.30 (1.08-1.55)
History of myocardial infarction	57 (5.7)	17,059 (3.5)	1.62 (1.24-2.12)
Peripheral arterial disease	27 (2.7)	10,616 (2.2)	1.20 (0.82-1.77)
Atrial fibrillation	59 (5.9)	16,314 (3.3)	1.65 (1.27-2.15)
Heart failure	135 (13.6)	30,468 (6.2)	1.87 (1.55-2.25)
Phlebitis/thrombophlebitis	34 (3.4)	13,642 (2.8)	1.21 (0.86-1.71)
<i>Other diseases potentially related to stroke</i>			
Lipid metabolism disorders	53 (5.3)	38,440 (7.8)	0.79 (0.59-1.04)
Coagulation/platelet abnormalities	10 (1.0)	1,937 (0.4)	2.47 (1.32-4.61)
Obesity	9 (0.9)	5,920 (1.2)	0.87 (0.45-1.69)
Chronic obstructive pulmonary disease (COPD)	145 (14.6)	53,773 (10.9)	1.34 (1.12-1.60)
Diabetes mellitus	163 (16.4)	49,321 (10.0)	1.76 (1.49-2.08)
Tumours (except for cerebral ones)	107 (10.7)	48,122 (9.8)	1.06 (0.87-1.30)
Pneumonia (within 3 months prior to ID)	3 (0.3)	1,311 (0.3)	0.96 (0.31-2.99)
<i>Neuropsychiatry diseases</i>			
Parkinson's diseases	7 (0.7)	3,651 (0.7)	0.81 (0.30-1.71)
Dementia	45 (4.5)	12,451 (2.5)	1.44 (1.06-1.95)
Migraine	11 (1.1)	5,632 (1.1)	1.16 (0.64-2.10)
<i>Prior use of cardiovascular medications</i>			
Diuretics	7 (0.7)	1,948 (0.4)	1.56 (0.74-3.29)
Digoxin	1 (0.1)	395 (0.1)	NA
ACE-inhibitors	2 (0.2)	1,509 (0.3)	NA
Sartanes	1 (0.1)	651 (0.1)	NA
Calcium-channel blockers	3 (0.3)	1,106 (0.2)	1.26 (0.41-3.93)
Beta-blockers	9 (0.9)	2,483 (0.5)	1.84 (0.95-3.57)
Lipid-lowering drugs	1 (0.1)	1,056 (0.2)	NA
Vasodilators	2 (0.2)	612 (0.1)	NA
Aspirin	4 (0.4)	1,687 (0.3)	1.15 (0.43-3.07)
Anticoagulants	15 (1.5)	1,585 (0.3)	4.29 (2.56-7.18)
<i>Concomitant use of psychotropic drugs</i>			
Benzodiazepines	4 (0.4)	1,462 (0.3)	1.20 (0.45-3.21)
Antipsychotic drugs	1 (0.1)	140 (0.1)	NA
Opioids	3 (0.3)	154 (0.1)	9.09 (2.87-28.4)
<i>Concomitant use of other drugs</i>			
Systemic corticosteroids	3 (0.3)	285 (0.1)	4.74 (1.51-14.83)
Antibiotics	3 (0.3)	711 (0.1)	2.10 (0.68-6.55)
NSAIDS	3 (0.3)	1,122 (0.2)	1.22 (0.39-3.81)

* Conditional logistic regression analysis;

NA= not applicable as too few cases

prior to the first ischemic stroke: 29 (2.9%) were current users of SSRI, 17 (1.7%) of TCA and 6 (0.6%) of other antidepressants. Compared to non-use, current use of SSRIs was associated with an increased risk of ischemic stroke (OR: 1.55; 95% CI: 1.07-2.25), while no significant associations were found for current use of TCA (OR: 1.18; 95% CI: 0.73-1.91) or other antidepressants (OR: 1.01; 95% CI: 0.45-2.25) (**Table 2**). Past use of either SSRI or TCA showed an increase in the risk of ischemic stroke as well. Compared to current use of TCA the risk of ischemic stroke with current use of SSRIs (OR: 1.32; 95% CI: 0.72-2.40) or other Ads (OR: 0.86; 95% CI: 0.34-2.18) was not statistically significant different. Among current users, SSRIs were used at a higher dosage (on average, 1 ± 0.05 DDD per day) and for longer periods (on average 270 days) than TCAs (on average 0.5 ± 0.1 DDD and 158 days) and other antidepressants (on average 0.8 ± 0.1 DDD and 245 days). These differences in mean dosage and duration of use across antidepressant types lowered if considering depressed patients only (SSRI: 1 ± 0.05 DDD, 259 days; TCA: 0.8 ± 0.1 DDD, 211 days; and other antidepressant: 0.8 ± 0.1 DDD, 248 days).

Table 2. Risk of ischemic stroke with use of different antidepressant groups, stratified by dosage** and duration** of use

Exposure category	Cases N=996 (%)	Controls N=491,276 (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)
Non Use	844 (84.7)	437,718 (89.1)	1.00	1.00
Current Use				
SSRI	29 (2.9)	9,410 (1.9)	1.67 (1.15-2.42)	1.55 (1.07-2.25)
≤1 DDD	26	8,508	1.65 (1.03-2.44)	1.52 (0.98-2.26)
>1 DDD	3	902	1.92 (0.62-5.99)	1.78 (0.57-5.54)
≤ 180 days	16	3,468	2.26 (1.36-3.78)	2.07 (1.24-3.46)
> 180 days	13	5,942	1.22 (0.70-2.11)	1.14 (0.65-1.97)
TCA	17 (1.7)	7,155 (1.5)	1.24 (0.77-2.01)	1.18 (0.73-1.91)
≤1 DDD	16	6,658	1.25 (0.76-2.06)	1.18 (0.72-1.93)
>1 DDD	1	477	1.22 (0.17-8.67)	1.19 (0.17-8.46)
≤ 180 days	13	4,938	1.37 (0.79-2.37)	1.27 (0.73-2.20)
> 180 days	4	2,217	0.98 (0.37-2.61)	0.96 (0.36-2.56)
Other ADs	6 (0.6)	2,995 (0.6)	1.06 (0.48-2.38)	1.01 (0.45-2.25)
≤1 DDD	6	2,595	1.21 (0.54-2.71)	1.15 (0.51-2.56)
>1 DDD	-	400	NA	NA
≤ 180 days	2	1,397	0.75 (0.19-3.00)	0.71 (0.18-2.83)
> 180 days	4	1,598	1.35 (0.51-3.62)	1.28 (0.48-3.44)
Combination	-	284 (0.01)	NA	NA
Recent/Past use				
SSRI	49 (4.9)	17,219 (3.5)	1.49 (1.11-2.00)	1.39 (1.03-1.86)
TCA	43 (4.3)	13,729 (2.8)	1.64 (1.21-2.24)	1.53 (1.12-2.08)
Others	8 (0.8)	2,766 (0.6)	1.46 (0.73-2.94)	1.35 (0.67-2.72)
Combination	-	-	NA	NA

*Analysis was adjusted for hypertension, angina, history of myocardial infarction, atrial fibrillation, heart failure, coagulation/platelet abnormalities, COPD, diabetes mellitus, dementia, concomitant use of anticoagulants, systemic corticosteroids and opioids.

** As cut off point for dosage and duration categories, the median values for all current users of antidepressant were considered.

There was no dose effect on the risk of ischemic stroke for current users of any antidepressant type. However, we did observe a duration effect, where shorter use (i.e. ≤ 180 days) of SSRIs was associated with a larger risk increase (OR: 2.07; 95% CI: 1.24-3.46) than longer use (i.e. >180 days, OR: 1.14; 95% CI: 0.65-1.97). Considering the affinity to the serotonin transporter, a significant increase in the risk of ischemic stroke was observed only for the current users of antidepressants with high affinity to the serotonin receptor (OR: 1.43; 95% CI: 1.00-2.15), compared to non users. The linear trend test of increasing affinity and the risk of ischemic stroke was statistically significant ($p < 0.05$) (Table 3). The indication of use was validated and assessed in all the cases (N=152) and in a sample of controls (N=425), who were currently or formerly exposed to an antidepressant drug. Among the 52 cases, 36 (69%) were currently treated with antidepressants because of depressive symptoms, and two thirds of these subjects received SSRIs (Table 4). For patients with depression as an indication for treatment, the risk of ischemic stroke with SSRIs use (OR: 1.99; 95% CI: 1.20-3.30) was higher than that with TCAs (OR: 1.07; 95% CI: 0.43-2.65), although the difference was not statistically significant. We still observed a risk increase with current use of SSRIs if the indication was not depression, but the OR was lower and not statistically significant (OR: 1.50; 95% CI: 0.54-4.19). We performed a stratified analysis on presence of ischemic cardiovascular disease and on age, which showed that these factors did not modify

Table 3. Risk of ischemic stroke associated to different antidepressant groups (classified according to affinity for serotonin reuptake receptor), compared to non-use

AD exposure based on serotonin transporter affinity	Cases N=996 (%)	Controls N=491,276 (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)
Non-Use	844 (84.7)	437,718 (89.1)	1.00	1.00
Current Use				
High affinity ¹	24 (2.4)	8,752 (1.8)	1.55 (1.05-2.27)	1.43 (1.00-2.15)
Intermediate affinity ²	21 (2.1)	7,863 (1.6)	1.40 (0.91-2.16)	1.30 (0.84-2.00)
Low affinity ³	6 (0.6)	2,926 (0.6)	1.05 (0.47-2.34)	0.98 (0.44-2.19)
Combination	1 (0.1)	303 (0.1)	NA	NA
Recent/Past Use				
High affinity ¹	43 (4.3)	15,978 (3.3)	1.44 (1.05-1.96)	1.34 (0.98-1.83)
Intermediate affinity ²	49 (4.9)	14,873 (3.0)	1.70 (1.27-2.27)	1.57 (1.18-2.10)
Low affinity ³	8 (0.8)	2,863 (0.6)	1.38 (0.68-2.77)	1.29 (0.64-2.59)
Combination	-	-	NA	NA

* Analysis was adjusted for hypertension, angina, history of myocardial infarction, atrial fibrillation, heart failure, coagulation/platelet abnormalities, COPD, diabetes mellitus, dementia, concomitant use of anticoagulants, systemic corticosteroids and opioids.

Legend:

1. Paroxetine, fluoxetine, sertraline, clomipramine;
2. Citalopram, fluvoxamine, amitriptyline, dothiepin, imipramine, venlafaxine;
3. Trimipramine, lofepramine, maprotiline, doxepin, nortriptyline, desipramine, bupropion, moclobemide, opipramol, dosulepin and reboxetine, mirtazapine, mianserine, nefazodone and trazodone.

the effect of the association between antidepressant and ischemic stroke (data not shown). To test for protopathic bias, we excluded patients who received the first prescription of antidepressant within 30, 60 and 90 days prior to the index date. Compared to non-use, the risk in current users was only somewhat diluted (from 1.55 to 1.42 for SSRI; from 1.18 to 1.01 for TCA; from 1.01 to 1.07 for other antidepressants). Although our analysis was underpowered to assess the risk of each individual drug, sertraline (4 exposed cases, OR: 2.03; 95% CI: 0.76-5.44) and paroxetine (18 exposed cases, OR: 1.59; 95% CI: 1.00-2.55) were associated with the greatest risks of ischemic stroke.

DISCUSSION

To our knowledge, this is the first observational study that explored specifically the association between antidepressant drug use and the risk of ischemic stroke in a cohort of elderly patients. The results show that in comparison to non use, current use of SSRIs confers a significantly increased risk of ischemic stroke (adj. OR: 1.55; 95% CI: 1.07-2.25), especially during the first 6 months of treatment.

Table 4. Risk of ischemic stroke associated with current use of different antidepressant types and different indications of use, with non use as reference (OR=1.00)

Antidepressant exposure by indication of use	Cases N=152 (%)	Control N=425 (%)	Adjusted* OR (95% CI)
Current use of SSRI			
Depression	24 (15.8)	43 (10.1)	1.99 (1.20-3.30)
Others	5 (3.3)	13 (3.1)	1.50 (0.54-4.19)
Current use of TCA			
Depression	7 (4.6)	23 (5.4)	1.07 (0.43-2.65)
Others	10 (6.6)	29 (6.8)	1.38 (0.68-2.81)
Current use of Other AD			
Depression	5 (3.3)	16 (3.8)	0.67 (0.23-1.96)
Others	1 (0.1)	5 (1.2)	1.00 (0.13-8.05)
Recent/Past use of SSRI			
Depression	32 (21.1)	97 (22.8)	1.30 (0.86-1.96)
Others	17 (11.2)	31 (7.3)	1.73 (0.94-3.19)
Recent/Past use of TCA			
Depression	13 (8.6)	31 (7.3)	1.58 (0.86-2.88)
Others	30 (19.7)	124 (29.2)	1.09 (0.72-1.65)
Recent/Past use of Other AD			
Depression	5 (3.3)	18 (4.2)	0.93 (0.34-2.53)
Others	3 (2.0)	4 (0.9)	2.32 (0.52-10.36)

* Analysis was adjusted for hypertension, angina, history of myocardial infarction, atrial fibrillation, heart failure, coagulation/platelet abnormalities, COPD, diabetes mellitus, dementia, concomitant use of anticoagulants, systemic corticosteroids and opioids

Legend: Others= neuropathic pain, headache, anxiety disorders, other or unspecified psychiatric disorders.

This increased risk instead does not appear to be dose-dependent. We did find a linear risk increase with increasing affinity to the serotonin transporter. Past use of both SSRIs and TCAs was associated with ischemic stroke as well.

The results of our study are mostly in line with the very few reports that have previously explored aspects of the association between SSRI use and stroke [16-18]. Barbui et al found no difference in the risk of cerebrovascular accidents between SSRI and TCA use (adj. OR: 1.31; 95% CI: 0.87-1.97) but could not differentiate between ischemic and hemorrhagic stroke [16]. A Danish study, which analyzed hemorrhagic and ischemic stroke separately, but considered only events leading to hospital admission, found that past use but not current use of SSRIs was associated with an increased risk of ischemic stroke (adj. OR: 1.3; 95% CI: 1.0-1.5 vs. non-use) [18]. In this study the analytic strategy could have resulted in a misclassification of the index date and, as a result, a misclassification of the exposure. We did find an association between past use of both SSRIs and TCAs and the risk of ischemic stroke. This finding could point at a potential effect of confounding by indication on our results. Depression itself is a known risk factor of cerebrovascular disorders in young patients [23-24], while the role of depression as predictor of stroke in elderly patients remains very controversial [24]. To deal with confounding by indication, Chen et al recently conducted a nested case-control study among patients with depression in a large population-based, U.S. medical claims database [17]. In line with our study, the risk of ischemic stroke for current users of SSRIs was significantly higher as compared to non-use (adj. OR: 1.55; 95% CI: 1.00-2.39), while the increase in the risk in current users of TCAs (OR: 1.59; 95%CI: 0.89-2.83) or other antidepressants (OR: 1.33; 95%CI: 0.81-2.17) was not statistically significant. Also, in our study, when we selected exclusively depressed elderly (depression as the indication for treatment), only SSRI use was associated with an increased risk of stroke. TCA or other antidepressants show no association whatsoever. This finding argues against the influence of confounding by indication. Possible mechanisms supporting a potential causal association between exposure to SSRIs and ischemic stroke have been previously hypothesized. Serotonergic activation secondary to SSRI use can induce a vasoconstrictive effect that is mediated by the 5-hydroxytryptamine-2 (5HT-2) receptor on smooth muscle cells [25-26]. A recent review about the cerebrovascular effects of SSRIs pointed out that use of these medications may increase the risk of ischemic stroke by triggering thromboembolism through its vasoconstrictive effect in patients with large cerebral arteries atherosclerosis [7]. A significant linear trend between the risk of ischemic stroke and the affinity to the serotonin transporter was evident in our study. Also, paroxetine and sertraline, antidepressants showing the highest affinity to the serotonin transporter [27], seemed to confer a greater risk of ischemic

stroke. These findings support the hypothesis that a serotonergic activation may play a role in the association between ischemic stroke and SSRI use. The effect of SSRIs was predominantly observed within the first six months of therapy, which could point at an immediate effect of SSRIs and depletion of susceptibles during continued use.

Strength and limitations

The strength of this study is the availability of information on many confounders and details on antidepressant use. Moreover, we were able to review the medical records of all potential cases to identify the real incident, first-ever ischemic strokes. However, several limitations warrant caution. As in any observational study, selection bias, information bias and residual confounding should be considered as alternative explanations for the study finding. Selection bias was minimal as all data were obtained from prospectively collected medical records that are maintained for patient care purposes. To minimize the potential effect of information bias by misclassification of the outcome a two-step case validation was undertaken and, for the same purpose, TIA itself was not considered as a study endpoint, due to high probability of misclassification for this event. However, if a stroke was preceded by a TIA occurring less than one month before, the case was retained and the onset of TIA was taken as the index date.

To exclude all patients with history of cerebrovascular events at the study entry, we required at least one year of data registered in the database as inclusion criteria. Nevertheless, we could have missed information on prior cerebrovascular events without sequelae occurring long time before the study entry. Misclassification of exposure cannot be excluded since we used outpatient prescription data and had no information about whether the drug prescriptions were actually filled and taken. Non-adherence to antidepressant medication may be a relevant issue particularly in older patients, although a U.K. study reported that the level of adherence did not differ across various antidepressant types in community dwelling elderly [28]. Not filling of prescriptions or non-adherence most likely results in non-differential misclassification of the exposure, in which case our study underestimates the actual risk. Moreover, we may have missed specialist prescriptions of antidepressants. Many risk factors for ischemic stroke were considered in our study. Despite this, residual confounding due to unmeasured confounders or severity of (underlying) disease cannot be excluded. It is however unlikely that highly prevalent and strong risk factors were missed in our study. Finally, since the study considered only community dwelling elderly, the findings may not be generalized to elderly inpatients or those living in nursing homes. Likewise, exclusion of patients with prior TIA

or stroke prevents the generalizability of the results to elderly patients with a prior history of cerebrovascular events.

In summary, our study shows that among elderly people living in the community current use of SSRI may increase the risk of ischemic stroke, especially within the first 6 months of treatment. Further studies employing larger samples are needed to confirm these results and to conclusively establish the effect of the affinity to the serotonin transporter. Meanwhile, it seems advisable that SSRI treatment is carefully tailored and that a close monitoring is established in the first few weeks of treatment.

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3.3. Preventing Drug Interactions with Antidepressants in The Elderly

Published on: Aging Health 2007; 3(2): 231-243. Review

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SUMMARY

The present article reviews and discusses critically the issue of drug interactions involving antidepressants in the elderly. With the progressive aging of the population, late-life depression will increase in importance as a public health problem and prescriptions of antidepressants will presumably grow so thus enhancing the likelihood of drug interactions. After considering the general mechanisms and the various factors predisposing elderly subjects to drug interactions, the interaction potential for each class of antidepressant drugs will be examined, in order to help the prescribing physician in the selection of the most appropriate agent for an elderly patient receiving concomitant medications. Some general recommendations to prevent or minimize the occurrence of adverse drug interactions in elderly patients with depression will be given. Potential intervention strategies, targeted to adequately supply health professionals with information on the risks of clinically relevant drug interactions are deeply discussed.

INTRODUCTION

Depression is the most common psychiatric disorder in late life. Although major depression has been reported to occur in approximately 3% of individuals aged >65 years, the prevalence of depressive symptoms in the elderly is estimated to range between 15 and 30% [1, 2]. Geriatric depression may cause disability and mortality and increases health care costs. Untreated depression in older people results in patient suffering, increased rates of death from medical illnesses and suicide, medical morbidity, inappropriate institutionalization and caregiver burden [2, 3]. Among drugs used to treat depressive disorders, newer antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs), are considered as first-line drugs in the treatment of late-life depression, due to a more favorable tolerability, safety profile and a relatively lower potential for drug interactions as compared to older compounds [2-4]. The pharmacological treatment of geriatric depression can be difficult because age-related physiological changes and comorbid medical conditions may alter drug response and, therefore, predispose older subjects to adverse effects. In addition, as a result of coexisting chronic illnesses, elderly depressive patients often take many medications simultaneously, and this increases the likelihood of adverse events due to drug interactions. The potential for drug interactions may therefore guide selection of an appropriate antidepressant, especially in old age. In this respect, comprehensive reviews of antidepressant drug interactions in the elderly have been published [5, 6].

The purpose of this article is to discuss critically drug interactions involving antidepressants in the elderly in the attempt to provide necessary information to prevent or minimize their occurrence. In addition to the basic mechanisms and factors predisposing elderly subjects to drug interactions, the interaction potential for each class of drugs will be examined, in order to help the prescribing physician in the selection of the most appropriate antidepressant for an elderly patient receiving concomitant medications.

GENERAL MECHANISMS OF DRUG INTERACTIONS

A drug interaction occurs when the effectiveness or toxicity of a drug is altered by the concomitant administration of another drug. Drug interactions can be classified as either pharmacokinetic or pharmacodynamic. However, many interactions are multifactorial in nature and may involve a complex sequence of events both at pharmacokinetic and pharmacodynamic level.

