Adverse events in the elderly population of Manitoba treated with antipsychotic pharmacotherapy

by

Irina Vasilyeva

A thesis submitted to the Faculty of Graduate Studies of
the University of Manitoba
in partial fulfillment of the requirements of the degree of
Master of Science

Faculty of Pharmacy
University of Manitoba
Winnipeg

THE UNIVERSITY OF MANITOBA
FACULTY OF GRADUATE STUDIES

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ABSTRACT

Objectives The safety of antipsychotic use in elderly persons has recently been questioned. The incidence of adverse events (AEs) (extrapyramidal syndromes (EPS), cerebrovascular and cardiac events, and all-cause mortality) in the elderly users of first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) was compared. Risks of AEs in antipsychotic-exposed persons and non-exposed individuals were also assessed.

Methods A population-based retrospective cohort study was conducted in the elderly Manitoba residents who received their first antipsychotic medication between April 1, 2000 and March 31, 2007. Cox proportional hazards models were built to compare risks of AEs in FGA and SGA users, as well as in non-exposed subjects.

Results SGAs were associated with a lower risk of all-cause mortality (adjusted HR 0.683, 95% CI 0.577–0.809) and a higher risk of myocardial infarction (1.614 [1.024–2.543]) compared to FGAs. No significant differences between FGAs and SGAs were found for cerebrovascular events, cardiac arrhythmia and congestive heart failure (CHF) but a higher incidence of EPS was observed for FGAs compared to risperidone. Both FGA and SGA users were at a higher risk of cerebrovascular events (FGAs 1.415 [1.114–1.797]; SGAs 1.611 [1.388–1.869]) and CHF (FGAs 1.228 [0.893–1.689]; SGAs 1.242 [1.003–1.536]) compared to non-exposed subjects. Only FGA-users were at a higher risk of death compared to non-exposed subjects (FGAs 1.387 [1.065–1.805]; SGAs 0.824 [0.708–0.959]). Both FGA and risperidone use were associated with a higher risk of EPS (FGAs 3.503 [2.271–5.403]; risperidone 1.733 [1.214–2.472]).

Conclusions Both classes of antipsychotics might lead to potentially life-threatening AEs. Neither FGAs nor SGAs seem to have a superior overall safety profile. Antipsychotic pharmacotherapy should be prescribed in elderly persons after careful consideration of all risks and benefits.

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The results and conclusions presented are those of the author. No official endorsement by Manitoba Health is intended or should be inferred.

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ABBREVIATIONS USED

CHF	Congestive heart failure
CI	Confidence interval
DPIN	Drug Product Information Network
EPS	Extrapyramidal syndromes
FGA	First-generation antipsychotic
HR	Hazard ratio
ICD	International Classification of Diseases
PCH	Personal care home
RCT	Randomized control trial
SGA	Second-generation antipsychotic
TD	Tardive dyskinesia

PREMISE

The Canadian population, similarly to what is happening in other western societies, is aging. An increasingly greater burden on our health care system is expected as the number of persons affected by age-related diseases like cancer and dementia will grow in the upcoming decades.

Pharmacotherapy is commonly used in the treatment of most age-related conditions; but, the use of medications is especially challenging in elderly persons. Major physiological changes in the aging body deeply affect pharmacokinetics and pharmacodynamics, and the common presence of multiple comorbid diseases further complicates the management of the elderly patient. Because of these factors elderly populations are often excluded from randomized controlled trials (RCTs) and data on the efficacy of many pharmaceuticals lack specific recommendations on their prescribing to older individuals. Furthermore, RCTs, designed to obtain market approval, often provide only short-term data on the safety of new medications. A full understanding of the risks associated with the chronic use of pharmaceuticals comes only from post-marketing surveillance.

Observational pharmacoepidemiological studies offer the unique opportunity to assess drug safety in "real world" conditions as data are collected from large populations over extended periods of time. In fact, pharmacoepidemiological research plays an important role in post-marketing evaluation of the safety of medications and provides clinicians with updated information on risks and benefits of pharmacotherapy.

Antipsychotic agents are a class of medications whose safety and effectiveness in the treatment of elderly patients have recently been brought into question.

The results of the study described in this thesis will provide insight into the risks associated with the use of antipsychotic medications in the entire elderly population of Manitoba.

BACKGROUND

Use of antipsychotics in elderly persons

Antipsychotic medications have been widely used in elderly persons in a variety of diagnoses. Originally developed to treat schizophrenia and bipolar disorder, antipsychotics are now used more broadly to include behavioural and psychological symptoms of dementia, chemotherapy-induced nausea and vomiting, insomnia, anxiety and, more recently, depression.

The introduction of chlorpromazine in 1954 was a major development in the field of psychiatry (Lopez-Munoz et al., 2005). The invention of chlorpromazine encouraged scientists to engage in further research for new molecules with antipsychotic activity and compounds such as thioridazine, trifluoperazine, haloperidol and fluphenazine were subsequently brought to market (Preskorn, 2007). Antipsychotic agents developed in the 1950s–1980s are now classified as first-generation antipsychotics (FGAs) (Shen, 1999). These agents are chemically subdivided into phenothiazines (chlorpromazine, promazine, triflupromazine, methotrimeprazine, mesoridazine, thioridazine, prochlorperazine, perphenazine), butyrophenones (haloperidol), thioxanthenes (flupenthixol, zuclopenthixol) and dibenzoxazepines (loxapine). FGAs are also classified into low-potency (e.g., chlorpromazine, pimozide) and high-potency (e.g., haloperidol, flupenthixol, perphenazine, prochlorperazine) agents. The effective dose of an FGA is closely related to its affinity for dopamine D_2 receptors. High-potency antipsychotics have a greater affinity for D_2 receptors than low-potency medications, and the effective dose required to treat psychotic symptoms is much lower than for low-potency antipsychotics (Baldessarini et al., 1984; Creese et al., 1976). Soon after the introduction