Pharmacokinetic interactions

Pharmacokinetic interactions consist of changes in the absorption, distribution, metabolism or excretion of a drug and/or its metabolites, or the quantity of active drug that reaches its site of action, after the addition of another chemical agent. Most pharmacokinetic interactions with antidepressants drugs occur at metabolic level and generally results from inhibition or induction of the hepatic cytochrome P450 isoenzymes (CYPs) responsible for the biotransformation of individual antidepressants as well as concomitantly prescribed medications [7]. The activity of CYPs is genetically determined and may be influenced by pathophysiological and environmental factors, including concomitant administration of other drugs. Over the past few years the different substrates, inhibitors and inducers of CYP isoenzymes in man have been identified [8]. As reported in Table 1, the major CYP enzymes involved in the metabolism of currently available antidepressants include CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. In addition, some newer antidepressants may also act as inhibitors of one or more of these isoenzymes (Table 2). This information may be of great value for clinicians

Table 1. CYP enzymes responsible for the biotransformation of currently available antidepressants

Antidepressants	CYP enzymes
Tricyclic antidepressants (hydroxylation)	CYP2D6
Tricyclic antidepressants (demethylation)	CYP1A2, CYP2C19, CYP3A4
Citalopram/Escitalopram	CYP2C19, CYP2D6, CYP3A4
Fluoxetine	CYP2D6, CYP2C9
Fluvoxamine	CYP1A2, CYP2D6
Paroxetine	CYP2D6, CYP3A4
Sertraline	CYP3A4
Venlafaxine	CYP2D6, CYP3A4
Duloxetine	CYP1A2, CYP2D6
Mirtazapine	CYP1A2, CYP2D6, CYP3A4
Reboxetine	CYP3A4
Bupropion	CYP2B6

Table 2. Inhibitory effect of newer antidepressants on CYP enzymes

	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Citalopram	0	0	0	+	0
Escitalopram	0	0	0	0/+	0
Fluoxetine	+	++	+/++	+++	+/+++
Fluvoxamine	+++	++	+++	+	++w
Paroxetine	+	+	+	+++	+
Sertraline	+	+	+	+/++	+
Venlafaxine	0	0	0	+	+
Duloxetine	0	0	0	++	0
Mirtazapine	0	0	0	+	0
Reboxetine	0	0	0	+	0
Bupropion	0	0	0	++	0

0 = minimal or no inhibition; + = mild inhibition; ++ = moderate inhibition; +++ = potent inhibition

in anticipating and eventually avoiding potential interactions. Co-administration of two substrates of the same enzyme, or co-administration of a substrate with an inhibitor or an inducer, entails the possibility of a drug interaction. As a consequence, plasma concentrations of the co-administered drugs may be increased or decreased, resulting in clinical toxicity or diminished therapeutic effect. Dosage adjustments may then be required to avoid adverse effects or therapeutic failure. For the reasons that will be mentioned in next section, the entity of these kinetic changes is likely to be higher in the elderly. Metabolic drug-drug interactions may initially be studied *in vitro* in order to predict the potential importance *in vivo*. However, not of all theoretically possible drug interactions that are predicted from *in vitro* studies will occur *in vivo*, and some may not be clinically significant anyway. The most relevant aspects that must be taken into account when evaluating the potential occurrence, extent and clinical significance of a metabolic drug interaction include *drug-related factors* such as potency and concentration of the inhibitor/inducer, therapeutic index of the substrate, extent of metabolism of the substrate through the affected enzyme, presence of active or toxic metabolites, *patient-related factors* such as individual inherent enzyme activity (e.g. phenotyping/genotyping information), risk level for each individual to experience adverse effects (e.g. the elderly), and *epidemiological factors* such as the probability of the interacting drugs being used concurrently [9]. In general, it is likely to expect a clinically significant interaction when a drug with a low therapeutic index is co-administered with a potent inhibitor or inducer of the major pathway of its metabolism. By contrast, as most drugs have several metabolic pathways, the inhibition of an enzyme playing a marginal role in the overall clearance of a given drug may have a limited impact on its disposition, presumably resulting only in a minimal increase in plasma concentrations, since another isoform may provide sufficient secondary metabolic pathways. Pharmacokinetic drug interactions with antidepressants may also involve drug transporters, in particular P-glycoprotein (P-gp). P-gp is a multidrug efflux transporter, highly expressed in the intestine, brain, liver and kidney, which acts as a natural defence mechanism against several substrates by limiting their absorption from the gut and penetration to the brain and promoting their elimination in the bile and urine [10]. Like CYPs, the activity of P-gp can be inhibited or induced by other agents, altering the level of substrate drug in circulation. Recent *in vitro* evidence suggests that some newer antidepressants, namely paroxetine, sertraline, citalopram and venlafaxine, may inhibit P-gp [11]. In theory, as many substrates for P-gp, such as digoxin, cyclosporin and various chemotherapeutic agents, have a narrow therapeutic range and are widely used in the elderly, coadministration with these antidepressants may result in adverse drug reactions. However, a recent population-based assessment of the

potential interaction between SSRIs and digoxin in elderly patients has indicated that this mechanism is unlikely to be of major clinical significance [12].

PHARMACODYNAMIC INTERACTIONS

Pharmacodynamic interactions take place at receptor sites and occur between drugs with similar or opposing mechanisms of action, resulting in additive, synergistic or antagonistic effects. The potential for pharmacodynamic interactions differ markedly between the various classes of antidepressants depending on the respective mechanism of action and receptor profile. In general, older compounds, such as TCAs or MAOIs, acting on a broad range of receptors or enzymes have a greater potential to interact pharmacodynamically with other medications affecting the same system(s) than newer agents with a more specific mechanisms of action [13].

FACTORS PREDISPOSING ELDERLY PATIENTS TO DRUG INTERACTIONS

Drug interactions in the elderly are usually more frequent and more severe compared with younger subjects [14, 15]. In fact, the large interindividual variability in drug response resulting from genetic, pathophysiological and environmental factors affecting pharmacokinetics and pharmacodynamics is further amplified in the elderly because of the effect of age-related changes, comorbid disorders and polypharmacy. As a consequence, any given dose of a given drug may produce a different, and sometimes unexpected, response in elderly patients and, therefore, predispose them to adverse effects and drug interactions.

Polypharmacy

Geriatric depression is often associated with chronic medical illnesses, such as diabetes, ischemic heart disease, poststroke, dementia, Parkinson's disease, as well as other psychiatric disorders. Based on this, elderly depressed patients often take many medications simultaneously and this may multiply adverse effects through drug interactions, both pharmacokinetic and pharmacodynamic. Several studies in different settings have unequivocally indicated that the number of prescriptions (and not the age) is the best predictor of adverse drug reactions [16-18]. The incidence of undesirable interactions rises exponentially when multiple drugs are administered [19]. Moreover, elderly patients often use to self-medicate with over-the-counter preparations and natural remedies (herbal products). In this respect,

there is an increased awareness about potential adverse drug interactions involving herbal medicines especially in older adults [20-21].

Age-related changes in pharmacokinetics and pharmacodynamics

Aging is characterized by the progressive loss of organ system functional reserve and this may result in changes in pharmacokinetics and pharmacodynamics. Many age-related physiological changes are known to affect drug absorption, distribution, metabolism and excretion [22]. While drug absorption is generally not significantly influenced by age, changes in body composition may affect drug distribution in the elderly. In particular, the decrease in total body mass with age is associated with an increase in the proportion of body fat. These alterations may lead to increased volume of distribution of lipid-soluble drugs, as antidepressants, that tend to accumulate and persist longer in the body. The most relevant age-related pharmacokinetic modifications involve drug elimination, through hepatic metabolism and/or renal excretion. In fact, hepatic metabolic capacity and renal function decline progressively with age, thereby resulting in a decreased elimination of many drugs. The decline in drug metabolism is mainly explained by changes in liver blood flow and liver mass, while it is still controversial if there is an age-dependent decrease in microsomal enzyme activity [23, 24]. Unfortunately, these age-related changes in hepatic drug metabolism are unpredictable and difficult to estimate. Changes in renal clearance are comparatively more predictable, as glomerular filtration rate decreases by approximately 10% per decade after 20 years of age. The reduced drug clearance may lead to higher and more variable steady-state plasma concentrations. As pharmacological effects, including the inhibitory/inducing effects on drug-metabolizing enzymes, are often concentration dependent, the likelihood of drug interactions is increased in the elderly. Published reports of pharmacokinetics of older and newer antidepressants in elderly have been reviewed [25-27]. In general, though methodological issues and confounding factors may complicate the interpretation of data, either no change or reduction in clearance has been documented. To compensate for such physiologic changes, reductions of one third to half of the usual initial dose are recommended in elderly patients [26]. Although age-related pharmacodynamic changes may be even more important than pharmacokinetic modifications, the pharmacodynamic alterations have been less extensively investigated. With aging, the response to a drug on its target organ may be modified. Consequently, elderly patients are usually more sensitive to the effects of any given serum drug concentration. Even if the pharmacokinetics of a drug are not modified, an elderly patient may require a smaller dosage because of a change in pharmacodynamic sensitivity. With regard to psychoactive drugs, structural, electrophysiological and biochemical changes

involving brain neurons and neurotransmission have been documented in the elderly [22]. These alterations may theoretically increase cerebral vulnerability and increase the risk for pharmacodynamically mediated drug interactions. In addition to age-related physiological changes, other genetic, pathological and environmental factors may contribute to variability in the pharmacokinetics and pharmacodynamics of each drug in an elderly patient, thereby increasing the likelihood of serious drug interactions. In particular, diseases of organs that alter the physiological mechanisms subserving the various pharmacokinetic phases may further compromise the elimination of drugs.

INTERACTION POTENTIAL OF VARIOUS ANTIDEPRESSANTS IN THE ELDERLY

Antidepressants drugs currently available differ in their potential for drug interactions, as summarized in Table 3. For more comprehensive information, the reader is referred to earlier reviews of drug interactions involving older and newer antidepressants [13, 28-34].

Table 3. Comparison of the potential for drug interactions among various classes of antidepressants in the elderly.

Antidepressant drugs	Potential for drug interactions in the elderly
Monoamine oxidase inhibitors	- elevated risk of potentially fatal pharmacodynamic interactions, particularly with tyramine-rich foods, sympathomimetic drugs and other antidepressants
Tricyclic antidepressants	- susceptible to enzyme inhibition by inhibitors of CYP2D6 (affecting mainly hydroxylation) and by inhibitors of CYP1A2, CYP2C19 and CYP3A4 (affecting mainly demethylation) and to enzyme induction by various anticonvulsants - high potential for pharmacodynamic interactions, particularly with anticholinergic drugs and medications affecting the central nervous and the cardiovascular system
Selective serotonin reuptake inhibitors	- differential inhibition at selective CYP isoenzymes fluoxetine potently inhibits CYP2D6 and moderately CYP2C9 and CYP3A4 paroxetine potently inhibits CYP2D6 fluvoxamine potently inhibits CYP1A2 and CYP2C19 and moderately CYP2C9 and CYP3A4 sertraline is a weak to moderate inhibitor of CYP2D6 citalopram/escitalopram are weak inhibitors of CYP isoenzymes - low potential for pharmacodynamic interactions, but possible involvement in pharmacodynamic interactions with other serotonergic drugs (serotonin syndrome) and increased risk of bleeding with nonsteroidal anti-inflammatory drugs, corticosteroids, oral anticoagulants and antiplatelet drugs (including low-dose aspirin)
Serotonin and noradrenaline reuptake inhibitors	- duloxetine is a moderate inhibitor of CYP2D6 - low potential for pharmacodynamic interactions, but possible involvement in pharmacodynamic interactions with other serotonergic drugs (serotonin syndrome)

Monoamine Oxidase Inhibitors (MAOIs)

Monoamine oxidase inhibitors (MAOIs) are rarely used today in the treatment of depression due to their high potential for severe pharmacodynamic interactions [28, 29]. Potentially fatal hypertensive crises may occur when nonselective MAOIs are coadministered with foods containing tyramine or other pressor amines, sympathomimetic agents and TCAs [28]. In addition, a serious and life-threatening toxic reaction, known as “serotonin syndrome” has been reported in patients receiving nonselective MAOIs in combination with highly serotonergic drugs such as an SSRI, clomipramine or tryptophan [35].

Tricyclic antidepressants (TCAs)

Despite proven efficacy, tricyclic antidepressants (TCAs) are generally reserved as alternative agents for treating late-life depression [2-4]. The clinical use of TCAs in the elderly may be particularly problematic due to their anticholinergic, sedative and cardiovascular side effects. Among cardiovascular adverse events, orthostatic hypotension is of particular concern in the elderly as it may lead to falls and hip fractures, cerebrovascular accidents and myocardial ischaemia. Moreover, TCAs have a relatively narrow therapeutic index as a result of dose- and concentration-dependent central nervous system and cardiac toxicity. In addition to tolerability and safety problems, the use of these agents in geriatric patients is further complicated by a relatively high potential for drug interactions with a variety of concomitantly prescribed medications. TCAs have a variety of pharmacological actions and may therefore interact pharmacodynamically with compounds acting on the same target(s). TCAs inhibit the neuronal reuptake of noradrenaline and serotonin, bind to multiple receptors types (M_1 cholinergic receptors, H_1 -histamine receptors, α_1 -adrenoceptors), and inhibit fast sodium channels. Based on this, TCAs should be avoided or used with extreme caution in elderly patients treated with anticholinergics and with drugs affecting the central nervous and cardiovascular systems [6, 13]. Concomitant administration of TCAs with other medications possessing antimuscarinic activity, such as phenothiazines and antiparkinsonian agents, may induce additive central and peripheral anticholinergic effects, including memory impairment, dry mouth, blurred vision and constipation. In geriatric patients, the interaction could also precipitate confusional states, acute glaucoma, adynamic ileus and urinary retention. TCAs may potentiate the sedative effects of alcohol and other central nervous system (CNS) depressants such as barbiturates, benzodiazepines, antihistamines, and antipsychotics, thereby impairing psychomotor and cognitive function, particularly dangerous in an elderly population. Undesirable interactions may also occur when TCAs are used in combination with a variety cardiovascular drug (e.g. antiarrhythmics, antihypertensives and

oral anticoagulants). TCAs are also susceptible to clinically relevant pharmacokinetic interactions when coprescribed with substantial inhibitors of CYP enzymes involved in their biotransformation [36]. These include CYP_{1A2} inhibitors such as fluvoxamine and ciprofloxacin, CYP_{2D6} inhibitors such as quinidine, fluoxetine, paroxetine and bupropion, and CYP_{3A4} inhibitors such as nefazodone, some azole antifungals and some macrolide antibiotics [37]. Inhibition of CYP enzymes may cause an increase in plasma concentrations of TCAs, possibly resulting in serious adverse reactions, such as anticholinergic effects, arrhythmias, convulsions and delirium. These effects are presumably more common and more serious in elderly patients because of age related changes in pharmacokinetics and pharmacodynamics. By contrast, co-administration with enzyme inducers, namely various anticonvulsants, may lead to decreased concentrations of TCAs and, therefore, attenuate their effects.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Owing to their efficacy, good tolerability and relative safety, the selective serotonin reuptake inhibitors (SSRIs) have become the most frequently prescribed antidepressants. The published clinical evidence suggests that SSRIs are first-line agents for treating geriatric depression [2-4]. The use of SSRIs in the elderly is associated with the possibility of clinically relevant pharmacokinetic interactions with other medications due to their inhibitory effect on CYP enzymes. The differential effects of various SSRIs on CYPs are well characterized *in vitro* [37, 38]. The various SSRIs available differ considerably in profiles with regard to inhibition of CYP enzymes *in vitro* and this may guide selection of an appropriate compound in the individual patient (Table 2). Based on this, it would appear that the potential for individual SSRIs to interact with other drugs is greater for fluvoxamine, fluoxetine and paroxetine and lower for sertraline, citalopram and escitalopram. In view of these considerations, caution is required when adding an SSRI to a multi-drug regimen in the elderly. In fact, as the inhibitory effect on CYPs is concentration dependent, the potential for drug interactions is presumably higher in the elderly, especially for compounds whose elimination is affected by age, such as citalopram and paroxetine, and for those which exhibit nonlinear kinetics, such as fluoxetine and paroxetine [6]. For drugs with long half-lives, e.g. fluoxetine and its active metabolite, the interaction potential may persist for weeks after treatment discontinuation. Conversely, it is unlikely that other drugs may cause clinically relevant changes in the pharmacokinetics of SSRIs. Substantial inhibitors or inducers of CYPs responsible for the biotransformation of the various SSRIs may affect their elimination leading to modifications in plasma concentrations. However, as these drugs have a wide therapeutic index, the consequences of these changes are unlikely

to be clinically relevant [30]. Due to their selective mechanism of action, SSRIs are usually considered at relatively low risk for pharmacodynamically mediated interaction. However, SSRIs may interact adversely with other drugs affecting serotonergic transmission, such as MAOIs, TCAs, triptophan, with possible occurrence of a potentially fatal serotonin syndrome [35]. According to postmortem forensic investigation, elderly patients, particularly those with atherosclerotic cardiovascular disease or preexisting heart disease, appear to be at high risk for this syndrome [39]. In addition, recent epidemiological evidence suggests that SSRI use is associated with an increased incidence of upper gastrointestinal bleeding. The prevention of serotonin uptake of from circulation into platelets induced by SSRIs, leading to reduced platelet aggregation and prolonged bleeding time, may be the underlying biological mechanism for this effect. Patients at particular risk of gastrointestinal bleeding include elderly persons and subjects receiving other bleeding risk-increasing medications such as nonsteroidal anti-inflammatory drugs, corticosteroids, oral anticoagulants and antiplatelet drugs (including low-dose aspirin) [40]. Examples of potentially clinically significant interactions between SSRIs and other medications commonly used in the elderly are given below. SSRIs are frequently prescribed in combination with other CNS drugs. Patients with depression refractory to treatment with a single agent are sometimes tried on combination therapy. While this practice may prove therapeutically advantageous in selected cases, its potential benefits should be weighed against the risk of adverse effects resulting from a wide range of interactions. Apart from the possibility of a serotonin syndrome when coadministered with other serotonergic antidepressants, various SSRIs may cause a remarkable elevation of plasma TCAs levels, through inhibition of CYPs [6, 13]. Concomitant administration of SSRIs with novel antipsychotics is relatively common, but may occasionally result in clinically important interactions. In this respect, paroxetine and fluoxetine have been reported to produce a clinically relevant increase in plasma concentrations of risperidone, presumably through inhibition of CYP2D6, whereas fluvoxamine may cause a significant elevation of plasma concentrations of clozapine and, to a lesser extent, olanzapine which are both substrates of CYP1A2 [41-45]. Compared with TCAs, SSRIs are less likely to produce additive CNS depressant effects when taken together with benzodiazepines and other CNS depressants. Fluvoxamine has been reported to inhibit the CYP1A2-mediated metabolism of tacrine, a cholinesterase inhibitor used for the treatment of Alzheimer's dementia, possibly increasing its hepatotoxicity [46]. Clinically relevant drug interactions between SSRIs and drugs used to treat concomitant cardiovascular disorders, in particular oral anticoagulants, beta-blockers and digoxin, have been occasionally documented in elderly patients. Case reports and literature reviews have suggested that SSRIs,

in particular fluvoxamine and fluoxetine, may interact with the oral anticoagulant warfarin to cause bleeding [47-51]. SSRIs may increase the risk of hemorrhage during warfarin treatment by two mechanisms. First, SSRIs may reduce platelet aggregation by depleting platelet serotonin levels, directly increasing the risk of bleeding, as earlier mentioned [40]. Second, some SSRIs, particularly fluvoxamine and fluoxetine, may inhibit the CYP_{2C9}-mediated oxidative metabolism of the more biologically active (S)-enantiomer of warfarin [50, 51]. However, a recent population study has not (failed to) documented a significant risk of gastrointestinal bleeding in elderly patients taking warfarin who had recently started a treatment with various antidepressants including fluoxetine and fluvoxamine [52]. Coadministration of fluoxetine with metoprolol or propranolol has occasionally resulted in serious adverse events such as bradycardia or heart block [53, 54]. Inhibition of CYP_{2D6}-mediated oxidative metabolism of beta-blockers by fluoxetine is the most likely explanation for this interaction. Isolated case reports have described a remarkable elevation of serum digoxin concentrations along with signs of toxicity in elderly patients after coadministration of fluoxetine or paroxetine [55, 56]. With regard to this, a large population-based, case-control study, in elderly patients has documented a slightly increased risk of hospital admissions for digoxin toxicity following initiation of SSRI therapy with no difference among the various compounds [12]. Interestingly, a similar risk was also found with TCAs or benzodiazepines compounds with no known pharmacokinetic interactions with digoxin. Finally, few cases of theophylline toxicity have been reported in elderly patients following addition of fluvoxamine [57, 58]. The potent inhibitory effect of fluvoxamine on CYP_{1A2}, main isoenzyme involved in theophylline metabolism, provides an explanation for this interaction.

Serotonin and noradrenaline reuptake inhibitors

Venlafaxine and duloxetine are serotonin and noradrenaline reuptake inhibitors (SNRIs). As SSRIs, they have a low affinity for multiple receptors. While venlafaxine has a weak inhibitory effect on the activity of the various CYP enzymes, duloxetine is a moderate inhibitor of CYP_{2D6} [59]. As a precaution, elderly patients taking duloxetine in addition to substrates of CYP_{2D6} with a narrow therapeutic index should be carefully monitored. Like all antidepressants that inhibit serotonin reuptake, SNRIs may interact pharmacodynamically with other serotonergic compounds and cause a “serotonin syndrome”.

Other antidepressants

Mirtazapine

Mirtazapine is a dual-action antidepressant whose effect appears to be related to the enhancement of central noradrenergic and serotonin 5-HT₁ receptor-mediated serotonergic neurotransmission. Mirtazapine is a weak inhibitor of the various CYP enzymes and has a very low potential for pharmacokinetic interactions with other drugs [60]. However, given its affinity for histaminergic receptors, mirtazapine may potentiate the sedative effects of coprescribed CNS depressants.

Reboxetine

Reboxetine is a selective noradrenaline reuptake inhibitor and it has a low affinity for cholinergic, histaminergic and α_1 -adrenergic receptors. Due to its weak inhibitory affinity for CYPs enzymes, it is unlikely that reboxetine may cause clinically significant pharmacokinetic interactions with other medications. On the other hand, due to the potentiation of noradrenergic neurotransmission, reboxetine should be used with caution in elderly patients in association with cardiovascular drugs [34].

Bupropion

Bupropion is an antidepressant which inhibits the neuronal reuptake of noradrenaline and dopamine. Its metabolism is not completely characterized, but one of its active products is metabolized by CYP2D6. In vitro and in vivo studies have shown that bupropion is a moderate inhibitor of CYP2D6 [34]. As bupropion increases dopaminergic activity the potential exists for interactions with other dopaminergic agents.

St. John's wort (Hypericum perforatum)

St. John's wort (*Hypericum perforatum*) is one of the most commonly used herbal antidepressants. This herbal extract, available in several countries as a dietary supplement, is effective in mild-to-moderate depression and has an encouraging safety profile [20, 21]. As with other natural products, St. John's wort is increasingly used in the elderly [62]. Recent evidence indicates that St. John's wort is a potent inducer of CYP3A4 (and possibly other CYPs) and P-glycoprotein and may therefore be involved in clinically relevant interactions with prescribed drugs [63, 64]. In this respect, interaction studies and case reports have documented that St. John's wort may cause a remarkable decrease in plasma concentrations of a number of medications including amitriptyline, cyclosporine, digoxin, indinavir, irinotecan, methadone, simvastatin, tacrolimus, theophylline, warfarin and

oral contraceptives, thereby reducing their efficacy. In addition, combined use of St. John's wort with serotonergic antidepressants (e.g. sertraline, paroxetine, nefazodone and venlafaxine) may result in symptoms characteristic of serotonin syndrome, presumably to a central pharmacodynamic mechanism [20, 21].

PREVALENCE OF CLINICALLY RELEVANT ANTIDEPRESSANT DRUG INTERACTIONS IN THE ELDERLY

From a public health perspective the issue of antidepressant drug interactions in the elderly is of great clinical relevance if we consider that the number of prescriptions of these compounds is generally growing in the population, particularly in old age [65]. In this respect, newer antidepressants are often used to treat psychiatric conditions other than depression (e.g. anxiety disorders) and are increasingly prescribed among general practitioners [66]. Moreover, the recommended duration of treatment tend to increase so thus elevating the likelihood of coprescription with other medications. Based on these considerations, drug interactions with antidepressants are certainly common in the elderly. However, the prevalence of clinically important interactions is not well documented. While the risk of potentially harmful drug interactions is well recognized with older antidepressants and has contributed to a gradual decline in their utilization in psychiatric practice, the clinical significance of drug interactions with newer compounds remains poorly defined despite millions of exposures. The question of the prevalence of clinically relevant drug interactions involving antidepressants has been debated in recently published articles [67, 68]. According to De Vane [67], antidepressant drug interactions are potentially, but rarely clinically significant. With regard to this, major concern about drug interactions with newer antidepressants derives from the possibility that SSRIs as well as other recently marketed compounds may cause pharmacokinetic interactions through their *in vitro* ability to inhibit various CYPs. These metabolically-based interactions may be easily predicted from *in vitro* studies. However, the current models for extrapolation of *in vitro* data to the *in vivo* situation have several limitations, so not all of them will occur in clinical practice [69]. Moreover not all inhibitory drug interactions occurring *in vivo* are clinically significant. Various factors may contribute to minimize their clinical consequences including compensatory mechanisms (e.g. the presence of alternative metabolic pathways) and a wide therapeutic index of the affected drug. Indeed, evidence for some antidepressant drug interactions is based on anecdotal case report or extrapolation of the results of pharmacokinetic studies conducted in healthy volunteers to patients. Consistent with this, epidemiological

and post-marketing surveillance data do not confirm a high prevalence of serious antidepressant-induced drug interactions [67].

Although clinically important interactions with newer antidepressants are likely to be unusual and severe adverse interactions are presumably rare events, it should be emphasized that elderly patients represent a population at risk for drug interactions. For the reasons earlier reported, the clinical consequences of a drug combination may be amplified in old age. Therefore, even if the risk is not well documented at epidemiological level, the choice of a pharmacological agent with a low potential for drug interactions appears as the most rational strategy in the elderly.

PREVENTION AND MANAGEMENT OF ANTIDEPRESSANT DRUG INTERACTIONS IN THE ELDERLY

Preventing the use of medications where there is the potential for serious drug interactions or minimizing their clinical manifestations is essential to ensure patient safety. Some general recommendations may be given to prevent or minimize the occurrence of adverse drug interactions in elderly patients with depression.

- The need for multiple drug therapy should be continuously evaluated and drugs that are no longer needed should be discontinued.
- Basic understanding of the mechanisms of drug interactions and the various factors predisposing elderly patients to adverse drug interactions may be useful for safe prescribing.
- Knowledge of the interaction potential of individual agents (especially with respect to pharmacodynamic effects and inhibition of CYP isoenzymes) may guide selection of an appropriate compound which is less likely to interfere with already taken medication(s).
- Clinical manifestations of most drug interactions, in particular those with a pharmacokinetic mechanism, can be prevented or compensated for by appropriate dosage adjustments based on clinical observation. Each elderly patient should be treated individually and monitored carefully during antidepressant therapy.

Correct and comprehensive information is a prerequisite for both prevention and adequate management of drug interactions. However, despite the relevant burden of drug-drug interactions, particularly in elderly population, prescribing physicians seem to be generally unaware of potential risks associated with concomitant prescription of medications that are frequently used in general practice,

as many newer antidepressants. A plausible explanation to such a poor awareness about drug interactions among health professionals might be related to the fact that current information provided to clinicians through standard information sources appear to be inconsistent, incomplete and outdated, in some cases reflecting scientific uncertainty and lack of documentation. The Summary of Product Characteristics (SPC) is the primary source of information concerning potential drug-drug interactions for health care professionals. However, due to obvious space limitations, potential drug-drug interactions cannot be listed exhaustively and critically evaluated for their clinical relevance. In this respect, a very low agreement on the risk for clinically relevant drug interactions has been reported between the SPC and other standard drug-related information sources such as the Drugdex System (Thomson Micromedex, Greenwood Village, Colo) [70]. Apart from accuracy and coherence of information sources, another critical issue is how to provide health professionals with wise and updated information on drug interactions. Potential intervention strategies, targeted to adequately supply prescribers with information on the risks of clinically relevant drug-drug interactions may be represented by computerized drug interaction alerts and active participation of pharmacists [71]. There is good evidence that electronic decision support systems, such as automated drug interaction alerts, being immediately integrated in the prescribing process, can dramatically increase clinicians' recognition of interacting drug pairs (including antidepressant drugs) by upward to 50%, thus leading to reduce the number of prescriptions with potentially hazardous combinations [72-73]. Finally, the pharmacists might have a predominant role in the management of drug-related issues, including drug-drug interactions, through screening, prevention and education strategy that are addressed to general population, in collaboration with physicians and other health professionals. Consistent with this, some studies have documented the effective contribution of pharmacists to the management of drug therapies in patients with depression both in primary care and hospital settings [74-75].

CONCLUSION

Drug treatment of depression in old age is associated with an increased risk of adverse pharmacokinetic and pharmacodynamic drug interactions. Due to comorbid medical conditions, elderly patients often take many medications simultaneously. In addition to polypharmacy, age-related physiological changes may modify drug response and, therefore, predispose elderly subjects to adverse effects and drug interactions. The risk of potentially harmful drug interactions is well documented

with older antidepressants and has contributed to a gradual decline in their utilization in clinical practice. By virtue of a more selective mechanism of action, newer antidepressants have a relatively low potential for pharmacodynamic drug interactions. However, the possibility of the serotonin syndrome should be taken into account when drugs affecting serotonergic transmission, such as SSRIs or SNRIs are coadministered with other serotonergic agents. On the other hand, newer agents have a differential potential for pharmacokinetic interactions due to their inhibitory effects on various CYP enzymes. Within the group of SSRIs, fluoxetine and paroxetine are potent inhibitors of CYP2D6, while fluvoxamine inhibits markedly CYP1A2. Duloxetine and bupropion are moderate inhibitors of CYP2D6. Although metabolic interactions with antidepressants are rarely involved in serious toxicity, are often predictable and can be managed by standard clinical practice, the use antidepressants with low inhibitory activity on different CYP enzymes appears particularly suitable in an elderly population. Correct and comprehensive information is a prerequisite for both prevention and adequate management of drug interactions with antidepressants in the elderly.

FUTURE PERSPECTIVE

With the progressive aging of the population, late-life depression is likely to become more and more important as a public health problem and prescriptions of antidepressants will presumably grow so thus increasing the likelihood of drug interactions. In recent years, different *in vitro* techniques have been developed and have become widely used as screening tools to predict potential for metabolic drug interactions before a drug reaches the clinical phases of development. Refinement of this methodology will certainly improve the predictive power. This information might be therefore applied not only in drug discovery (through design and selection of new agents devoid of undesirable interaction potential) and in drug development (though rational identification of drug interactions to be assessed in the clinical setting), but also in making informed decisions when adding or withdrawing comedications in routine clinical practice. Systematic studies are needed to test the clinical relevance of drug interactions and the complex nature of multiple medication use in routine clinical practice. In this respect, epidemiological studies and large post-marketing database are the most clinically relevant guide to drug combinations likely to cause adverse reactions. Correct and comprehensive information is a prerequisite for both prevention and adequate management of drug interactions. Intervention strategies to prevent potentially harmful drug interactions both in primary and secondary have been developed

including computerized drug interaction alerts and active participation of pharmacists. Future research should focus on improving these strategies in accurately and precisely identifying adverse drug interactions in the elderly.

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CHAPTER 4

Anti-Parkinson drugs in elderly: use and safety



4.1. Prescribing pattern of Anti-Parkinson drugs in Southern Italy: cross-sectional analysis in the years 2003-5

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ABSTRACT

Aim of this study was to evaluate prevalence of use and prescribing pattern of Anti-Parkinson Drugs (APDs) in general practice of Southern Italy. Among 120,000 individuals registered in the lists of 93 general practitioners of Southern Italy, we estimated one-year prevalence and incidence of APD use in the years 2003-2005. Overall, prevalence of APD use remained stable over the years and it strongly increased in subjects over 70 years of age. L-Dopa with a dopa decarboxylase inhibitor was the most frequently prescribed APD, although the use of both ergot and non-ergot derivative DAs has increased, particularly, in the elderly. A high proportion of APD users (15-20%) received only one prescription during the study period.

INTRODUCTION

Parkinson's disease (PD) is a chronic neurodegenerative disorder, with an estimated prevalence ranging from 66 to 257 per 100,000 inhabitants in Italy [1,2]. To date, Levodopa (L-Dopa) has been largely demonstrated to be the most effective drug in Parkinson's disease (PD) treatment, although this medication is associated with limiting and poorly tolerated motor and non-motor side effects, particularly, in the advanced stages of the disease [3]. Other anti-Parkinson drugs (APDs) are commonly used in clinical practice either as monotherapy or as adjunctive therapy with L-Dopa, to delay or reduce its motor and non-motor complications and to maximise drug effectiveness [4-6]: dopamine agonists (ergot and non-ergot derivatives), anticholinergic drugs, amantadine, selegiline and catechol-O-methyltransferase (COMT) inhibitors. When they were first introduced, the indication for dopamine agonists (DAs) was as adjunctive therapy with L-Dopa in advanced PD, with the aim of reducing dyskinesias, by decreasing L-Dopa daily dosage [7]. In the last decade, however, these medications have been increasingly used as monotherapy in early PD to delay the start of L-Dopa treatment [8,9]. Dopamine agonists are divided into ergot and non-ergot-derivative medications. Ergot-derivatives, pergolide and cabergoline are also used to treat hyperprolactinemic disorders, while non-ergot derived pramipexole and ropinirole are also approved for use in restless leg syndrome [10]. Since 2002, however, a number of case reports and observational studies have highlighted the risk of valvular heart disease associated with ergot-derivative DA use [11-13]. Anticholinergic drugs are not widely prescribed in PD, with the exception of young onset tremor dominant PD, due to the high frequency of adverse drug reactions (ADRs), like xerostomya, urinary retention, confusional state, hallucinations and cognitive impairment, mostly in older people [14]. Amantadine is NMDA-receptor antagonist that shows a good efficacy in reducing L-Dopa-induced dyskinesia [15], while selegiline is an irreversible MAO-B inhibitor with symptomatic effect in 10% of *de novo* patients [16]. The most recently marketed APDs are COMT inhibitors that are used in combination with L-Dopa [17]. During the last decade, several studies have been performed to explore anti-Parkinson drug utilization in different settings [18-21]; however, the majority estimated prevalence of PD using the drug tracer methodology [19,20]. In an Italian cross-sectional study [18], L-dopa was the most commonly used APD (but in association with other APDs in older onset idiopathic PD), followed by dopamine agonists and anticholinergic agents. Apart from this study, recent investigations aimed at assessing APD prescribing patterns in Italy are lacking. This investigation was performed to measure the prevalence of APD use and to analyse the prescribing pattern of these medications in general practice in the south of Italy.

METHODS

Data source

Data were extracted from the Arianna database during the years 2003-2005. This database was set up by the Local Health Agency of Caserta in the year 2000. It currently contains information on a population of almost 300,000 individuals living in the catchment area of Caserta and registered in the lists of 225 general practitioners (GPs). This sample of physicians accounts for 73.7% (225/305) of the total number of GPs who practice in the same area. Participating GPs record data during their daily clinical practice through dedicated software, and, once a month send complete and anonymous data concerning their patients to the Arianna Database. Information collected includes patient demographics, drug prescriptions (reimbursed by Health National System) coded according to the Anatomical Therapeutic Chemical (ATC) classification system, and medical diagnoses coded by the ninth edition of International Classification of Diseases (ICD-9). All participating GPs received extensive training in data collection techniques. A number of data quality checks are routinely performed, including the analysis of several parameters such as missing patient codes, the number of prescriptions filled daily and the regularity of their monthly of data submission. Any variation within defined ranges is investigated and returned to each participating GP, in order to receive immediate feedback about data quality and completeness. GPs failing to meet these standard quality criteria are dropped from epidemiological investigations, according to basic standards in the conduct of pharmaco-epidemiological studies [22]. So far, the Arianna database has been shown to provide accurate and reliable information on drug utilization [23-25].

Study population

Ninety three GPs that regularly sent data to the Arianna database during the years 2003-2005 were selected for this study. Among 119,393 individuals registered in their lists at 30 December 2005, users of Anti-Parkinson Drugs (APDs) were identified; these were defined as individuals receiving at least one APD (ATC: N04) prescription during the study period. Patients were included in the study irrespective of whether APD treatment was initiated by GPs or by specialists working either in the public or private sector, leading in this case thereafter, to prescriptions provided by GPs that is the most common situation with APDs. Indeed in Italy, outpatients receiving prescriptions from specialists in the public or private sector subsequently receive their drugs free of charge through prescriptions the are provided by GP. The following cohorts of APD users were identified according to the drug type that was used: (1) Levodopa, alone or in combination

with Dopa Decarboxylase Inhibitor (DDCI); (2) Ergot derivative dopamine agonists (bromocriptine, pergolide and cabergoline); (3) Non-ergot derivative dopamine agonists (pramipexole and ropinirole) and (4) Anticholinergic agents (trihexyphenidyl, biperidene, metixene, procyclidine and bornaprine). Other APDs, such as selegiline, COMT inhibitors, amantadine and apomorphine were not included in the analysis since either the National Health System does not reimburse them in Italy or, alternatively, these medications are dispensed directly in hospital setting, thus bypassing general prescription. After identification of APD users, the following information was retrieved using the Arianna database: patients' demographics, APD prescription data (including product name, dispensed quantity and indication of use) recorded during the years 2003-5. The first APD prescription date was considered as index date.

Outcome definition

Annual prevalence of APD treatment was calculated, overall and by drug type, as the number of APD users per year divided by the number of subjects alive and registered in the GPs' lists during the observation years.

We defined "new user" as a patient receiving a first APD prescription during the years 2004 or 2005, without any recorded APD prescription in the previous year. One-year incidence of APD use was measured as the number of "new users" divided by the number of subjects who did not receive an APD prescription in the previous year. Both prevalence and incidence were calculated for APDs, overall and by drug type, and were expressed as rates per 100,000 inhabitants, together with 95% Confidence Interval (CI).

An analysis was performed to specifically evaluate APD prescribing pattern in treatment of PD, taking into account only those patients who received more than one APD prescription during the study period with a medical diagnosis of idiopathic, secondary or unspecified PD. Within each drug type, the proportion of patients that was treated with monotherapy or add-on therapy with different APD classes was evaluated separately.

Statistical analysis

Chi-Square test for categorical variables and Student t-test for continuous variables, with a significance level of $P < 0.05$, were used for assessing the differences among users of various APD types at the index date. Statistical analyses were performed using STATA 6.0 (STATA Corporation, Texas, USA).

RESULTS

In Table 1, main characteristics of APD type users are described. As expected, Levodopa (plus a DDCI) was the most frequently used APD (620 patients) during the study years, followed by anticholinergic drugs (434). Users of these last medications were significantly younger ($p < 0.05$) compared to other APD users. Use of any APD type was equal between the sexes and no differences were shown among various APD classes.

Table 1. Characteristics of APD users (at least 1 prescription) within the study years

Variables	L-Dopa N= 620	Ergot derivatives DA N= 211	Non-Ergot derivatives DA N= 214	Anticholinergic agents N= 434
Median age, years	78	72	73	56
Gender (%)				
Males	300 (48.4)	97 (46.0)	103 (48.1)	221 (50.9)
Females	320 (51.6)	114 (54.0)	111 (51.9)	213 (49.1)
N. User of APD Px*(%)				
1 Px	92 (14.8)	41 (19.4)	14 (6.5)	90 (20.7)
2 Px	48 (7.7)	14 (6.6)	5 (2.3)	58 (13.4)
3 Px	29 (4.7)	5 (2.4)	7 (3.3)	34 (7.8)
>3 Px	451 (72.7)	151 (71.6)	188 (87.9)	252 (58.1)

Legend: DA= dopamine agonists. Use of different drug types is not mutually exclusive.

* In this analysis, APD users have been stratified by the number of APD prescriptions (Px) that they received within study years.

A relatively high proportion of APD users received only one prescription during the study years: 20.7% of anticholinergic agent users, 19.4% of ergot derivatives DA users and slightly lower proportion (14.8%) of Levodopa (plus a DDCI) users. On the contrary, the proportion of non-ergot derivative DA user receiving only one prescription within study years was very low (6.5%).

Overall, prevalence of APD use appeared to be stable over the years (in 2005: 601 per 100,000 inhabitants; 95% Confidence Interval: 559.1-646.9), with a strikingly increasing trend in advanced age: 2,142 (1,963-2,337) per 100,000 in subjects older than 65 years, in 2005 (Figure 1).

However, after excluding anticholinergic agents from the analysis, the prevalence of APD use significantly decreased in each study year: 392 (358-439) per 100,000 in 2005.

The one-year prevalence of use of APD classes is reported in Figure 2. The prevalence of use of L-Dopa (plus a DDCI) was markedly higher than other APD classes and it did not change during the study years: 307 (278-340) per 100,000 inhabitants in 2005.

Figure 1. Prevalence of APD use per 100,000 inhabitants, stratified by age groups and calendar years.

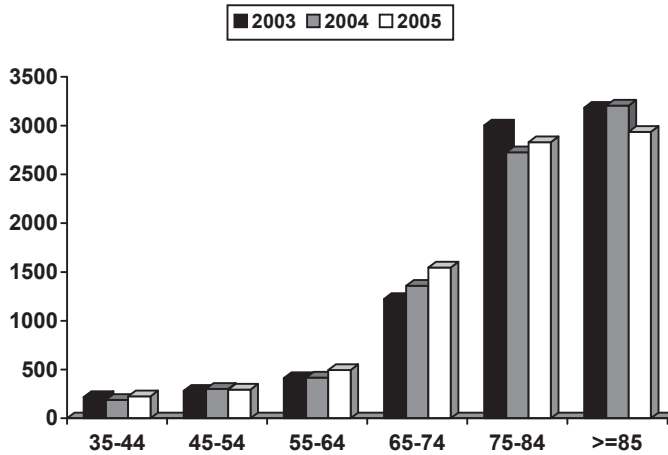
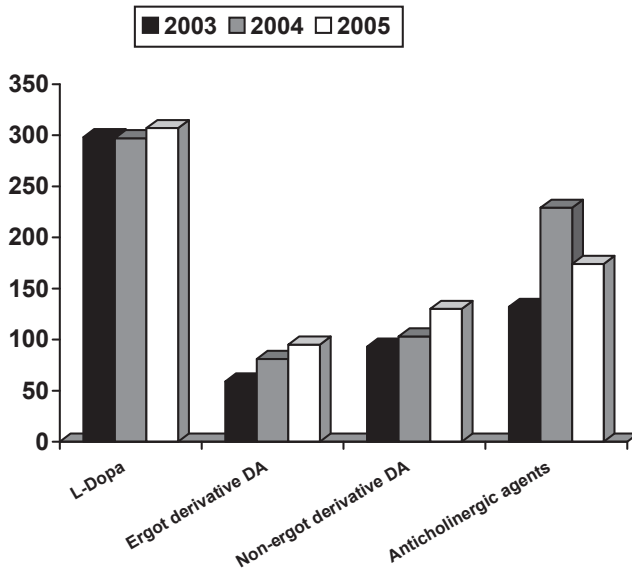


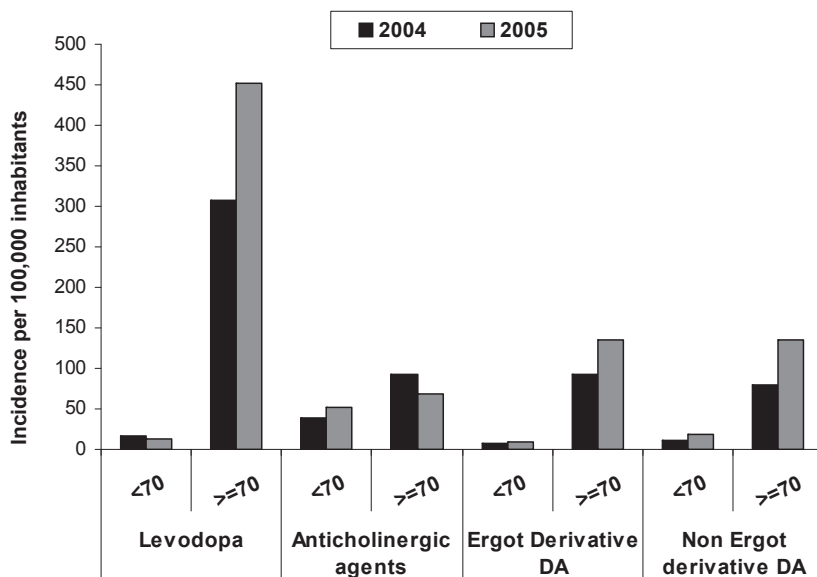
Figure 2. Prevalence of APD use[^] per 100,000 inhabitants, due to Parkinson's disease or Parkinsonism, stratified by drug types and calendar years.



[^] In this analysis, only patients receiving more than 1 APD prescription have been included.

On the other hand, prevalence of use of both ergot and non-ergot derivative DA continuously increased during the study years, going from 59 (47-74) per 100,000 in 2003 to 95 (79-114) in 2005, and from 93 (77-112) to 130 (111-152).

A peculiar trend in the prevalence in the use of anticholinergic agents was shown during the study period, with a peak in 2004: 229 (203-258) per 100,000.

Figure 3. One-year incidence of treatment[^] with APD in the years 2004-2005, stratified by drug type, age groups and calendar year.

[^] In this analysis, only patients receiving more than 1 APD prescription have been included.

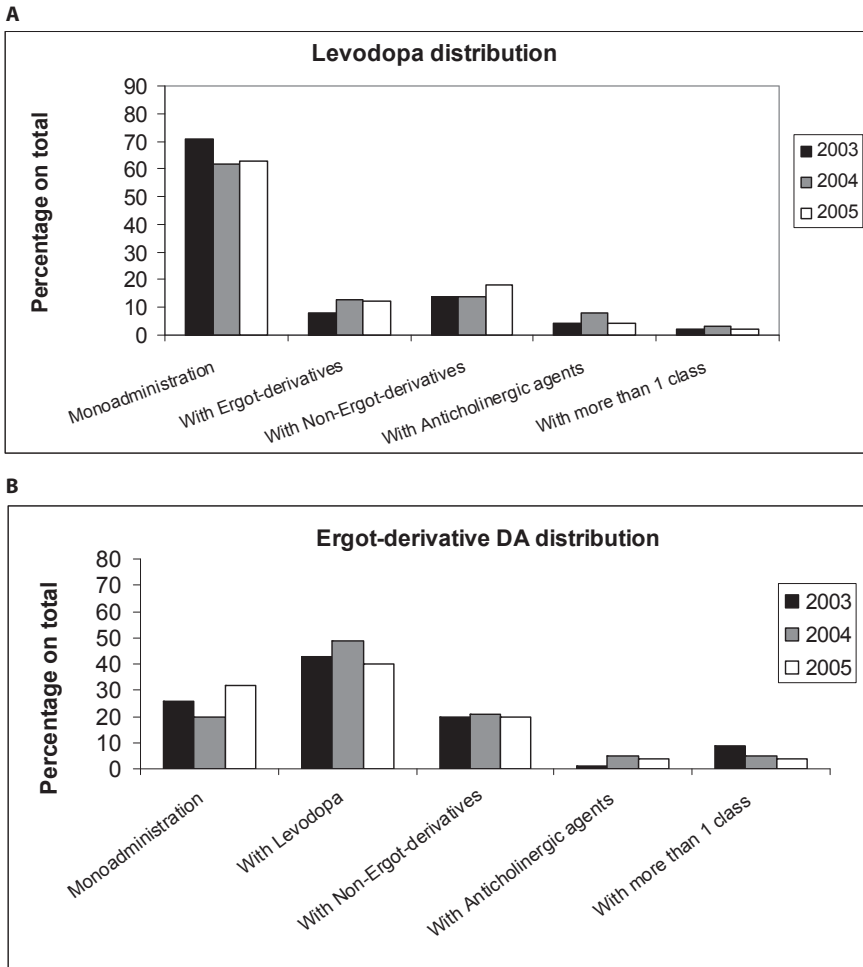
Compared to 2004, the prevalence of anticholinergic agents decreased, particularly in patients over the age of 70 years in 2005 (308, 232-409 vs 446, 353-565), while it was reduced to a lesser extent in those ≤ 70 years old: 155 (133-180) versus 196 (171-225).

The one-year incidence of treatment with different APD types in the years 2004-2005, stratified by age groups, is reported in **Figure 3**. One-year incidence of APD use was, 113 (96-134) per 100,000 inhabitants in 2004 and 161 (140-185) in 2005. With the exception of anticholinergic drugs, rates of new treatment with APD were very low in patients <70 years old during the observation years.

In older patients, the highest incidence of use was reported for L-Dopa (plus a DDCI) that markedly increased from 2004 (307 per 100,000; 95% CI: 232-404) to 2005 (453; 360-569). Even though the incidence of L-Dopa (plus a DDCI) use more than doubled, compared to ergot and non-ergot derivative DA, new treatments with these medications seemed to increase moderately during the study years, as well.

The prescribing pattern of different APD types did not change remarkably during the study years, as shown in Figures 4 a-d. Among L-Dopa (plus a DDCI) users, however, a reduction of monotherapy use (71% in 2003 vs. 63% in 2005) is highlighted, partly due to the increased proportion of patients that are more recently being treated using combined therapy with an ergot-derivative DA (8% in 2003 vs. 12% in 2005) and non-ergot derivative DA (14% in 2003 vs. 18% in 2005).

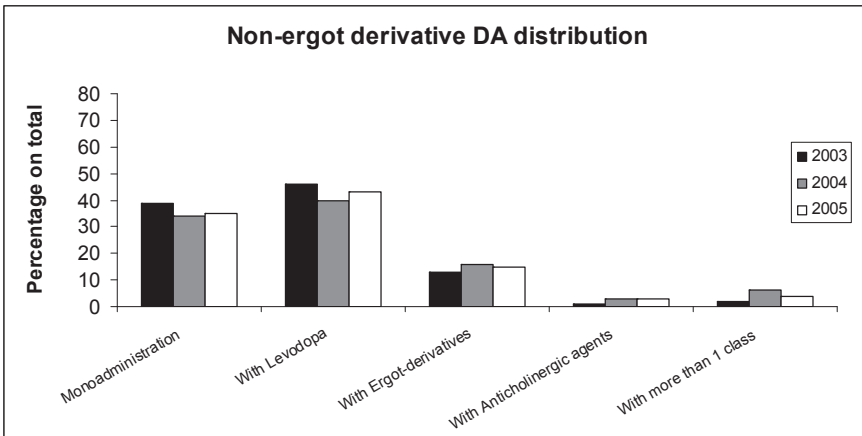
Figure 4 a-d. Prescribing pattern* of L-Dopa (a), ergot derivative DA (b), non-ergot derivative DA (c) and anticholinergic agents (d), stratified by calendar year



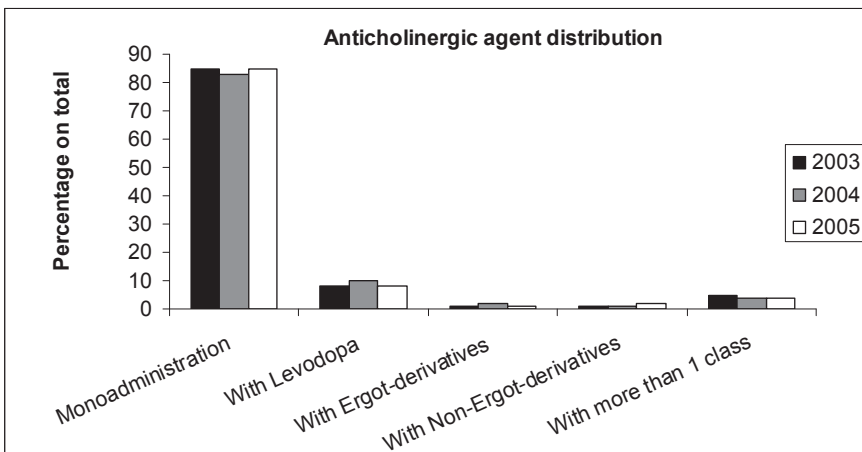
With regard to dopamine-agonists, almost 50% of both ergot and non-ergot derivative users received concomitant treatment with L-Dopa (plus a DDCI), while the remaining proportion was treated with these medications as monotherapy or with both DA subtypes.

With regard to anticholinergic agents, almost 90% of users were treated as monotherapy, with the remaining proportion of patients being treated mainly with combined treatment with Levodopa.

C



D



*In this analysis, only patients receiving more than 1 APD prescription, have been included. Combination with other drug types was defined as at least 1 prescription of APD and 1 of other drugs belonging to different APD types that were registered within 3 months period.

DISCUSSION

To our knowledge this is the first observational study that was targeted to explore the pattern of use of anti-Parkinson drugs in Southern Italy. Earlier Italian analyses [18, 26-28] looked primarily at APD use as drug tracer to estimate PD prevalence.

Another recent investigation [17] evaluated APD prescribing pattern in Northern Italy and it reported L-Dopa (plus a DDCI) as being the most frequently used APD, followed by dopamine agonists and anticholinergic agents, in agreement with our results.

A crude prevalence of 257 per 100,000 for PD was estimated in an area of Southern Italy through a door-to-door survey [2]. In our study, we calculated a prevalence of APD use of 601 per 100,000 (95% CI: 559-647). Large use of APD for indications other than PD, particularly with regards to anticholinergic drugs, might partly explain such a difference. It is well known that anticholinergic agents are prescribed by GPs to treat extrapyramidal side effects induced by other medications, like neuroleptics [29]. Indeed, prevalence of APD use was strongly reduced to 392 (358-439) per 100,000, in our study, after excluding anticholinergic drugs from the analysis.

Moreover, a significant proportion of APD users received only one prescription (about 15%) in our study, in part due to misdiagnosed Parkinsonism or patient's death, thus contributing to the overestimation of the prevalence of APD use. In addition, this finding might suggest that both GPs and specialists commonly prescribe a trial of dopaminergic medications and assess response rather than carry out more complex diagnostic procedures.

An earlier Italian investigation reported that 18% of APD users also only received one prescription [30].

Interestingly, we found that both ergot and non-ergot derivative dopamine agonists were increasingly used during the study years, in line with another European investigation [21]. However, an increased risk of valvular heart disease associated with pergolide and cabergoline use has been reported since 2002 [11,12] and this has also recently been confirmed [13,31].

Concerning the prescribing pattern of anti-Parkinson drugs, some critical points identified in our analysis merit discussion, on the basis of international [32,33] and Italian [34] guidelines for the treatment of PD and parkinsonisms.

As previously mentioned, the use of dopamine agonists, measured as one-year incidence, has been increasing during the last years; however, such an increase related mainly to older people, apparently in contrast with guidelines that suggest DA use at early stage of PD.

On the other hand, more than 20% of DA users were treated concomitantly with ergot and non-ergot derivative medications; such a proportion might be, however, overestimated since we considered a polytherapy as prescriptions of both DA types that were registered within 3 months period.

Anticholinergic drugs were prominently prescribed as monotherapy even though these medications are not recommended in PD treatment due to the high frequency of adverse events, particularly in the elderly; however, the high proportion of patients (about 20%) receiving only one prescription of these medications during the study years would suggest their wide utilization in indications, other than PD [29].

Limitations

Some study limitations warrant caution. First, certain APDs, such as amantadine, apomorphine, COMT inhibitor and selegiline, were not taken into account in this investigation, since either Italian National Health System does not reimburse them or, alternatively, these medications are directly dispensed in hospital setting. In both cases, prescriptions of these medications cannot be retrieved through a general practice database. Second, we used outpatient prescription data and we had no information whether the APD prescriptions were actually filled and taken. This limitation should be taken into account since approximately half of the drugs prescribed for people with chronic conditions are not actually taken [35]. This investigation provides new insight into the APD prescribing pattern in a large Local Health Unit of Southern Italy. Therefore, data may not exactly reflect other Countries or an Italian national trend. Nevertheless, previous investigations [23-25] seem to support comparability and reliability of data derived from this general practice database in conducting drug utilization studies. A further nationwide study might be performed to evaluate the APD prescribing pattern by geographical area in Italy.

In conclusion, the study findings highlight that L-Dopa is strikingly the most widely used anti-parkinson drug in general practice in Southern Italy, in spite of the fact almost 15% of users receive only one prescription. On the other hand, a progressively increasing use of both ergot and non-ergot derivative dopamine agonists has been reported, particularly in older people, during the last years. More attempts should be tried to achieve a widespread diffusion of treatment guidelines on Parkinson's disease and other extrapyramidal disorders also among general practitioners.

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4.2. Burden of Cardiovascular Diseases in Elderly with Parkinson's Disease who Start a Dopamine Agonist Agent

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To the Editor:

Dopamine agonist (DA) agents are widely prescribed in the treatment of Parkinson's Disease (PD). In the last years, some concerns have been raising about the association between the use of pergolide, an ergot-derived DA, and the development of fibrotic valvular heart disease, particularly, when it is administered at high doses over long periods [1]. Recently, two epidemiologic investigations have shown that also another ergot-derived DA, cabergoline, would be associated with an increased risk of heart valvular fibrosis [2-3]. Both ergot derived DAs would induce fibrotic valvular damage through preferential activation of the 5-hydroxytryptamine 2B (5-HT_{2B}) receptor expressed on heart valves, thus inducing a prolonged mitogenic effects in cardiac fibromyoblasts [4]. On the other hand, such a risk would not be increased among patients treated with other Ergot derived DA (bromocriptine and lisuride) and DA that are not ergot derived (pramipexole and ropinirole), since these medications have respectively antagonistic properties and low affinity to the human 5-HT_{2B} receptor [5]. In light of these new scientific evidences, clinicians who decide to start a therapy with ergot-derived DAs in patients with PD should pay more attention to concomitant cardiovascular diseases. To characterise the users of both ergot and not ergot-derived DAs in clinical practice, with particular regard to cardiovascular diseases, we carried out an analysis using a general practice database of Caserta-1 Local Health Unit. Such a database contains all antiparkinson drug prescriptions filled by GPs or by specialists in the catchments area of Caserta. Indeed, outpatients receiving prescriptions in the public or private sector by specialists get the medicines free of charge through GP prescriptions in Italy. Among almost 120,000 subjects registered in the lists of 93 general practitioners enrolled in this database, we selected one-year incident users of ergot- (cabergoline, lisuride, pergolide and bromocriptine) and not ergot-derived DA (pramipexole and ropinirole) that were affected by PD during the years 2004-2005. Incident users were defined as patients receiving at least one DA prescription in the years 2004 or 2005 without any DA prescription recorded in the previous year. Within study sample, we identified all diagnoses of cardiovascular (CV) disease and CV medication prescriptions that were registered prior to the first prescription date of ergot and not ergot-derived DA users. Data on prescriptions and clinical diagnoses are recorded into this database starting from 2002. Therefore, at least two years of observational time prior to first DA prescription date was available to define and characterise all incident users. Overall, 144 and 102 patients with PD that started a therapy with ergot and not ergot-derived DA, respectively, were identified during the study years. Demographic and clinical characteristics of DA agonist users are reported in **Table 1**. Our findings show that almost 70% of incident users of Ergot derived DA are older than 65 years (despite this percentage is lower than Not-

Characteristics of Ergot and Not Ergot derived Dopamine agonist users (at least 1 prescription) with Parkinson's disease during the study years

Variables	Ergot derived DA N= 144 (%)	Non-Ergot derived DA N= 102 (%)
Median age, years	73.0	71.5
Age groups		
<65 years	47 (32.6)	25 (24.5)
≥ 65 years	97 (67.4)	77 (75.5)
Gender (%)		
Males	64 (44.4)	52 (51.0)
Females	80 (55.6)	50 (49.0)
Cardiovascular (CV) disease[^]:		
None	51 (35.4)	32 (31.4)
1 disease	34 (23.6)	37 (36.3)
2 diseases	30 (20.8)	24 (23.5)
≥ 3 diseases	29 (20.1)	9 (8.8)
Hypertension	80 (55.6)	62 (60.8)
Coronary heart disease	32 (22.3)	15 (14.7)
Peripheral arterial disease	14 (9.7)	7 (6.9)
Cardiac arrhythmias	14 (9.7)	5 (4.9)
Heart failure	15 (10.4)	2 (2.0)
Concomitant CV medications[^]: Number		
None	48 (33.3)	23 (22.5)
1 drug type	16 (11.1)	26 (25.5)
2 drug types	20 (13.9)	18 (17.6)
≥ 3 drug types	60 (41.7)	35 (34.3)
Concomitant CV medications[^]: Type		
Digoxin	19 (13.2)	5 (4.9)
Anti-hypertensive medications	86 (59.7)	64 (62.8)
Lipid-lowering drugs	22 (15.3)	15 (14.7)
Vasodilators	29 (20.1)	12 (11.8)
Platelet aggregation inhibitors	67 (46.5)	46 (45.1)

Legend: Ergot derived DA (dopamine agonists)= cabergoline =121 (84.0%), pergolide=4 (2.8%), lisuride=6 (4.2%), and bromocriptine=13 (9.0%); **Not Ergot derived DA** = ropinirole and pramipexole. [^] Prior to the first prescription date. Chi-Square test for categorical variables, with a significance level of $p < 0.05$, was used for assessing the differences among users of Ergot and Not-Ergot derived DAs."

Ergot derived DA users), in contrast with international guidelines [6]. The burden of CV diseases appears to be a clinically relevant issue in DA users, as expected. However, a higher proportion (20%) of Ergot derived DA users are affected by more than 3 concomitant CV diseases than Not Ergot derived users (8%). In particular, patients who start a therapy with Ergot DAs are more likely ($p < 0.05$) to be affected by heart failure, compared to Not Ergot users. The occurrence of valvular heart disease due to ergot derived DA use might dramatically worsen the clinical conditions in patients with heart failure [7]. In line with these results, a significantly higher proportion ($p < 0.05$) of patients starting a treatment with Ergot-derived DAs concomitantly received 3 or more cardiovascular medications, compared to Not Ergot derived DA users. Overall, incident users of Ergot derived

DA (almost 85% of these being cabergoline users) seem to have a more severe cardiovascular profile, compared to Not Ergot derived DA users. This finding should be considered in light of the warning on the heart valvular fibrosis risk associated with Ergot DA use in PD patients.

Clinicians should evaluate the burden of cardiovascular disease of PD patients before starting therapy with ergot derived dopamine agonists, in order to prevent further cardiovascular damage.

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4.3. The risk of cardiac valve regurgitation with ergot and non-ergot derived dopamine agonist use in Parkinson's disease

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ABSTRACT

Objectives: To assess the association between ergot and non-ergot derived dopamine agonists (DAs) and newly diagnosed cardiac valve regurgitation in patients with Parkinson's disease.

Methods: New users of DAs or levodopa (L-Dopa) for Parkinson's disease were identified from THIN (UK), Health Search-Thales (Italy), and IPCI (NL) general practice databases between 1996 and 2007. Cases of newly diagnosed valve regurgitation were detected and validated by an expert panel, blinded to exposure status. Crude incidence rates have been calculated for each drug class. A nested case-control design was used to assess the association between use of DAs and the outcome. All eligible controls were matched to the cases on age, gender, index date and database. Relative risks for current users of either ergot or non ergot derived DA were compared to L-Dopa use. Adjusted relative risks were estimated as odds ratio (OR) using conditional logistic regression, while adjusting for covariates univariately associated with the outcome.

Results: The study population included 8,451 and 10,306 new users of DAs or L-Dopa, respectively. During follow-up, 85 definite cases were identified. Crude incidence rates were 29.7 (20.1-42.3), 13.1 (8.6-19.1), and 12.3 (8.6-17.1) per 10,000 person-years for patients starting on ergot-, non-ergot derived DA and L-Dopa, respectively.

Compared to L-Dopa use, use of ergot-derived DAs was associated with a significantly increased risk of newly-diagnosed valve regurgitation (OR: 4.44; 95%CI: 2.43-8.10). This increase in risk was observed for cabergoline (OR: 5.10; 95%CI: 2.67-9.76) and pergolide use (OR: 4.04; 95%CI: 1.53-10.72), and in those exposed longer than 6 months.

Conclusions: Use of either pergolide or cabergoline for more than 6 months was associated with an increased risk of newly diagnosed valve regurgitation in patients with Parkinson disease. There was no evidence for an increased risk with the use of non-ergot derived DAs.

INTRODUCTION

The prevalence of Parkinson's disease (PD) in persons above 65 years is 1.8% in Europe [1]. To date, Levodopa (L-Dopa) is the most effective drug for the treatment of Parkinson's disease [2]. In the last decade, however, dopamine agonists (DAs) have been increasingly used as monotherapy in early PD to delay the start of L-Dopa treatment [3-4]. Other indications for use of DAs include hyperprolactinemia and restless leg syndrome.

Since 2002, a number of case reports of fibrotic valvular heart disease during the use of the ergot-derived DA pergolide were published, particularly for high dose and longer duration of pergolide use [5-9]. On echocardiography, patients had mild to severe cardiac valve regurgitation, often involving more than one valve [10-12]. Several cross-sectional echocardiographic studies in patients with Parkinson's disease showed that the prevalence of valve regurgitation was higher in patients who were treated with ergot derived DAs (see Appendix). Schade was the first to look at symptomatic/ diagnosed valve problems on a large scale in the UK General Practice Research Database by conducting a nested case-control study in a large UK electronic medical record database [13]. As a consequence of the growing evidence on the risk of cardiac valve regurgitation pergolide was withdrawn from the US market, while in Europe cabergoline as well as pergolide are now second line treatment for Parkinson's disease [14]. Fibrotic heart valve damage is thought to occur through preferential activation of serotonin 5-HT_{2B} receptor expressed on heart valves [15]. Cabergoline and pergolide are potent agonists of these receptors, which may explain the observed effect on valves. However, mitral tenting and valvulopathy have also been occasionally observed with non-ergot DAs [12,17] as well as with ergot DAs that are only partial agonists of 5-HT_{2B} receptors (e.g., bromocriptine) [18]. Previous epidemiologic [13, 19-21] and echocardiographic studies [14] showed that ergot-derived dopamine agonists are associated with cardiac valve regurgitation but they lacked the power and exposure variability to examine multiple individual dopamine agonists.

The aim of our study was to determine the comparative risks of newly diagnosed valve regurgitation associated with ergot and non-ergot derived DAs in a cohort of patients treated for Parkinson's disease.

METHODS

Data Sources

To gain statistical power and heterogeneity in exposure, for this study we combined data from three different European population-based general practice databases, which are described below.

The Health Improvement Network (THIN)

THIN is a database of electronic primary care medical records from the United Kingdom. General practitioners are trained to record their medical records using a dedicated computer system. Data recorded in THIN include demographics, details from general practitioner's visits, such as medical diagnoses and prescriptions (with BNF-code and MULTILEX code), diagnoses from specialist referrals and hospital admissions that are recorded using READ codes or free text, laboratory tests, and lifestyle characteristics, with electronic medical records that date back to 1985. Currently, the database has 2.7 million active patients registered within 358 participating practices. Data from THIN have been demonstrated to be valid for pharmacoepidemiology research and undergo different levels of quality control [22]. The Ethical committee (MRec) approved this study protocol.

Health Search-Thales Database (HSD)

The HSD is an Italian database of electronic primary care medical records. It was established in 1998 by the Italian College of General Practitioners. HSD currently contains data from computer-based patient records from over 900 GPs (covering a total of around 1,600,000 patients) located throughout Italy. These GPs voluntarily agreed to collect data for the database and attend specific training courses. The database includes information on the age and gender of the patient, and drug prescription information, clinical events and diagnoses, hospital admission, and causes of death. All diagnoses are coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9 CM). Drug names are coded according to the anatomical therapeutic chemical (ATC) classification system. To be included in the study, GPs must meet standard quality criteria pertaining to: levels of coding, prevalence of well-known diseases, and mortality rates. The HSD complies with European Union guidelines on the use of medical data for research. The HSD has been the data source for a number of peer-reviewed publications on the prevalence of disease conditions, drug safety and prescription patterns in Italian primary care [23-24]. Approval for use of data was obtained from the Italian College of Primary Care Physicians.

Integrated Primary Care Information (IPCI)

The IPCI database is a longitudinal general practice research database set up in 1992 and containing data from electronic medical records from a group of 360 Dutch general practitioners (GPs). In the Netherlands, all persons have their own general practitioner who serves as the gatekeepers to medical care and files all relevant medical details on their patients from primary care visits, hospital admissions and visits to outpatient clinics. Details of the database have been previously described [25]. Briefly, the database contains the medical records of approximately 1,000,000 patients with an age and gender distribution representative of the Netherlands. The electronic records contain coded and anonymous data on patient demographics, reasons for visits (in free text), signs and symptoms, diagnoses (using the International Classification for Primary Care [26] and free text) from general practitioners and specialists, referrals, hospitalizations, as well as drug prescriptions, including product name, ATC classification, dispensed quantity, dosage regimen and indication. To maximize completeness of the data, general practitioners participating in the IPCI project are not allowed to maintain a system of paper-based records, aside from the electronic medical records. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research [27]. The Scientific and Ethical Advisory Board of the IPCI project approved the study.

Study population

The study population comprised all individuals from the three databases, who had at least one year of valid data and who received a first prescription for a dopamine agonist or levodopa for the treatment of Parkinson's disease. All individuals were followed from the date of study entry (first prescription of the study drug starting from January 1st, 1996) until one of the following events, whichever came first: newly diagnosed valvulopathy (valve regurgitation, stenosis or prolapse or mixed valve disorder), death, moving out of the practice area, last data drawdown, or end of the study period (December 31st, 2007). Occurrence of valve stenosis or prolapse during the follow up was considered as a censoring factor as valve regurgitation could no longer be reliably assessed in these patients. From the cohort we excluded all persons, who at any time prior to the study entry, were diagnosed with rheumatic heart disease, congenital heart disease, dilated or hypertrophic cardiomyopathies, arrhythmogenic right ventricular cardiopathy, pericardial, pleural, pulmonary or retroperitoneal fibrosis, endocarditis, myocarditis, or carcinoid syndrome, or who had been treated with fenfluramine, dexfenfluramine or amiodarone. These drugs are known to potentially induce fibrotic reactions

[28-29]. All patients with a history of cardiac valve replacement or valvulopathy prior to study entry were excluded as well.

Case ascertainment and validation

The primary study outcome was newly diagnosed cardiac valve regurgitation. The case identification and ascertainment process included three phases. First, we identified all potential cases within the cohort by searching on diagnosis codes and free text in the electronic medical records. Second the electronic medical records for all potential cases were manually reviewed by two medical doctors to exclude obvious false positive cases (KV and GT). For the remaining potential cases from all the three databases additional information (i.e. GP's confirmation, specialist letters or additional free text) was requested.

Third, a representative sample of the potential cases was judged as either case or no case by an endpoint adjudication committee which included six expert medical doctors (GT, RS, GB, MM, GM, AC and WH). This committee developed a validation algorithm which was applied independently by two medical doctors. Case validation was based on careful manual review of the entire clinical diary and additional free text plus specialist and discharge letters. Cases were considered definite if the diagnosis of cardiac valve regurgitation was clearly mentioned and confirmed by echocardiography or cardiac catheterization or if it was reported by a specialist. In case of disagreement in the case validation, consensus was reached through discussion. If cases of unspecified valvulopathy or cardiac valve replacement were identified and further information to validate the case was missing, the case was classified as not assessable. The endpoint adjudication committee defined the primary index date as the date of first diagnosis of valve regurgitation. A secondary index date was defined as the first date of related symptoms (dyspnea, edema, syncope, arrhythmia, or chest pain). Blinding to exposure was guaranteed throughout the entire validation process. For the nested case control analysis each case was matched to all eligible controls within the study cohort in the respective database with the same age (± 2 year) and sex. Controls were assigned the same primary and secondary index date as the case.

Exposure

We included in the study new users of either L-Dopa or DAs. New users of DAs were further classified as ergot-derived (pergolide, cabergoline, bromocriptine, lisuride and dihydroergocryptine mesylate) or non-ergot derived (pramipexole, ropinirole, apomorphine) compounds. Piribedil, rotigotine, metergoline, quina-
golide were rarely or not used at all for the treatment of PD in the study cohort. New users of L-Dopa, alone or combined with a decarboxylase inhibitor, had not

been treated with DAs anytime prior. Since L-Dopa has never been associated with an increased risk of valve regurgitation, L-Dopa users served as a reference cohort to calculate the background incidence rate of cardiac valve regurgitation in patients with PD. The start of DA use in L-Dopa users was considered as a censoring factor to avoid overlapping person time between the two cohorts. Information on DA or L-Dopa use was obtained from the prescription files of the respective databases. We calculated the legend duration by dividing the total number of units per prescription by the prescribed daily number of these units (IPCI/THIN) or the defined daily dose (HSD). The first type of drug at cohort entry was used for calculation of incidence rates. To estimate the association between study drugs and cardiac valve regurgitation in the nested case control analysis, we created exposure categories based on drug type, timing and duration of use. Drug use was defined as current if the prescription duration covered the index date or ended ≤ 180 days (to account for the carry-over effect) prior [13]. Drug use was classified as past if the last prescription ended more than 180 days prior to the index date. Among current users of study drugs, we studied the risk of valve regurgitation for the most widely prescribed compounds, by different dose (<0.5 , $0.5-1$ and >1 defined daily dosage) and cumulative durations of use (≤ 6 and > 6 months). We considered the defined daily dosages (DDDs), as defined by the World Health Organization (see website: <http://www.whocc.no/atcddd/indexdatabase/>). As in the HSD there was no information on the dosing regimen, this database could not be used for the assessment of the effect of dose.

Covariates

As potential confounders, we considered age, sex, database and calendar time (matching factors), presence of cardiovascular disease (heart failure, hypertension, coronary heart disease, history of cerebrovascular disorders, peripheral arterial disease, aortic aneurysm, arrhythmias, venous thromboembolism), autoimmune disorders (rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease and others), and other chronic diseases, such as dementia, gastrointestinal disorders, chronic obstructive pulmonary disease (COPD), chronic renal failure, diabetes mellitus, obesity, and lipid metabolism disorders. We also considered the use of anti-Parkinson drugs other than L-Dopa and DAs (selegiline, amantadine, tolcapone, entacapone, and anticholinergic drugs).

To describe the characteristics of the two study cohorts, all covariates were assessed prior to study entry (first prescription of either L-Dopa or DA). In the nested case control analysis, covariates were assessed prior to the index date (date of newly diagnosed valve regurgitation).

Data analysis

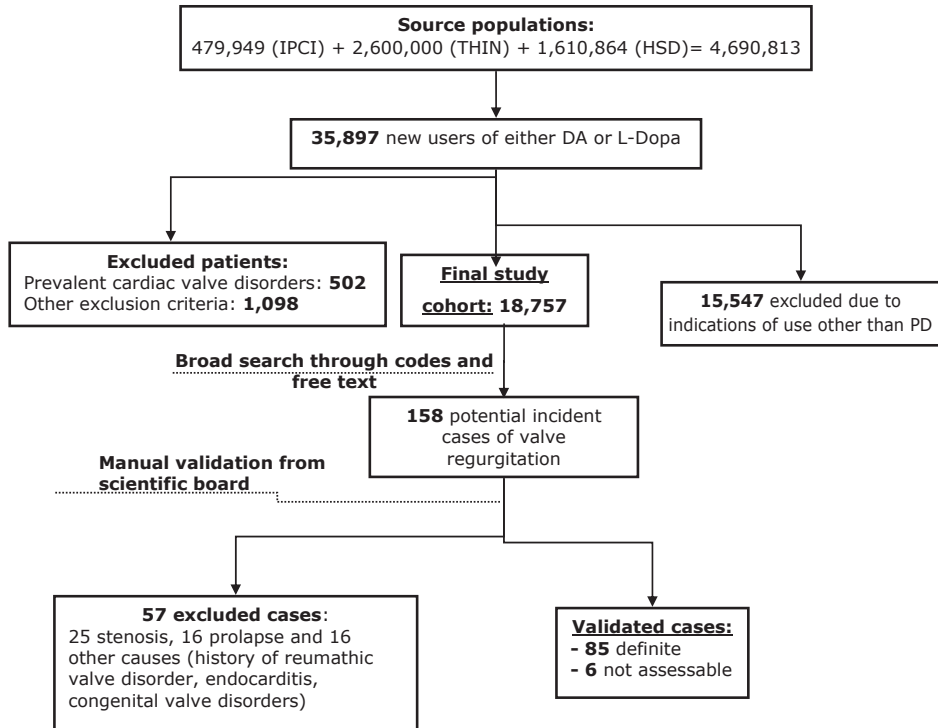
For each database we described and compared demographic and clinical characteristics of DA and L-dopa users at study entry by using chi-square tests or t-tests for categorical and continuous variables, respectively. Patient characteristics were also compared between databases in order to evaluate baseline differences. For each database and each study drug we measured follow-up time, expressed as person-years (PYs). An intention to treat analysis was carried out to estimate the crude incidence rate of valve regurgitation in each study cohort, and for ergot and non ergot DAs separately, considering the first drug being used during the entire study period (i.e. not censored for treatment switch or discontinuation). Relative risks of cardiac valve regurgitation were estimated by calculating odds ratios (OR) using conditional logistic regression analysis, while adjusting for all covariates that were associated significantly ($p < 0.10$) with the study outcome in the univariate analysis. ORs (plus 95% confidence intervals [CIs]) were calculated for current use of DAs altogether and for ergot and non-ergot derived DAs separately, compared to any use of L-Dopa (current and past use together). We chose this comparator under the assumption that the risk does not differ between current and past use of L-Dopa. Among current users we tested the linear trend across the products ranked on their affinity for the 5-HT_{2B} receptor (from highest to lowest: cabergoline, pergolide, apomorphine, pramipexole, ropinirole and L-Dopa), by including 5-HT_{2B} receptor affinity as an ordinal variable in the conditional logistic regression model. Bromocriptine that has agonistic as well as antagonistic effects (partial agonist) and lisuride that is an antagonist were not included in this analysis [16]. To inspect the effect of diagnostic suspicion bias that might have resulted in differential work up of exposed cases after the alert on the risk of cardiac valve regurgitation with pergolide use that was published in 2003, we conducted a subgroup analysis including only cases and controls for whom the diagnosis (primary index date) was made before September 2003. Since patients with cardiac disease who undergo frequent examinations may have more opportunity to be diagnosed with valve regurgitation (e.g. myocardial infarction history and heart failure) we conducted sensitivity analyses in which patients with a history of these diseases were excluded. Other sensitivity analyses have been performed to inspect the issues of potential protopathic bias (using the date of first related symptom as index date that is the secondary index date) and misclassification of exposure (varying the period to account for the carry-effect in the exposure window from 180 to 365, 90 and 0 days). All analyses were conducted in SPSS/PC, version 13 (SPSS Inc, Chicago, Ill). The level of significance for all statistical tests was 2-sided $P < 0.05$, unless otherwise specified.

RESULTS

The source population from the three electronic health record databases included overall 4,690,813 persons (**Figure 1**). We identified 35,897 (0.8%) patients who started a new treatment with either DA or L-Dopa during the study period. From this study sample, we then excluded all the patients who were treated for indications other than Parkinson's disease (N=15,547, 43.3%), or who had prevalent cardiac valvulopathy (N=502, 1.4%) or at least another exclusion criteria (N=1,098, 3.1%) prior to cohort entry.

The final study cohort consisted of 8,451 new users of DAs and 10,306 new users of L-Dopa. On average, L-Dopa users were followed for 2.6 years and DA users for 3.3 years, with a similar follow up for users of ergot or non-ergot derived compounds. As first medication, cabergoline (N=1,172, follow-up=3,478 Person-Years (PYs)), pergolide (N=711, 3,207 PYs) and bromocriptine (N=272, 1,398 PYs) were the most widely prescribed ergot DAs, while pramipexole (N=2,580, 6,552 PYs), apomorphine (N=1,555, 5,914 PYs) and ropinirole (N=1,893, 5,858 PYs) were the most frequently used non-ergot DAs. There were major differences in drug

Figure 1. Selection of incident cases of valve regurgitation in patients with Parkinson's disease from the source populations



prescribing data between the countries. Apomorphine was almost exclusively used in UK (THIN), while ropinirole and pramipexole were extensively prescribed in Italy (HSD). Cabergoline was not used for Parkinson's disease in The Netherlands (IPCI) since this medication is approved only for the treatment of hyperprolactinemia. Various patient characteristics differed significantly between dopamine agonist and levodopa users and between the databases (**Table 1**). New users of DA were younger compared to new users of L-dopa (mean ages: 65-73 years versus 73-81 years), and both DA and L-dopa users were significantly ($p < 0.05$) older in Italy than in UK and NL. No differences in gender distribution were observed between DA and L-Dopa in Italy and NL, while in the UK males were more often using dopamine agonists than levodopa ($p < 0.05$). Concerning co-morbidity, L-Dopa users were more likely to be affected by cardiovascular diseases, such as heart failure, hypertension and cerebrovascular disorders, than DA users, and significant differences in the frequency of co-morbidities were observed across the databases. In the study cohort we identified 85 (0.5%) definite cases of newly diagnosed cardiac valve regurgitation (**Fig.1, Tables 1-2**). Details, on the type and the valves that were involved, are reported in Table 1. Six cases were judged as non-assessable (lack of additional information) and were therefore not included in the analysis. On the basis of the intention to treat analysis, patients who started with an ergot-derived DA had a higher crude incidence rate (29.7 per 10,000 PYs) of valve regurgitation, compared to patients starting on either L-dopa (12.3 per 10,000 PYs) or non-ergot derived DAs (13.1 per 10,000 PYs). This difference was consistent across the databases, although the absolute rates differed (**Table 2**).

Case control analysis

A total of 6,362 controls could be matched to the 85 cases of valve regurgitation by age (± 2 years), gender, database and index date. The mean age of the cases was 85. Cases had more cardiovascular diseases than controls. However, only arrhythmias and hypertension were univariately ($p < 0.10$) associated with cardiac valve regurgitation. In the pooled analysis, as compared to persons using L-Dopa, the risk of cardiac valve regurgitation was significantly increased among patients who were currently exposed to ergot-derived DA (adjusted OR: 4.44; 95% Confidence Interval: 2.43-8.10), but not in those exposed to non-ergot derived DA (adj. OR: 1.32; 95% CI: 0.70-2.52) (**Table 3**). The risk was strikingly higher in patients who were cumulatively exposed to ergot-derived DAs for 6 months and more (adj. OR: 6.58; 95% CI: 3.37-11.84) (**Table 4**). No significant differences in the prescribed daily dose (standardized to defined daily dose (DDD) units) were observed between current users of ergot (mean dosage: 0.93 ± 0.1 DDD) and non-ergot (0.91 ± 0.1 DDD) derived DAs. The risk increased linearly ($p < 0.001$) with increasing dosages

Table 1. Characteristics of new users of either dopamine agonist or L-Dopa for Parkinson's disease in different databases

	HSD (Italy)		IPCI (Netherlands)		THIN (United Kingdom)	
	DA N= 4,685 (%)	L-Dopa N=6,093 (%)	DA N=232 (%)	L-Dopa N=447 (%)	DA N=3,534 (%)	L-Dopa N=3,766 (%)
Mean age ± SE	72.6 ± 0.2	80.8 ± 0.1	66.0 ± 0.9	72.7 ± 0.6	65.0 ± 0.2	76.3 ± 0.2
Gender						
Males	2,136 (45.6)	2,759 (45.3)	104 (44.8)	204 (45.6)	2,682 (75.9)	1,992 (52.9)
Females	2,549 (54.4)	3,334 (54.7)	128 (55.2)	243 (54.4)	852 (24.1)	1,774 (47.1)
Potential cases of valve regurgitation	54 (1.2)	50 (0.9)	2 (0.9)	-	32 (1.0)	22 (0.6)
Validated cases	30 (0.6)	24 (0.5)	2 (0.9)	-	23 (0.7)	12 (0.3)
Definite	30	22	2	-	20	11
Not assessable	-	2	-	-	3	1
Definite case: N (%)						
<i>Type of lesion</i>						
Valve regurgitation	30	20 (99.1)	2 (100.0)		18 (90.0)	11 (100.0)
Mixed valve disorder	-	2 (0.9)			2 (10.0)	-
<i>Valve affected</i>						
Mitralis	8 (25.8)	3 (13.6)	1 (50.0)		9 (45.0)	7 (63.6)
Aortic	6 (19.4)	5 (22.7)			7 (35.0)	1 (9.1)
Pulmonary	-	-				
Tricuspid	1 (3.2)	2 (9.1)			2 (10.0)	1 (9.1)
More than one valve	15 (50.0)	12 (54.5)	1 (50.0)		2 (10.0)	2 (18.2)
Covariates						
Other anti-Parkinson drugs	828 (17.7)	375 (6.2)	64 (27.6)	55 (12.3)	742 (21.0)	512 (13.6)
Cardiovascular co-morbidities						
Heart Failure	99 (2.1)	174 (2.9)	7 (3.0)	28 (5.6)	84 (2.4)	204 (5.4)
Coronary heart disease	302 (6.4)	451 (7.4)	9 (3.9)	10 (2.2)	299 (8.5)	259 (6.9)
Hypertension	1,941 (41.4)	2,669 (43.8)	33 (14.2)	83 (18.6)	2,219 (62.8)	2,549 (67.7)
Arrhythmias	239 (5.1)	367 (6.0)	12 (5.2)	23 (5.1)	170 (4.8)	282 (7.5)
History of cerebro-vascular disorders	477 (10.2)	944 (15.5)	14 (6.0)	35 (7.8)	298 (8.4)	670 (17.8)
Peripheral arterial disease	42 (0.9)	55 (0.9)	3 (1.3)	6 (1.3)	94 (2.7)	89 (2.4)
Venous thromboembolism	24 (0.5)	48 (0.8)	-	-	89 (2.5)	121 (3.2)
Aortic aneurism	22 (0.5)	36 (0.6)	2 (0.9)	3 (0.7)	33 (0.9)	37 91.0)
Other co-morbidities						
Diabetes	657 (14.0)	1,015 (16.7)	22 (9.5)	54 (12.1)	694 (19.6)	435 (11.6)
Lipid metabolism disorders	870 (18.6)	976 (16.0)	33 (14.2)	52 (11.6)	1,122 (31.7)	864 (22.9)
Obesity	126 (2.7)	103 (1.7)	2 (0.9)	5 (1.1)	168 (4.8)	99 (2.6)
Chronic renal failure	83 (1.8)	145 (2.4)	1 (0.4)	3 (0.7)	28 (0.8)	22 (0.6)
COPD	837 (17.9)	1,008 (16.5)	14 (6.0)	23 (5.1)	768 (21.7)	806 (21.4)
Gastrointestinal disorders	1,264 (27.0)	1,537 (25.2)	57 (24.6)	83 (18.6)	1,105 (31.3)	1,183 (31.4)
Dementia	747 (15.9)	772 (12.7)	2 (0.9)	28 (6.3)	30 (0.8)	205 (5.4)
Autoimmune co-morbidities						
SLE	13 (0.3)	14 (0.2)	2 (0.9)	-	3 (0.1)	6 (0.2)
RA	31 (0.7)	50 (0.8)	6 (2.6)	13 (2.9)	38 (1.1)	58 (1.5)
IBD	23 (0.5)	27 (0.4)	4 (1.7)	2 (0.2)	34 (1.0)	48 (1.3)
Other autoimmune disorders	234 (5.0)	242 (4.0)	4 (1.7)	5 (1.1)	82 (2.3)	125 (3.3)

Legend: Other anti-Parkinson drugs= amantadine, selegiline, anticholinergic drugs, tolcapone, entacapone; COPD= chronic obstructive pulmonary disease; SLE= systemic lupus erythematosus; RA=rheumatoid arthritis; IBD=inflammatory bowel disease.

Table 2. Incidence rate (IR) of valve regurgitation per 10,000 Person-Years of follow-up by exposure to dopamine agonist or L-Dopa.

Drug Exposure*	Pooled analysis			HSD	THIN	IPCI
	Cases	Follow-up (P/Y)	Crude IR (95% CI)	Crude IR (95% CI)	Crude IR (95% CI)	Crude IR (95% CI)
Dopamine agonist (DA)**	52	27,790	18.7 (14.1-24.3)	19.0 (13.1-25.5)	17.4 (11.0-26.4)	36.7 (7.3-1-17.6)
Ergot derived DA	28	9,437	29.7 (20.1-42.3)	21.4 (12.5-34.5)	52.7 (27.9-91.2)	57.1 (11.4-183.0)
Non-Ergot derived DA	24	18,353	13.1 (8.6-19.1)	17.1 (10.0-27.5)	9.6 (4.7-17.5)	-
L-Dopa	33	26,768	12.3 (8.6-17.1)	13.4 (8.6-19.9)	11.7 (6.2-20.2)	-

Legend: Ergot-derived DA= Cabergoline, pergolide, bromocriptine, dihydroergocryptine mesylate, lisuride, metergoline; Non-ergot-derived DA: pramipexole, ropinirole, apomorphine, piribedil, rotigotine, quinagolide.

* Treatment at the cohort entry. ** DA users may have switched to L-Dopa.

Table 3. Risk of valve regurgitation with dopamine agonist use as compared to L-Dopa use

	Cases N=85 (%)	Controls N=6,362 (%)	Crude* OR (95% CI)	Adjusted** OR (95% CI)
Current and past use of L-Dopa	33 (38.8)	3,053 (48.0)	1.00	1.00
Current Use[^]				
Ergot derived DA^{^^}	20 (23.5)	477 (7.5)	3.90 (2.16-7.05)	4.44 (2.43-8.10)
Cabergoline	16	398	4.74 (2.50-8.99)	5.10 (2.67-9.76)
Pergolide	6	106	3.27 (1.26-8.47)	4.04 (1.53-10.72)
Bromocriptine	1	15	1.85 (0.23-15.16)	2.60 (0.31-21.56)
Non Ergot derived DA^{^^}	16 (18.8)	1,195 (18.8)	1.26 (0.67-2.37)	1.32 (0.70-2.52)
Pramipexole	4	455	1.63 (0.79-3.38)	1.73 (0.83-3.61)
Ropinirole	11	709	0.86 (0.30-2.48)	0.95 (0.33-2.74)
Apomorphine	2	87	2.04 (0.41-10.10)	1.91 (0.37-9.79)
Combination of ergot and non-ergot derived DAs	2 (2.4)	66 (1.0)	3.50 (0.80-15.41)	4.12 (0.93-18.28)
Past use				
Ergot derived DA	7 (8.2)	606 (9.5)	1.18 (0.50-2.76)	1.29 (0.55-3.05)
Non-Ergot derived DA	7 (8.2)	947 (14.9)	0.63 (0.25-1.58)	0.65 (0.26-1.63)
Combination of more classes	-	18 (0.3)	-	-

Legend: OR=Odds Ratio, DA=Dopamine agonists, L-Dopa= Levodopa. * Conditional logistical regression analysis (age, sex, database and index date as matching factors). ** Adjusted for hypertension and arrhythmias. [^] Current use means use within 180 days before the index date; past use means that use ended more than 180 days before. ^{^^} No mutually exclusive use within the class of Ergot derived DA or Non-Ergot derived DA

for ergot-derived DA users. However, a significant increase in the risk was reported not only for those receiving dosages higher than 1 DDD (13.90; 4.16-46.44), but also for those who received dosages lower than 0.5 DDD (6.97; 1.98-24.48). For non-ergot derived DAs no such a trend was observed (**Table 4**).

Considering the individual compounds, the risk of valve regurgitation was significantly increased for users of cabergoline (adj. OR: 5.10; 95% CI: 2.67-9.76) and pergolide (adj. OR: 4.04; 95% CI: 1.53-10.72) (**Table 3**). There was a significant ($p < 0.001$) linear trend between the risk of cardiac valve regurgitation and affinity to

Table 4. Risk of cardiac valve regurgitation for current users of dopamine agonist use compared to levodopa use, stratified by dosage and duration

	Cases N=85	Controls N=6,362	Crude RR** (95% CI)	Adjusted*^ RR (95% CI)
Current or past use of Levodopa	33	3,053	1.00	1.00
Daily dose effect *				
Ergot derived DA				
<0.5 DDD	5	63	6.27 (1.84-21.34)	6.97 (1.98-24.48)
0.5-1 DDD	-	35	-	-
> 1 DDD	5	46	11.43 (3.52-37.08)	13.90 (4.16-46.44)
Non-Ergot derived DA				
<0.5 DDD	4	228	1.80 (0.52-6.24)	1.81 (0.51-6.42)
0.5-1 DDD	1	82	1.28 (0.16-10.12)	1.41 (0.18-11.26)
> 1 DDD	-	130	-	-
Duration effect				
Ergot derived DA				
< 6 months	4	194	1.86 (0.63-5.49)	1.95 (0.66-5.73)
6 months or more	16	283	5.42 (2.82-10.43)	6.58 (3.37-11.84)
Non-Ergot derived DA				
< 6 months	9	556	1.49 (0.69-3.23)	1.49 (0.68-3.26)
6 months or more	7	639	1.12 (0.48-2.62)	1.26 (0.54-2.99)

*excluding HSD for which the daily dose was not available

the 5HT_{2b} receptor. These findings were confirmed if the analyses were performed in the single databases. IPCI had two cases only and therefore we could not look at the analysis limited to this specific database. Various sensitivity analyses were conducted to look at the robustness of the results. When the first date of specific symptom was used as the index date, the study results did not materially change (current use of Ergot derived DA: OR=5.11; 95% CI=2.61-10.02; current use of non Ergot derived DA: 1.10; 0.51-2.38). Patients who had stopped using either ergot or non-ergot derived DAs more than six months prior to the diagnosis of valve regurgitation (i.e. past users) did not have an increased risk. History of myocardial infarction and heart failure were no effect modifiers of the association between ergot-derived DA use and valve regurgitation. Exclusion of patients with a history of myocardial infarction or heart failure yielded similarly increased risks for ergot-derived DAs. Varying the exposure risk window to account for potential carry-over effects did not change the results for ergot derived dopamine agonists. Using current use of levodopa as comparator instead of current or past did not change the results substantially

Of the 85 case patients with cardiac-valve regurgitation identified in this study, 4 (4.7%) patients were subsequently affected by newly diagnosed heart failure, while 16 (18.8%) died within 2 years from the date of valve regurgitation diagnosis. Among the controls, 79 (1.2%) subjects were newly diagnosed with heart failure and 566 (8.9%) died after two years from the index date.

DISCUSSION

This multi-country database study found that the use of ergot-derived dopamine agonists is associated with an increased risk of incident cardiac valve regurgitation among patients with Parkinson's disease from three different countries. The risk increased with increasing dosage of ergot-derived dopamine agonists and was most pronounced in persons using the drugs for at least six months. This increase in risk was shown only for cabergoline and pergolide. We did not observe any increase in the risk of valve regurgitation for the use of non-ergot derived DAs pramipexole, ropinirole and apomorphine, although the odds ratio for Pramipexole was elevated. Our findings confirm previous evidence from case-reports and observational studies [14]. In a similar way to our study, Schade et al performed a nested case-control study, using electronic health care data from the UK General Practice Research Database, and documented a dose-dependent increased risk of cardiac valve regurgitation for exposure to cabergoline or pergolide [13]. Our incidence rate of valve regurgitation in ergot derived DA users with Parkinson's disease was similar to the estimate from Schade et al (30 per 10,000 PYs). This rate contrasts with the high prevalence rates reported from cross sectional echocardiographic studies. In these studies 1% of patients with Parkinson's disease taking ergot-derived DA had severe valvulopathy [14]. The difference may be explained by the fact that many patients with valvulopathy remain without symptoms and do not get diagnosed quickly [14]. Most of the previously performed studies included only a small number of patients and explored the effect of a limited number of DAs. By combining the data from three different databases in three different countries, we could better assess the comparative risk of valve regurgitation for individual ergot and non-ergot DAs and rank on the basis of receptor affinity. There are mechanistic grounds to believe that not all DAs are equally likely to play a role in the development of cardiac valve regurgitation. Preferential activation of the 5-hydroxytryptamine 2B (5-HT_{2B}) receptor, which is expressed on heart valves, has been shown to induce prolonged mitogenic effects in cardiac fibrocytoblasts, thus potentially leading to heart valve fibroplasia and regurgitation [15-16]. In line with this hypothesis, we found an increased risk of valve regurgitation only for pergolide and cabergoline which are both potent agonists of the 5-HT_{2B} receptor [30]. Patients who had stopped using ergot derived DAs more than 6 months prior to the diagnosis of valve regurgitation were not associated with an increased risk of valve regurgitation in our study. According to this finding, the effect of ergot DAs on the valve regurgitation may be reversible, as previously suggested [5,7,9].

Strengths and limitations of the study

The strength of this study was the availability of a large amount of data drawn from three electronic health record databases from three different countries. These data sources offered us the opportunity to take into account the heterogeneity of different populations and different prescribing patterns of DAs in a cohort of patients with Parkinson's disease. Furthermore, it allowed us to evaluate the effect of individual ergot and non-ergot derived DAs on the risk of valve regurgitation. However, some possible limitations warrant cautious interpretation of the results. As for all observational studies, selection bias, information bias due to misclassification of outcome or exposure, and residual confounding should be considered as alternative explanations for our study finding. Selection bias was minimal as all data were obtained from prospectively collected medical records that are maintained for patient care purposes, irrespective of any research question. Diagnostic suspicion bias could be of concern, since pergolide was discussed as a possible cause of cardiac valvulopathy before the end of the study period. The British Committee on Safety of Medicines published an alert on pergolide-associated valvulopathy in September 2003 [31] and this alert may have led to an increased use of diagnostic measures in patients receiving pergolide and other ergot derived DAs in order to detect valvulopathies. To investigate this potential source of bias, we conducted a subgroup analysis involving only 28/85 (32.0%) patients in whom cardiac valve regurgitation had been diagnosed before September 2003. This analysis did not substantially change our results. Likewise, differential work up and detection probability can be expected in patients with heart failure or a history of myocardial infarction since they are more likely to receive an echocardiographic test. We demonstrated however that exclusion of these cases did not alter the study findings. Misclassification of exposure may have occurred due to non-compliance, despite the fact that all the study medications are on prescription basis only and entry into the cohort was based on a prescription. However, this misclassification is likely to be non-differential and would therefore lead to underestimation of the true effect. We may have missed specialist prescribed medication but the extent of this is likely to be equal for all Parkinson drugs. Finally exposure misclassification may have occurred because of incorrect exposure window and errors in the index date. Sensitivity analyses in which we varied the exposure window did not substantially change the results. Notably, defining the date of first symptoms as the index date rather than the date of diagnosis tended to make the results even stronger. Misclassification of the outcome may have occurred due to lack of inclusion of false negative (undiagnosed cases with valve regurgitation) or inclusion of false positive cases. The effect of the false negatives (inclusion as controls) is probably limited since the prevalence of severe valvulopathy is 1% in users of anti-Parkinson

drugs. The effect of false positives is considered to be limited due to the extensive case validation process. The effect of false positives is considered to be limited due to the extensive case validation process. Unmeasured confounding can never be excluded, though it is unlikely that strong risk factors for cardiac valve regurgitation may have gone undetected. Therefore, the strong effect of ergot derived DA that was observed in our study is unlikely to be explained by unmeasured or residual confounding. Finally, there was heterogeneity in the prevalence of co-morbidity between the databases due to differences in coding schemes and health care structure. The association between valve regurgitation and ergot derived dopamine agonists was highest in UK and NL (despite limited number of exposed case) and lowest in Italy, but it was consistently documented in all databases. Future research should specifically explore the risk of valvular regurgitation in association with the use of individual ergot-derived DAs in patients with hyperprolactinemia, who are treated at much lower dosages than patients with Parkinson's disease. Only few echocardiographic studies, including a limited study sample, have been conducted in these patients so far. All of them reported no increase in risk for clinically relevant valvulopathy with pergolide or cabergoline use in patients with prolactinoma or other endocrine diseases [32-37]. A recent echocardiographic study documented an increased risk of valvulopathy in users of bromocriptine. We only identified one case and 15 controls that were currently exposed to bromocriptine. Although we pooled data from three different electronic medical record databases, our study was probably underpowered to detect any effect for bromocriptine, and therefore an increase in the risk also for this drug cannot be excluded, as recently documented in an echocardiographic study [38].

In conclusion, our study shows that treatment with either pergolide or cabergoline was associated with a dose and duration dependent increased risk of newly diagnosed valve regurgitation in patients with Parkinson disease. There was no evidence of such an increase in risk with the use of non ergot derived dopamine agonists.

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APPENDIX

Publications of observational investigations on the risk of valve regurgitation in association with dopamine agonist use in patients with Parkinson's disease.

First author, journal, year*	Study Design	Outcome	Exposure	Main findings
Steiger M¹ , <i>J Neural Transm</i> , 2009	Systematic review	Cardiac valve regurgitation	Pergolide, cabergoline, and non-ergot-derived DA in PD patients	The use of ergot-derived DAs in patients with PD was associated with increased risk for cardiac valve regurgitation
Oeda T² , <i>J Neural Transm</i> , 2009	Nested case control study	Valvular heart disease	Ergot-derived dopamine agonists	Use of pergolide or cabergoline is an independent risk factor for developing valvular heart disease
Tan L³ , <i>Movement Disorders</i> , 2009	Echocardiographic study	Valvular heart disease	Use of bromocriptine	The risk of both mild regurgitation and moderate-severe regurgitation was increased with increasing cumulative dose of bromocriptine
Yamashiro K⁴ , <i>Movement Disorders</i> , 2008	Echocardiographic study	Cardiac valve regurgitation	Low dose dopamine agonists	The frequency of mild or above mild regurgitation of the aortic valve was significantly higher in the cabergoline group
Rasmussen VG⁵ , <i>J Inter Med</i> , 2008	Echocardiographic study	Valvular regurgitation	Ergot and non-ergot derived DA use in PD	Ergot derived DA was associated with moderate valve regurgitation
Zadikoff C⁶ , <i>Can J Neurol Sci</i> , 2008	Retrospective, population-based cohort study	Hospital admissions for VHD or HF	Pergolide use in PD	Pergolide is associated with a higher risk of hospital admission for VHD or HF, particularly with 1-4 years treatment
Zanettini R⁷ , <i>NEJM</i> , 2007	Echocardiographic study	Valvular regurgitation	Pergolide, cabergoline, and non-ergot-derived DA in PD patients	Pergolide and cabergoline are associated with clinically important valve regurgitation
Corvol JC⁸ , <i>Archives Neurology</i> , 2007	Echocardiographic study	Moderate to severe regurgitation	Pergolide use in PD patients for longer than three months	Pergolide use in PD patients is associated with valve regurgitation and correlates with cumulative dose

Simonis G⁹, Movement Disorders, 2007	Meta-analysis of observational studies	Heart valve disease	Ergot and non-ergot derived DA use in PD	Valvular heart disease occurs not only in patients treated with pergolide, but also in patients treated with cabergoline at a comparable frequency
Schade R¹⁰, NEJM, 2007	Nested case control study, using GPRD	Newly diagnosed cardiac-valve regurgitation	Levodopa, romocriptine, cabergoline, pergolide, lisuride, pramipexole, and ropinirole	Pergolide and cabergoline are associated with an increased risk of newly diagnosed cardiac-valve regurgitation
Dewey RB¹¹, Arch Neurol, 2007	Echocardiographic study	Valve functionality score	Pergolide vs non-ergot DA use in PD	Pergolide contributes to cardiac valve regurgitation as long term use for PD.
Kenangil G¹², Clinical Neurology and Neurosurgery, 2007	Echocardiographic study	Valvular regurgitation	Cabergoline and pergolide use in PD patients	Ergot derived DA are associated with moderate valvular regurgitation
Junghanns S¹³, Movement Disorders, 2007	Echocardiographic study	Valvular regurgitation	Pergolide, cabergoline, ropinirole, pramipexole use in PD	ergot DA is associated with higher prevalence of VHD compared to non-ergot DA
Kim J¹⁴, Movement disorders, 2006	Echocardiographic study	Valvular thicknesses	Bromocriptine and pergolide use in PD patients	No increase in the frequency of valvulopathy with bromocriptine or pergolide
Ruzicka E¹⁵, J Neurol, 2006	Echocardiographic study	Restrictive valvular regurgitation	Pergolide use in PD patients	No cases of restrictive valvular heart disease in PD patients treated with pergolide (3mg per day).
Peralta C¹⁶, Movement Disorders, 2006	Echocardiographic study	Valvular regurgitation	Ergot and non ergot DA use in PD patients	No differences in valvular regurgitation risk between ergot and non ergot DA
Yamamoto M¹⁷, Neurology, 2006	Echocardiographic study	Valvular abnormalities	Ergot and non ergot DA use in PD patients	The frequency of valvulopathy is increased in the cabergoline group
Waller EA¹⁸, Mayo Clin Proc, 2005	Echocardiographic study	Valvular heart disease	Pergolide use in PD	The frequency of aortic regurgitation appears to be increased in patients taking pergolide. This increase may be dose dependent.
Baseman DG¹⁹, Neurology, 2004	Echocardiographic study	Valvular regurgitation	Pergolide use in PD	Pergolide may injure cardiac valves, resulting most commonly in tricuspid regurgitation.
Van Camp G²⁰, Lancet, 2004	Echocardiographic study	Restrictive valvular heart disease	Pergolide use in PD patients	Restrictive valvular heart disease is not a rare finding in patients treated with pergolide

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CHAPTER 5

General Discussion



GENERAL DISCUSSION

Prescribing of psychotropic drugs to elderly with neuropsychiatric disorders is challenging due to limited scientific evidence on the effectiveness as well as problematic tolerability and large potential of drug-drug interactions. Rational use of psychotropic drugs may improve the quality of life and the functional status of elderly patients with neuropsychiatric diseases. However, currently psychotropic medications are often misused and overused in these patients [1]. The availability and secondary use of databases with longitudinal electronic health records of millions of persons offer the opportunity to get better insight into real life psychotropic drug use and the risks and benefits of those medications in community dwelling elderly persons.

In this chapter, the main findings of this research and the main methodological issues of pharmaco-epidemiological studies are discussed to facilitate a proper interpretation of the results described in this thesis.

MAIN FINDINGS

Use and safety of antipsychotic drugs in elderly

Typical antipsychotics (sometimes referred to as first generation antipsychotics, conventional antipsychotics, or neuroleptics) are a class of psychotropic drugs that were developed in the 1950s. Chlorpromazine was the first typical antipsychotic to enter clinical use. Typical antipsychotics are used in elderly population to treat acute and chronic psychoses, mania, agitation, and other geriatric psychiatric disorders. Generally, these medications are divided on the basis of their chemical structure into butyrophenones, phenothiazines, and substituted benzamides. Fatal and life-threatening arrhythmias and severe extrapyramidal adverse events that are a cluster of symptoms consisting of akathisia, parkinsonisms, and dystonias represent the main limitations on the use of typical antipsychotics in elderly. For this reason, new antipsychotics (atypicals) were developed with a supposedly better safety profile. Atypical antipsychotics have been marketed since the 1990s starting with clozapine. The *atypicality* of this newer class consists of different efficacy in the treatment of negative symptoms (i.e. catatonia, apathy) of schizophrenia and the lower risk of extrapyramidal adverse events, compared to conventional antipsychotics. For these reasons, the use of atypical antipsychotics has been rapidly expanding worldwide, particularly in elderly, even for unlicensed indications of use.

We found that the use of atypical antipsychotics increased approximately five times between 1999 and 2002 in Italy, mostly because of their increased use in the

treatment of behavioral and psychotic disorders of dementia (BPSD). This indication was also the main reason for off-label use. These findings are in line with data from the UK where use of atypical antipsychotics increased nearly six-fold between 1997 and 2001 [2]. In the U.S., olanzapine and risperidone were the most commonly prescribed antipsychotic drugs, already in 1997 [3].

Safety warnings

Since 2004, regulatory agencies started to release warnings about the potential risks of atypical antipsychotics in BPSD in particular. The Committee on Safety of Medicines (CSM) highlighted a 3-fold increased risk of cerebrovascular events in elderly with dementia, who were treated with either risperidone or olanzapine in March 2004 [4]. This risk was identified from a pooled analysis of placebo-controlled clinical trials. In April 2005, another warning was issued by the Food and Drug Administration (FDA) to inform health professionals about the results of a pooled analysis of 17 RCTs reporting a 1.7 times increased risk of all-cause mortality associated with atypical antipsychotic use in elderly dementia patients [5]. In June 2008, the FDA extended this warning also to the typical antipsychotics [6].

Effects of safety warning on drug utilization

We and others studied the effect of the safety warnings on the utilization of the antipsychotics in elderly population. A Canadian study demonstrated that the safety alerts had slowed down the increase in prescription of atypical antipsychotic drugs in patients with dementia, but it had not changed the overall prescription rate of antipsychotics [7]. In our study in Italy, we also demonstrated a significant decrease in the use of atypical agents in elderly demented patients between 2003 and 2005. Like in Canada, the overall prescription rate of antipsychotics was not reduced. Haloperidol was the most frequently prescribed antipsychotic to elderly patients with dementia in Italy. However, the scientific evidence on the efficacy of this typical antipsychotic in the management of behavioural and psychotic symptoms of dementia is controversial [8-9]. In our study more than 3% of the community dwelling elderly received at least one antipsychotic drug prescription in 2005, and 40% of them were treated for dementia and related disorders. Our and the Canadian study indirectly documented the switch between atypical and typical antipsychotics, as a result of the safety warnings on cerebrovascular adverse events and risk of death that addressed the atypicals initially. The effect of the most recent alerts that concerned the conventional antipsychotics as well should be evaluated.

Ongoing randomized clinical trials comparing atypicals and conventional antipsychotics will provide more evidence on the best choice in these patients. Mean-

while observational studies have been done by us and other groups to compare the safety risks associated with the atypical and typical antipsychotic use drugs in elderly and demented elderly in particular.

Observational safety studies on cerebrovascular events

Following the safety alerts, several observational studies were done to address the potential risk of cerebrovascular adverse events associated with antipsychotic use in elderly [10-16]. In summary, these studies suggested no difference in the risk of stroke with atypicals compared to conventional antipsychotics, whereas the risk of stroke was higher during use than non-use for both classes. We also conducted a retrospective cohort study, comparing the risk of stroke in elderly using either conventional or atypical antipsychotics versus non users. For this study we used the Health Search/Thales database, which is an electronic health record database that stores medical information on about 1.5% of the total Italian population. We demonstrated that the use of any antipsychotic as compared to non-use was associated with an increased risk for first-ever stroke. Interestingly, the risk for stroke with phenothiazines was two-fold higher than the risk with atypical antipsychotic use. This finding would support a differential effect across subgroups of conventional antipsychotics. In light of this finding, the safety of subgroups of conventional antipsychotics should be evaluated separately, contrary to what was generally done in previous investigations.

Observational safety studies on mortality

The increased mortality warning was first launched in 2005; this warning resulted in various observational studies. All the studies confirmed that antipsychotic drug use is associated with an increased risk of all-cause mortality compared to non use. Conventional antipsychotics have a similar, if not higher risk of mortality than atypical agents [17-23].

We conducted a subsequent study to further evaluate the risk of all-cause mortality in association with antipsychotic use. A case control study was conducted that was nested in a cohort of elderly demented patients. For this study, we used the Integrated Primary Care Information (IPCI) database, which is a Dutch electronic health record database containing information from 500 general practitioners distributed all over The Netherlands and with a current population of approximately 1.1 million patients. In a cohort of 2,385 community dwelling elderly with dementia, we found no difference in the risk of death between atypical and typical antipsychotics; however, both antipsychotic classes were associated with a significant and dose-related increase in risk of all-cause mortality when compared to non-use. Due to the limited sample size of the dementia cohort we did not

have enough power to study specific causes of death in our study. The FDA alert mentioned that cerebrovascular events (CVEs), pneumonia and arrhythmias were the most frequently reported causes of death in elderly demented patients treated with antipsychotic drugs. While the association between antipsychotic drug use and cerebrovascular adverse events as well as arrhythmias or sudden cardiac death has been extensively explored [24-28], epidemiologic evidence on the risk of fatal and non-fatal pneumonia with antipsychotic use in elderly is currently missing. To fill this gap, we performed a case control study nested in a cohort of community dwelling elderly, using data from the IPCI database again but not restricting to elderly patients with dementia only to increase the power. In a cohort of 2,560 elderly, who were newly treated with antipsychotic drugs, it was shown that the use of either atypical or typical antipsychotics was associated with a dose-dependent increase in the risk of community acquired pneumonia. According to our findings, one case of pneumonia would occur respectively in every 29 patients treated with atypical antipsychotics and in every 73 patients who are treated with typical antipsychotics. Atypical antipsychotics were also associated with a higher risk of fatal pneumonia, despite the limited number of fatal cases that were exposed to atypical antipsychotics (N=7) in our study. Although our design was different, the conclusions of our study are in line with those of a previous Dutch investigation [29]. The possible mechanisms by which exposure to antipsychotics could be associated with the development of pneumonia remain speculative. Excessive sedation as a result of histamine-1 receptor blocking in the central nervous system is a well-known cause of swallowing problems, which could facilitate aspiration pneumonia [30]. In line with this hypothesis, our study showed a higher risk of pneumonia for atypical antipsychotics and phenothiazines compared to butyrophenones, which have the lowest affinity for antihistaminergic receptor H₁.

Use and safety of antidepressant drugs in elderly

Utilization of antidepressants

SSRIs are currently considered as first-line drugs in the treatment of late-life depression, due to similar efficacy but more favorable tolerability. This has contributed to the increasing use of SSRI in both adults and elderly persons in Europe and other countries in the last decade [31-33].

To provide an updated picture on the use of antidepressants, we performed a drug utilization study, using the Arianna database. This database was set up by the Local Health Service of Caserta (Southern Italy) in 2000 and currently contains electronic health records from more than 300,000 persons that are registered by one of the 225 participating general practitioners. The prevalence of antidepres-

sant drug use increased in all age groups during the years 2003-2004, mostly as a result of the increase in use of SSRIs. In 2004, 9.9% of patients aged 65-74, 13.8% of those aged 75-84, and 12.4% of those ≥ 85 years were treated with antidepressants. SSRIs accounted for about two-thirds of all newly initiated antidepressant treatments in the elderly and were mainly prescribed for the treatment of late life depression, which is in line with guideline recommendations. We also found that newly marketed drugs (such as escitalopram) ranked high in frequency of use, which confirms that new drugs have quick uptake in general practice [34]. A substantial proportion of elderly persons received trazodone as first line antidepressant, probably in light of its sedative properties. This may raise clinical problems in view of the propensity of this antidepressant to cause orthostatic hypotension, which is associated with falling, fractures and cerebrovascular events in elderly patients [35].

Drug-drug interactions

Both TCAs and SSRIs and other antidepressants carry the risk of pharmacokinetic and pharmacodynamic drug-drug interaction (DDI), especially in elderly. In general, a drug interaction occurs when the effectiveness or toxicity of a drug is altered by the concomitant administration of another drug. A review was conducted to discuss drug-drug interactions with antidepressants and methods to prevent them in elderly patients.

There are important factors that predispose elderly to suffer from DDI with antidepressants in general. First, age-related changes in pharmacokinetics and pharmacodynamics negatively influence drug elimination through hepatic metabolism and/or renal excretion. Second, as a result of coexisting chronic illnesses, elderly depressive patients often take many concomitant medications.

SSRIs have a potential for pharmacokinetic interactions due to their inhibitory effect on cytochrome P450 (CYP P450) enzymes. The differential effects of various SSRIs on CYPs are well characterized in vitro. Fluvoxamine, fluoxetine and paroxetine have the largest potential for interaction [36]. Older compounds, such as tricyclic antidepressants or monoamine oxidase inhibitors, which act on a broad range of receptors, have a greater potential for pharmacodynamic DDI than newer agents with a more specific mechanisms of action [37].

TCAs inhibit the neuronal reuptake of noradrenaline and serotonin, bind to multiple receptors types (M1 cholinergic receptors, H1-histamine receptors, α_1 -adrenoceptors), and inhibit fast sodium channels. Based on this, TCAs should be avoided or used with extreme caution in elderly patients treated with anticholinergics or with drugs affecting the central nervous and cardiovascular systems [38]. Concomitant administration of TCAs with other medications possessing

antimuscarinic activity, such as phenothiazines and antiparkinsonian agents, may induce central and peripheral anticholinergic effects, including memory impairment, dry mouth, blurred vision, constipation, confusional states, and urinary retention. Furthermore, TCAs may potentiate the sedative effects of other central nervous system (CNS) depressants such as barbiturates, benzodiazepines, antihistamines, antipsychotics, thereby impairing psychomotor and cognitive function in elderly population. Undesirable interactions may also occur when TCAs are used in combination with a variety of cardiovascular drug (e.g. anti-arrhythmics, antihypertensives and oral anticoagulants).

Awareness about the risks of drug-drug interactions with individual antidepressant may lower the potential of DDI in elderly patients that are treated with these psychotropic drugs.

Cerebrovascular safety of antidepressants

The potential effects of SSRIs and other antidepressants on cerebral circulation and platelets have received a lot of attention after preliminary reports suggested an association between SSRI exposure and risk of bleeding, including hemorrhagic stroke [39-41]. Several observational studies explored the association between SSRI use and hemorrhagic stroke but could not show any significant associations [42-44]. Although an association with hemorrhagic stroke could not be confirmed, there is contrasting evidence on the association with ischemic stroke. Given the serotonin depleting effect of SSRIs on platelets, a protective effect of SSRIs against thrombotic event might be anticipated [45]. To investigate the effect of SSRIs on ischemic stroke, we conducted a cohort study in Dutch elderly outpatients using the IPCI database. A significant increase in the risk of ischemic stroke was found for current use of SSRIs, compared to non use (adj. OR: 1.55; 95% CI: 1.07-2.25), particularly in the beginning of the treatment, though the association was not dose-dependent. Past use of either SSRIs or TCAs was associated with ischemic stroke as well, in line with a Danish study [46]. Our finding supports the possibility that depressive symptoms, which is the main reason for use of antidepressants in elderly, act as a confounder on the association between antidepressants and stroke. To deal with confounding by indication, Chen et al recently conducted a nested case control study within patients with depression in a large population-based U.S. medical claims database [47]. Their findings, however, were in line with ours, the risk of ischemic stroke was increased only for current users of SSRIs (adj. OR: 1.55; 95% CI: 1.00-2.39). Possible mechanisms supporting the causal association between exposure to SSRIs and ischemic stroke have been hypothesized. Serotonergic activation secondary to SSRI use may induce a vasoconstrictive effect that is mediated by the 5-hydroxytryptamine-2 (5HT-2) receptor on smooth

muscle cells [48-49]. A recent review on the cerebrovascular effects of SSRIs showed that SSRI use may increase the risk of ischemic stroke by triggering a thromboembolic phenomenon in patients with cerebral atherosclerosis through its vasoconstrictive effect in large cerebral arteries [45]. In our study we support this hypothesis as we found a significant linear trend between the affinity to the serotonin transporter and the risk of ischemic stroke.

Use of and safety of anti-Parkinson drugs in elderly

Utilization of anti-Parkinson drugs

Levodopa (L-Dopa) is the most effective drug in Parkinson's disease (PD) treatment, but it is associated with limiting and poorly tolerated motor and non-motor side effects, especially in the advanced stages of the disease [50]. Other anti-Parkinson drugs are commonly used as monotherapy or as adjunctive therapy with L-Dopa, to delay or reduce its use and the occurrence of motor and non-motor complications while maximizing treatment effectiveness [51]. These other drugs include ergot and non-ergot derived dopamine agonists (DAs), anticholinergic drugs, amantadine, selegiline and catechol-O-methyltransferase (COMT) inhibitors. Due to lack of recent data on APD use in Europe, we explored the prescribing pattern of anti-Parkinson drugs in the Arianna database in Southern Italy during the years 2003-2005. In our study, the prevalence of Parkinson drug use was 6.0 per 1,000 persons per year. We observed that L-dopa was the most widely prescribed Parkinson drug in this area. This was in line with other European studies [52-53]. Almost 20% of either L-Dopa or ergot derived DA users received only one prescription. This finding suggests that physicians commonly prescribe a trial of dopaminergic medications to diagnose Parkinson's disease rather than carrying out more complex diagnostic procedures.

In the same setting, we looked at the characteristics of patients and we observed that the burden of existing cardiovascular disease differs between new users of ergot-derived DAs. This finding should be considered in light of the warnings on the risk of fibrotic heart valve disorder associated with the use of pergolide and cabergoline in patients with Parkinson's disease.

Risk of fibrotic heart valve disease with anti-Parkinson drugs

Starting from 2002, first a number of case reports, and subsequently several cross-sectional ecocardiographic studies and one retrospective database study have highlighted the risk of valvular heart disease associated with ergot derivative DA use [54-57]. As a consequence of the growing evidence on the risk of fibrotic heart valve disease (i.e. valve regurgitation), pergolide was withdrawn from the U.S.

market, and pergolide as well as cabergoline are now second line treatments for Parkinson's disease in Europe, and their use requires monitoring [58]. This risk of valve regurgitation seems to be dose-dependent and may be potentially reversible with the withdrawal of drug treatment. Due to the limited sample size of previous studies, however, the comparative risk of individual ergot and non-ergot derived DAs need further assessments using large amount of exposed persons.

With the aim to better investigate the relationship between fibrotic heart valve disorder and use of ergot/non-ergot DA use, we undertook an observational investigation using information from three electronic health record database (Health Search/Thales from Italy, IPCI from The Netherlands and THIN from UK). The results of our multicentre study showed that the use of ergot-derived DAs longer than 6 months was associated with an increased risk of newly diagnosed valve regurgitation in a cohort of patients with Parkinson's disease from three different Countries. The risk increased with the increasing dosage, although a significant increase was observed already in those users of ergot derived DA that received dosage lower than 0.5 DDD. This increase in the risk could be demonstrated only for cabergoline and pergolide. On the contrary, we did not observe any increase in the risk for the use of non-ergot derived DA pramipexole, ropinirole and apomorphine, despite more than doubled prevalence of exposure to these drugs in controls, compared to ergot-derived DAs. These findings are in line with previous evidence from echocardiographic and epidemiologic studies [58]. So far, only one case control study had been conducted using electronic medical records [57]. In line with this paper, we found a crude incidence rate of valve regurgitation of 30 per 10,000 PYs for users of ergot-derived DAs. Furthermore, we observed a significant linear trend of the affinity to $5HT_{2b}$ receptor for current users of the study drugs in the risk of valve regurgitation, thus confirming a major role for the pharmacological action on this receptor in the drug-induced fibrotic heart valve disorders [59]. Further research is needed to evaluate the comparative risk of valve regurgitation with the use of individual ergot derived DA in patients with hyperprolactinemia, who are treated with much lower dosage of ergot derived DA and on average are much younger than patients with Parkinson's disease.

METHODOLOGICAL CONSIDERATIONS

Study setting

A shift of long term management of mental illness from psychiatric hospitals to the community took place in European Countries in the past 20 years. As a result, general practitioners (GPs) have been increasingly involved in the pharmacologi-

cal management of neuropsychiatric disorders in the elderly [60-62]. In several European countries (e.g. UK, Netherlands, Spain, and Italy) citizens have their own GP, who serves as the gatekeeper to medical care. These GPs file all relevant medical details on their patients from primary care visits, hospital admissions and visits to outpatient clinics. The primary care setting is therefore suitable for population-based epidemiologic investigations on the use and safety of psychotropic drugs. In all the observational studies presented in this thesis, data have been drawn from three general practice databases that are located in two different Countries (Italy and The Netherlands):

- a) The Health Search/Thales database, which was set up by the Italian College of General Practitioners (SIMG) in 1998, currently contains information on more than 1 million patients, who are registered with one of the participating 800 GPs. The GPs are distributed homogeneously all over Italy. This database has been validated and used frequently for epidemiological studies [63-65].
- b) The Arianna database is a longitudinal general practice database from Southern Italy, which was set up in 2000. It currently contains information on a population of almost 300,000 individuals (225 GPs) living in the catchments area of Caserta. This database has been used for some epidemiological studies [66-67].
- c) The Integrated Primary Care Information (IPCI) database is a Dutch longitudinal general practice research database, which was set up in 1992. To date, IPCI contains data from electronic medical records of approximately 1 million of patients from a group of 500 Dutch GPs. The IPCI database has been validated and used in more than 50 publications on the drug safety and effectiveness [68-70].
- d) The Health Information Network (THIN) that is a database of primary care medical records from the United Kingdom.

Currently, the database has 2.7 million active patients registered within 358 participating practices. Data from THIN have been demonstrated to be valid for pharmacoepidemiology research [71].

Databases were chosen for logistical and accessibility reasons, and finally, in the safety studies, for availability of information and size. In the study on the association between valvular regurgitation and dopamine agonist use in Parkinson's disease, databases were combined to profit from the heterogeneity of drug prescribing patterns across countries and to increase the sample size. Secondary use of electronic medical records stored in these databases brings various advantages. First these longitudinal databases allow for enumeration of the source population and provide a good denominator for utilization studies and disease rates. Secondly, the availability of information in the records of all patients avoids selection bias,

which often is a problem if field studies need to be conducted. Thirdly, most databases allow for long follow-up, which will even increase with time. Fourthly, these database, have real life clinical information on a large number of patients, including information on diseases, symptoms, signs, drug prescriptions, laboratory and diagnostic instrumental tests, hospital and specialist referral and death. Another advantage of using these databases is the possibility to go back to the GP to ask for additional information (i.e. letters from specialist and GPs' confirmation of diagnoses).

On the other hand, some limitations of these data sources should be acknowledged as well. First, information is collected in the outpatient setting only and as a consequence the study findings (especially those from drug utilization studies) may not directly pertain to patients that are treated in different settings, like hospital or nursing homes and long term care facilities. Second, the use of medications, which are not prescribed by GPs, is not consistently and completely registered. As a consequence, missing information on over the counter medications and prescriptions that are issued directly from psychiatric local health services should be always taken into account, when interpreting results of the research presented in this thesis. Third due to the non-random assignment of drugs, channeling, resulting in confounding by indication always occurs.

Observational studies: bias and confounding

Studying the relationship between psychotropic drug use and new onset of adverse events in electronic heal record databases is extremely challenging due to a variety of potential biases and confounders. In all observational studies, various types of bias, e.g. selection bias, protopathic bias, information bias and confounding by indication, may influence the study findings, as briefly discussed below. The primary study design that was adopted in almost all the epidemiologic studies focusing on drug safety was the nested-case control study. These case control studies were nested cohorts of either specific drug users (i.e. antipsychotic or anti-Parkinson drugs), elderly or demented elderly. Nesting was done to reduce potential for confounding by indication. Case control studies are more efficient in studying dose, duration and exposure responses than cohort studies, whereas their validity is the same when using already recorded information from electronic medical records.

The potential for selection bias was minimal in our studies as all data were obtained from prospectively collected medical records that are maintained for patient care purposes on a population based level. In each country from which the databases were used, there is no threshold to access GPs and patients are registered independent of disease status.

Information bias can occur as result of misclassification of either exposure or outcome. To minimize the potential effect of information bias by misclassification of the outcome a two-step case validation process was undertaken for all the studied outcomes (all-cause mortality, stroke, pneumonia and valvular regurgitation). First, all the potential cases were identified through broad searches of coded diagnoses and narratives in the electronic medical record of the study patients. Second, the electronic medical records of all potential cases were reviewed and validated manually by at least two expert and trained medical doctors, who were blinded to the exposure.

In all the observational studies presented in this thesis, misclassification of exposure is possible since we used outpatient prescription data and had no information about actual filling and use of the medications. Around half of the medicines prescribed for people with chronic conditions are ultimately not taken in the US [72]. Although this percentage may be lower in the EU where generally patients do not have to pay for their medications, this misclassification is most likely equal (non-differential) between cases and controls and, therefore, the actual risk may have possibly been underestimated. To deal with misclassification due to irregular intake we performed various sensitivity analyses in our studies by varying the exposure window. Two main epidemiologic issues were frequently encountered in our studies and they merit a careful and extensive discussion: confounding by indication and protopathic bias.

Confounding by indication is a commonly used term that refers to an extraneous determinant of the outcome parameter that is present if a perceived high risk or poor prognosis is an indication for intervention. The indication is a confounder because it correlates with the intervention and is a risk indicator for the illness [73]. Confounding by indication is likely in the studied associations, since the choice of psychotropic drug is often associated with the prognosis or condition of a patient, which in itself can be a risk factor for stroke, pneumonia or death. Confounding by indication was addressed in the design (restriction, matching) and analysis phases of all studies.

In the study on the risk of all-cause mortality with antipsychotic drug use, we restricted the study population to elderly patients with dementia only. Dementia itself is a strong risk factor of death in the elderly population [74] and behavioral and psychotic symptoms requiring antipsychotic treatment may themselves be predictors of mortality within older demented patients. This means that there is a strong potential for confounding by severity, when comparing the risk of death between current users of antipsychotics and non users [75]. In the analysis phase, we dealt with confounding by indication by stratifying or adjusting for the indication of use in the multivariate regression models. In the study on the risk of

ischemic stroke in users of antidepressants our basic strategy was adjustment and stratification for indication. In the study on anti-Parkinson drugs and valvular regurgitation we compared patients with the same indication (restriction) using levodopa as reference group, and we adjusted for many covariates.

Due to the use of electronic health records, we could consider (adjust or match for) many risk factors. However, residual confounding is always possible due to insufficiently or selectively registered covariates (i.e. smoking and alcohol or severity of disease). Only strong and highly prevalent risk factors would be able to explain the findings of our studies and it is unlikely that these covariates have been omitted.

Protopathic bias occurs when a drug is used to treat prodromic symptoms of the study outcome, thereby it may appear that the drug is causing the outcome [76]. For example, SSRIs are frequently prescribed for the treatment of late life depression, which may represent a manifestation of subtle cerebrovascular disorders resulting to stroke in the elderly [77]. Similarly, severe pneumonia may induce delirium and trigger subsequent antipsychotic drug use in elderly patients [78]. In both situations, wrong assessment of the date of onset could result in protopathic bias, thus mistakenly attributing stroke and pneumonia onset respectively to SSRI and antipsychotics. To deal with this protopathic bias, we performed sensitivity analyses excluding from the exposure category those patients who started the therapy within a short period prior to the occurrence of the outcome.

CONCLUDING REMARKS

What this thesis adds

This thesis shows that secondary use of data from electronic health record databases is a very valuable tool to evaluate both the use and the safety of psychotropic medications in elderly as well as the effects of risk minimization strategies or health regulatory warnings. This type of epidemiologic investigations may be of great interest for various stakeholders ranging from clinicians to patients and regulators at national and international level. These data allow for monitoring of new compounds, safety warnings, changes in the reimbursement criteria, and other health policy interventions on the prescribing pattern of neuropsychiatric medications in advanced age.

In the research presented in this thesis, we showed the increases in use of second generation antidepressants (SSRI) and antipsychotics (atypical agents) and the effects of regulatory warnings on the utilization patterns of antipsychotics. Use of psychiatric medications is not without risk in the elderly, and therefore

we explored the extent of some of these safety issues. Regarding the safety of antipsychotics, we demonstrated that no significant differences exist in the risk of all-cause mortality between atypical and conventional antipsychotic drugs in elderly demented patients and of fatal/non fatal pneumonia in community dwelling elderly. However, both atypical and conventional antipsychotics seem to be associated with a dose-dependent increase of those risks compared to non-use. Regarding the risk of stroke which was the cause of the first safety warnings on the off-label use of atypical antipsychotics in elderly patients with dementia, we documented an increased risk for both atypical and typical antipsychotic use, compared to non-use. The study on the association between use of antidepressants and ischemic stroke showed that use of SSRI does not reduce the risk of ischemic stroke, as previously hypothesized, while could be associated with a slight increase in the risk, especially using those drugs with the highest affinity to the serotonin transporter. The safety study on the association between anti-Parkinson drugs and newly diagnosed valvular regurgitation confirmed that only the treatment with either pergolide or cabergoline longer than 6 months was associated with an increased risk in patients with Parkinson disease. The increase in the risk was dose dependent. Aggregation of data from multiple databases provided us with amounts of data enough to observe that there was no evidence of such an increase in risk with the use of non ergot derived dopamine agonists.

Future directions

This thesis shows both the potential and pitfalls of secondary use of electronic health records for assessing utilization and safety of psychotropic drug use in the elderly. A great need exists to better describe and explore the use and the effects of these drugs in elderly, due to their wide use in real practice setting and little clinical trial evidence availability. Future research on psychotropic drugs in elderly should therefore take three different directions:

1. Encouraging research on special geriatric populations, such as elderly living in nursing home and long term care facilities, for whom electronic medical information is currently limited;
2. Exploring and testing new methodologies for assessing not only the safety but also the effectiveness of these drugs through the use of electronic health record databases;
3. Identifying the best strategies for the aggregation of data coming from multiple electronic health record databases in studies on rare outcomes and exposures.

In Europe there is a general deficiency of evidence about drug use and effects in special geriatric populations, such as the oldest old (patients aged 85 and older) and frail medically ill elderly patients who are commonly nursing home residents [79].

This may partly be explained by the fact that currently very little electronic health record data is available from these settings. Future research in Europe should be aimed at unlocking information from these settings for research. In such a way the use and safety of psychotropic drugs in nursing home settings could be properly described and monitored, which is the setting in which these medications are often misused and overused [1].

The research that is shown in this thesis was aimed at exploring the prescribing pattern and the most relevant safety issues of the most widely used psychotropic drugs in the community dwelling geriatric population. Ideally, a more comprehensive assessment would need to be done combining all safety issues and weighing these against the effectiveness of psychotropic drugs. New methodologies are warranted and in development to evaluate also the drug effectiveness and quantify the overall benefit-risk profile of available medications [80]. Use of electronic medical record databases seem key in these assessments since they reflect reality rather than artificial clinical trials circumstances and allow for longer term follow-up. The field of effectiveness assessment in these databases is currently a field of high attention due to the high potential for confounding by indication, and the future should show whether valid estimations are possible while using a non-randomized approaches [81]. In case of severe rare clinical outcomes, a single electronic health record database may not provide sufficient subjects and heterogeneity in exposure to conduct a full comparative pharmacoepidemiologic drug safety study. For this reason we tried to combine data from different electronic health record to study the association between dopamine agonist use and cardiac valve regurgitation. Although aggregation of data from multiple databases is ambitious, currently it is challenging, especially in Europe, due to the differences in terminology and language systems being adopted as well as the differences in quality and type of gathered information. This strategy however may provide the statistical power to study rare adverse events and rare drug exposures. The best methodologies for analyzing aggregated data that are drawn from different sources should be sought in the future.

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CHAPTER 6

Summary of thesis



6.1. Summary

The world's population in the older ages continues to increase and two billions of persons over 65 years are expected by 2050. Likewise, the burden of neuropsychiatric disorders, including Alzheimer's disease (AD) and Parkinson's disease (PD), increases as well. Late life neuropsychiatric disorders are disabling conditions that result in a lower quality of life of elderly patients and their caregivers, earlier institutionalization, and excess mortality. Amelioration of these conditions can be achieved with rational prescribing of psychotropic drugs in these patients, but this is challenging due to the limited scientific evidence on the effectiveness, restricted tolerability and potential of drug-drug interactions of available medications.

The increasing amount of electronic health records offers the opportunity to generate a constantly updated picture on psychotropic drug use in clinical practice and to provide a better insight on the risks of those medications in geriatric population.

The general objective of the research described in the present thesis was to obtain a better understanding of the use and safety of antipsychotic (**chapter 2**), antidepressant (**chapter 3**), and anti-Parkinson drugs (**chapter 4**) in community dwelling elderly patients.

Antipsychotic drugs

In a population-based Italian study, we found a rather stable one-year prevalence of antipsychotic use (1.4%) during the years 1999-2002. However, the use of atypical antipsychotics increased approximately fivefold during the study years (0.7 per 1,000 in 1999 vs. 3.4 per 1,000 in 2002). This growth was mostly due to their growing use in the treatment of behavioral and psychotic disorders of dementia, which was the main reason for off-label use (**chapter 2.1**). A number of alerts were launched by health regulatory agencies on the risks of cerebrovascular events and all-cause mortality in association with the off-label antipsychotic use in elderly demented patients, starting in 2003. In the Italian primary care setting, we documented a significant decrease in the use of atypical agents in elderly patients with dementia after the issuing of safety alerts, although the overall prescription rate of antipsychotics was not reduced in these patients. Despite the decrease, however, more than 3% of Italian community dwelling elderly patients received at least one antipsychotic drug prescription in 2005, and around 40% of them being treated for dementia and related disorders (**chapter 2.2**). In the **chapter 2.3**, we undertook a retrospective cohort study in the same setting and we observed a similarly increased risk of first-ever stroke with use of either typical or

atypical antipsychotics, compared to non use, in elderly persons. Such a risk was however more than two-fold higher for phenothiazines than atypical agents. We thereafter explored the risk of all-cause mortality with the antipsychotic use in elderly demented patients, employing a nested case control approach with data from the Dutch longitudinal general practice database, IPCI (**chapter 2.4**). We documented a dose-dependent increase in the risk of death for users of either atypical or typical antipsychotic, in comparison to non users. No differences in the mortality risk were reported between use of atypical and typical agents in community dwelling elderly with dementia.

In the IPCI database, we also investigated the risk of fatal and non-fatal community acquired pneumonia in elderly persons. We observed a dose-dependent increased risk for pneumonia in current users of either atypical or typical antipsychotics, compared to past use of antipsychotics. Fatal pneumonia was associated with atypical agents only, although our analysis was underpowered. The risk of pneumonia increased linearly with the increasing affinity to histaminergic H₁ receptor from antipsychotic classes (**chapter 2.5**).

In **chapter 2.6**, we performed a comprehensive review on the safety of atypical and typical antipsychotics in elderly demented patients. Results from meta-analyses of clinical trials and observational studies report overall a similarly increased risk in all-cause mortality and cerebrovascular adverse events in users of both atypical and conventional antipsychotics. When prescribing antipsychotics, specific safety issues to consider are the pro-arrhythmic activity and extrapyramidal symptoms for conventional antipsychotics, and the metabolic effects (i.e. increased risk of diabetes and obesity) for the atypical agents.

Antidepressants

Regarding antidepressant drugs, we first conducted a drug utilization study in Southern Italy. The prevalence of antidepressant use increased in all age groups during the years 2003-2004, as a result of a dramatic increase in the prescriptions for SSRIs. In 2004, 9.9% of patients aged 65-74, 13.8% of those aged 75-84, and 12.4% of those ≥ 85 years were treated with antidepressants. SSRIs accounted for about two-thirds of incident treatments with antidepressants in elderly patients. In line with guideline recommendations, SSRIs were mainly prescribed for the treatment of late life depression (**chapter 3.1**). Using the IPCI database, we found that SSRI and other antidepressants have no protective effect against ischemic stroke in elderly, as previously postulated (**chapter 3.2**). Compared to non-use, use of SSRIs, and particularly of those with the highest affinity to serotonin transporters, may be associated with a slight increase in the risk of ischemic stroke in geriatric population, early after the start of therapy.

We then carried out a review of the current evidence on drug-drug interactions with antidepressant medications in elderly patients, focusing on the available prevention strategies (**chapter 3.3**). TCAs, SSRIs as well as other new antidepressants are potentially involved in the development of both pharmacokinetic and pharmacodynamic harmful drug-drug interactions. Correct and comprehensive information is a prerequisite for both prevention and adequate management of drug interactions with antidepressants in the elderly. Electronic decision support systems, such as automated drug interaction alerts, can dramatically reduce the number of concomitant prescriptions of antidepressants and other medications with potentially hazardous combinations.

Anti-Parkinson drugs

With respect to anti-Parkinson drugs, we first documented that levodopa was the most frequently prescribed medication for Parkinson's disease in Southern Italy during the years 2003-2005. However, almost 20% of either levodopa or ergot-derived dopamine agonist users received only one medication (**chapter 4.1**). In light of the growing evidence on the risk of fibrotic heart valve disorder with the use of pergolide and other ergot-derived dopamine agonists, we then evaluated the cardiovascular profile of parkinsonian patients, who were newly treated with either ergot or non-ergot derived dopamine agonists (DAs) in the same setting (**chapter 4.2**). We found that the burden of cardiovascular diseases is a relevant concern in incident users of ergot-derived DAs. Our last study was a study on the effect of ergot and non-ergot derived DAs on the risk of valvular regurgitation. For this study the data from three databases (Health Search/Thales from Italy, THIN from UK, and IPCI from The Netherlands) were combined. We confirmed that a dose dependent increase in the risk of symptomatic valvular regurgitation was associated with the treatment with either pergolide or cabergoline longer than 6 months in a cohort of patients with Parkinson disease. Aggregation of data from multiple databases provided us with enough amounts of data to observe that there was no increase in risk with the use of individual non-ergot derived DAs (**chapter 4.3**).

In the general discussion in **chapter 5**, the main findings of the research are summarized and some methodological issues are discussed in depth to facilitate the interpretation of the results. Finally, some recommendations for future research are reported.

6.2. Samenvatting

Het percentage ouderen neemt naar verwachting wereldwijd toe tot een aantal van 2 miljard 65-plussers in 2050. Hand in hand met de toenemende vergrijzing zal ook het aantal patiënten met neuropsychiatrische aandoeningen, zoals Parkinson en Alzheimer, toenemen. Deze ouderdomsziekten zijn invaliderende aandoeningen die gepaard gaan met een afgenomen kwaliteit van leven, institutionalisering op jonge(re) leeftijd en een verhoogde mortaliteit. De ziektelast kan worden vermindert door gebruik van psychotrope geneesmiddelen. Problemen zijn echter dat er weinig studies zijn gedaan naar werkzaamheid van psychotrope geneesmiddelen in ouderen, dat de tolerantie vaak slecht is en er een hoge kans is op interacties met andere medicijnen.

Hoewel er weinig klinische studies naar werkzaamheid en veiligheid zijn gedaan is er wel veel ervaring in de praktijk opgedaan doordat deze mensen vaak wel worden behandeld. Door de grote hoeveelheid zorggegevens die tegenwoordig in geautomatiseerde vorm in databases worden bewaard, is het nu mogelijk om op basis van deze data te bestuderen wat het gebruik van deze psychotrope geneesmiddelen in ouderen is en wat de potentiële gezondheids risico's zijn.

Het doel van het in dit proefschrift beschreven onderzoek was daarom om meer inzicht te krijgen in het gebruik en de veiligheid van antipsychotica (**hoofdstuk 2**), antidepressiva (**hoofdstuk 3**) en anti-Parkinson middelen (**hoofdstuk 4**) in niet geïnstitutionaliseerde ouderen.

Antipsychotica

We bestudeerden het gebruik van antipsychotica vooral in Italië. Daarbij toonden we aan dat de jaar prevalentie van antipsychotica gebruik redelijk constant was in de periode 1999-2002 (1.4%). Ondanks deze stabiele prevalentie was het gebruik van de nieuwere atypische antipsychotica vijf keer toegenomen (0.7 per 1.000 in 1999 vs. 3.4 per 1.000 in 2002) en nam het gebruik van de conventionele antipsychotica dus af. De toename in gebruik van de atypische antipsychotica was vooral te wijten aan het toenemende gebruik ervan in gedragsstoornissen en psychoses die optreden bij dementie. Deze toepassing is niet in overeenstemming met het registratiebesluit en wordt daarom als off-label geassocieerd (**hoofdstuk 2.1**).

Vanaf 2003 hebben verscheidene overheden waarschuwingen doen uitgaan over het risico op beroertes als gevolg van het gebruik van antipsychotica in demente ouderen. We hebben bestudeerd welke effecten deze waarschuwingen hadden op het voorschrijven van antipsychotica in ouderen. -We hebben waargenomen dat

in de Italiaanse huisartsenpraktijken het gebruik van atypische antipsychotica bij ouderen met dementie significant is afgenomen na de waarschuwingen hoewel het totale antipsychoticagebruik gelijk gebleven is, 3% van de ouderen krijgt tenminste één antipsychoticum van de huisarts. Ongeveer 40% hiervan werd voorgeschreven voor dementie en gerelateerde aandoeningen (**hoofdstuk 2.2**).

In **hoofdstuk 2.3** beschrijven we een retrospectief cohort onderzoek dat werd uitgevoerd door gebruik te maken van de Health Search Database, een database met elektronische medische dossiers van huisartsen in Italië. Hierbij vonden we dat er in vergelijking met niet-gebruikers een toegenomen risico is op hersenbloeding bij het gebruik van typische en atypische antipsychotica in ouderen. Vervolgens hebben wij het overlijdensrisico bij gebruik van antipsychotica in ouderen onderzocht middels een genest patiënt-controle onderzoek in een Nederlandse longitudinale database met elektronische medische dossiers, namelijk IPCI (**hoofdstuk 2.4**). Hierin zagen we dat het risico op overlijden hoger is tijdens gebruik van antipsychotica en ook nog dosis afhankelijk is. Het verhoogde risico was gelijk voor gebruikers van atypische en typische antipsychotica, terwijl de waarschuwingen van de overheden zich eigenlijk alleen hadden gericht op de atypische antipsychotica. Als vervolg op het onderzoek naar mortaliteit waarin bleek dat veel mensen overleden aan een pneumonie, hebben we een additioneel onderzoek in dezelfde IPCI database gedaan naar de relatie tussen gebruik van antipsychotica en het risico op fatale en niet-fatale longontsteking. Hierin zagen we dat het gebruik van antipsychotica leidt tot een dosis-gerelateerde toename van het risico op pneumonie. Fataal aflopende longontstekingen waren vooral geassocieerd met het gebruik van atypische antipsychotica. Het risico op het krijgen van een longontsteking nam rechtlijnig toe met de affiniteit van antipsychotica voor histaminerge H₁ receptoren waarmee een mogelijk mechanisme tussen gebruik van deze middelen en de effecten kan worden voorgesteld (**hoofdstuk 2.5**).

In **hoofdstuk 2.6** hebben wij de beschikbare literatuur over de veiligheid van typische en atypische antipsychotica in demente ouderen, samengevat. Meta-analyses van klinische en observationele studies laten over het algemeen een vergelijkbare toename zien van het risico op mortaliteit en cerebrovasculaire bijwerkingen in conventionele en atypische antipsychoticagebruikers. Bij het voorschrijven van conventionele antipsychotica moet daarnaast nog rekening gehouden worden met een aantal specifieke additionele veiligheidsrisicos, namelijk artimiëen, extrapyramidale symptomen en metabole effecten (e.g. toegenomen risico op diabetes en obesitas).

Antidepressiva

Om antidepressiva te onderzoeken hebben we allereerst het gebruik hiervan in kaart gebracht. De prevalentie van antidepressivagebruik in Zuid Italië nam toe in 2003-2004 door een sterke toename van het gebruik van selectieve serotonine inhibitoren (SSRIs). In 2004 werden 9,9% van de patiënten tussen de 65 en 74 jaar, 13,8% van de patiënten tussen de 75 en 84 jaar en 12,4% van de patiënten van 85 jaar en ouder behandeld met antidepressiva. SSRIs werden voorgeschreven in ongeveer tweederde van de nieuwe antidepressiva behandelingen. SSRIs werden vooral voorgeschreven voor depressie op oudere leeftijd, hetgeen in overeenstemming is met bestaande richtlijnen (**hoofdstuk 3.1**).

Het gebruik van antidepressiva is in verband gebracht met hersenaandoeningen, maar er is geen uitsluitsel of het risico nu verlaagd (beroerte) of juist verhoogd (hersenvloeding) is. Op basis van de IPCI database hebben wij aangetoond dat, in tegenstelling tot eerdere berichtgeving, SSRIs en ander antidepressivumgebruik geen beschermend effect hebben op beroertes in ouderen (**hoofdstuk 3.2**). In vergelijking met niet-gebruikers is het gebruik van SSRIs mogelijk geassocieerd met een kleine toename van het risico op een beroerte in de geriatrische bevolking, vooral vlak na de start van de behandeling.

Vervolgens hebben wij de literatuur samengevat over interacties tussen antidepressiva en andere geneesmiddelen (**hoofdstuk 3.3**). TCA's, SSRI's en andere nieuwe antidepressiva zijn mogelijk betrokken bij het ontstaan van schadelijke farmacokinetische en farmacodynamische interacties tussen medicijnen. Een goede informatieverstrekking en surveillance is daarom een vereiste zowel voor preventie als voor adequate behandeling van interacties tussen antidepressiva en andere medicijnen in ouderen.

Anti-Parkinson medicatie

Met betrekking tot anti-Parkinson medicatie hebben we in een geneesmiddel gebruik studie allereerst vastgesteld dat levodopa het meest gebruikte medicament was voor de ziekte van Parkinson in Zuid Italië in 2003-2005. Opvallend was dat veel gebruikers van dopamine agonisten slechts één voorschrift kregen (**hoofdstuk 4.1**).

Er is toenemend bewijs dat dopamine agonisten die afgeleid zijn van ergot derivaten, zoals pergolide en cabergoline, het risico op fibrotische hartklepafwijkingen verhogen. Daarom hebben we in eerste instantie onderzocht wat het cardiovasculaire profiel was van Parkinson patiënten die voor het eerst behandeld werden met ergot- en niet-ergot-gederiveerde dopamine agonisten (DA's) (**hoofdstuk 4.2**). We vonden dat nieuwe gebruikers van ergot-gederiveerde DA's een hoger basis risico hebben op het ontstaan van cardiovasculaire aandoeningen,

dit is belangrijk indien vergelijkende studies worden gedaan. Onze laatste studie betreft de vergelijking het risico op valvulaire regurgitatie tussen gebruikers van ergot- en niet-ergot-gederiveerde dopamine agonisten en levodopa gebruikers. Voor deze studie hebben wij data van drie databases (Health Search uit Italië, THIN uit Engeland en IPCI uit Nederland) gecombineerd. In deze studie werd bevestigd dat personen die langdurig pergolide of cabergoline gebruiken voor Parkinson een verhoogd risico hebben op symptomatische valvulaire regurgitatie in vergelijking met mensen die levodopa gebruiken. Er was geen bewijs voor een toegenomen risico bij gebruik van niet-ergot-gederiveerde dopamine agonisten (**hoofdstuk 4.3**).

In de algemene discussie in **hoofdstuk 5** worden de belangrijkste bevindingen samengevat en wordt verder ingegaan op enkele methodologische zaken om de interpretatie van de resultaten te vergemakkelijken. Als laatste volgen er enkele aanbevelingen voor toekomstig onderzoek.

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My third scientific family is in Rotterdam, at the Department of Medical Informatics of the Erasmus University Medical Center, where I was adopted since 2005. There is a person that trusted me and my working skills since the beginning, this person is prof.dr. Miriam Sturkenboom! Thank you, Miriam for your brilliant scientific supervision as well as for the immense psychological support and the empathy when listening to my typically Italian complaints on Dutch weather and food, and thanks also for your advices in all the critical situations that I faced with in the last four years. If we call you “Grande Madre” is not just by coincidence.

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1. PHD TRAINING

Research skills

Statistics and methodology

- 2002-2006 Post-graduation Degree in Clinical Pharmacology at the University of Messina, Messina, Italy.
- 2006-2008 Master of Science in Clinical Epidemiology, Netherlands Institute for Health Sciences, Erasmus University, Rotterdam, The Netherlands.

Oral Presentations

- 2008 24th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Copenhagen – Denmark. Fatal and Non-Fatal Pneumonia Associated with Atypical and Typical Antipsychotic Use in Elderly Patients.
II meeting “The contribution of Alzheimer evaluation centres in the management of patients with dementia”, Italian National Health Institute, Rome, Italy. “Prescribing pattern of antipsychotic drugs in Italian general population: Focus on dementia in the years 2000-2005”.
8th Annual Meeting of International Society of Pharmacovigilance, Buenos Aires – Argentina. Data mining on large health record databases for detecting adverse reactions: which events to monitor?
- 2007 8TH Congress Of European Association For Clinical Pharmacology And Therapeutics (EACPT), Amsterdam – the Netherlands. “Did the marketing of new antiepileptic drugs (AEDs) change the prescribing pattern of AEDs in Italy?”

- 2006 XV National Conference of Italian NeuroPsychoPharmacology Society (SINPF). Genova, Italy. “Monitoring models for neuropsychiatry medications: limits and advantages of databases”.
- XV National Conference on the “EVALUATION OF DRUG UTILIZATION AND SAFETY: EXPERIENCES IN ITALY”, Italian National Health Institute, Rome, Italy. “Risk of mortality associated with the use of antipsychotic drugs. A population-based study”

Seminars and workshop

- 2008-2009 Advanced topics in Pharmacoepidemiological methods, special skill workshop, International Conference on Pharmacoepidemiology and Therapeutic Risk.
- 2006-2008 Research seminars, Department of Epidemiology and Medical Informatics, Erasmus MC, Rotterdam, The Netherlands.
- 2006-2008 Dutch National meeting of Medical informatics PhD

Teaching

- 2005-2008 Supervising and teaching medical students at the University of Messina, Messina, Italy.
- 2006-2007 Teaching on the drug prescribing at the Local Health Unit of Caserta, Italy.
- 2005-2007 Teaching at the Master course on the drug management for health professionals at the Local Health Units of Palermo, Enna, Messina – Italy.

Others

- 2008-current Work package Leader of the European project “Exploring and Understanding Adverse Drug Reactions by integrative mining of clinical records and biomedical knowledge (EU-ADR)”
- 2006-current Referee activities for various international journals (Pharmacoepidemiology and Drug Safety, Expert Opinion on Drug Safety, Psychiatric Services, Epilepsy Research, Neuroepidemiology).
- 2007 Expert in the Seventh Research Framework Programme for European Union (‘FP7-HEALTH-2007-Drug Safety’).

ABOUT THE AUTHOR

The author of this thesis was born in Messina (Italy) on 30th January, 1978. After obtaining a grammar diploma with full grades at the Liceo Classico “F. Maurolico” in Messina in 1996, he started to study Medicine and Surgery at the University of Messina, for which he graduated *cum laude* in 2002. In 2005, he started to work as a PhD student at the Department of Medical Informatics of Erasmus Medical Center (EMC) in collaboration with the Department of Clinical and Experimental Medicine and Pharmacology of the University of Messina. Meanwhile, in 2006 he obtained the Postgraduate degree *cum laude* in Clinical Pharmacology at the University of Messina. In 2008, he obtained a Master of Science degree in Clinical Epidemiology at the National Institute of Health Sciences (Nihes) in The Netherlands.

Aside the research that is presented in this thesis, he is currently involved in the scientific management of the European Project “Exploring and Understanding Adverse Drug Reactions by integrative mining of clinical records and biomedical knowledge (EU-ADR)” that is coordinated by the Department of Medical Informatics of the EMC. Furthermore, he collaborates as expert in pharmacoepidemiology with the Research Institute “IRCCS Centro Neurolesi - Bonino-Pulejo”, Messina (Italy) and the Health Search/Thales database of the Italian College of General Practitioners (SIMG), Florence (Italy). From SIMG he received in 2006 a grant for a project that was funded by Italian Drug Agency: “Evaluation of prescribing pattern and safety profile of antidepressant and antipsychotic medications in Italian general practice”. In 2007, he was expert in the Seventh Research Framework Programme for European Union (call ‘FP7-HEALTH-2007-Drug Safety’).

Additionally, he is a scientific collaborator for the update and management of the website on pharmacovigilance (www.farmacovigilanza.org) owned to Clinical Pharmacology section of Italian Society of Pharmacology.

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