of FGAs, it was noted that their use was associated with the development of involuntary movement disorders, also called extrapyramidal syndromes (EPS) (Snyder, 1976). These adverse events limited the use of FGAs in fragile elderly individuals who were highly susceptible to EPS (Caligiuri et al., 2000). The development of clozapine broke the paradigm that to be classified as an antipsychotic, a drug had to also cause EPS (Hippius, 1989). Clozapine's affinity for the 5-HT_{2A} and D_4 receptors combined with weak blockade of the D_2 receptors contribute the most to its advantages (Meltzer, 1994). Although the use of clozapine was not found to be associated with occurrence of EPS, agranulocytosis (decrease in the number of granulocytes), a potentially life-threatening adverse event, was observed in approximately 1% of clozapine users (Alvir et al., 1993). A successful clinical trial of clozapine in patients with treatment-resistant schizophrenia in 1988 proved the superior efficacy of clozapine and showed that the risk of agranulocytosis could be managed by blood monitoring (Kane et al., 1988). The agent was soon approved for treatment-resistant schizophrenia, yet clozapine was not safe enough to be recommended for use in elderly patients (Gareri et al., 2008; Hippius, 1999). Inspired by clozapine's successful trial, further research and development soon brought to the market a number of newer medications, collectively called second-generation antipsychotics (SGAs) (Shen, 1999). There are seven SGAs currently available on the Canadian market: clozapine, risperidone, olanzapine, quetiapine, ziprasidone, paliperidone and aripiprazole.

Late-onset schizophrenia and bipolar disorder

Antipsychotic medications were developed to treat schizophrenia and related conditions (e.g., schizotypal and delusional disorders) (Crilly, 2007), and their use is

approved for these conditions in Canada. Although schizophrenia is generally diagnosed in late adolescence or early adult life, some patients do become ill in middle or old age (Howard et al., 2000). According to the Consensus Statement of the International Late-Onset Schizophrenia Group, schizophrenia with age of onset over 60 years is classified as a very-late-onset schizophrenia-like psychosis (Howard et al., 2000), and it is often secondary to dementia and other neurodegenerative disorders (Folsom et al., 2006). In 2003, a Cochrane review found no trial-based evidence for developing treatment guidelines for patients with late-onset schizophrenia (Arunpongpaisal et al., 2003). A randomized controlled trial of risperidone and olanzapine in elderly patients with schizophrenia found that both medications improved psychotic symptoms and had a relatively low risk of adverse events (Jeste et al., 2003). Presently, antipsychotic medications are used in patients with late-onset schizophrenia and lower daily doses are typically required compared to patients with an early-onset of the disorder (Folsom et al., 2006).

Bipolar disorder, a chronic disease characterized by alternating periods of mania and depression, may be divided into early-onset (age less than 50 years at first diagnosis) and late-onset (age greater than 50) (Vasudev & Thomas, 2010). Recent data indicate that there are vascular changes in the brain that lead to late-onset bipolar disorder (Tamashiro et al., 2008). RCT data are not available and extrapolation of evidence from studies conducted in younger age groups is used in current pharmacotherapy decision-making (Vasudev & Thomas, 2010). Pharmacological (Oostervink et al., 2009) (e.g., antipsychotic, lithium or anticonvulsant medication) and non-pharmacological (Fagiolini et al., 2009) (e.g., education, management of disease, support for patients and their

families) options are available in late-onset bipolar disorder therapy and both classes of antipsychotics (FGAs and SGAs) have been prescribed to patients with late-onset bipolar disorder (Oostervink et al., 2009). In open-label studies, quetiapine and aripiprazole were found to be effective in older adults with bipolar mania (Sajatovic et al., 2008; Sajatovic, Coconcea et al., 2008).

Chemotherapy-induced nausea and vomiting

Nausea and vomiting occur in people with cancer as a consequence of chemotherapy. Antipsychotics are among the treatment options for controlling these symptoms (Lichter, 1996). Despite the lack of evidence from RCTs, haloperidol, methotrimeprazine, prochlorpromazine and olanzapine have been widely used for prevention and treatment of chemotherapy-induced nausea and vomiting (Keeley, 2009). The results of two recent open-label trials suggested that treatment with methotrimeprazine reduces nausea and vomiting in cancer patients. Improvement was documented in 20 out of 34 patients (58%) at day 5 of the trial with no significant changes in side effects compared to baseline in one trial (Kennett et al., 2005), and in 49 out of 53 patients (92%) with sedation reported as an adverse event in another (Eisenchlas et al., 2005).

Olanzapine has affinity for the D_2 and 5-HT_3 receptors, which appear to be involved in nausea and emesis (Bymaster et al., 1996; Bymaster et al., 2001). Antiemetic properties of olanzapine have recently been evaluated in a number of studies. A case-series study in palliative care patients found that treatment with olanzapine was well tolerated and successful in reducing nausea (Jackson & Tavernier, 2003), and an open-

label trial showed that olanzapine was effective as an antiemetic and well tolerated by cancer patients (15 out of 16 patients completed the protocol with 87% of them having no vomiting episodes) (Passik et al., 2004). These findings were further confirmed as the use of olanzapine was tested at maximum tolerated dose (no vomiting episodes in 8 out of 10 patients receiving highly emetogenic chemotherapy and in 17 out of 20 patients receiving moderately emetogenic chemotherapy) (Navari et al., 2005) as well as in combination with other agents (no vomiting episodes in 6 out of 8 patients receiving highly emetogenic chemotherapy and in 23 out of 32 patients receiving moderately emetogenic chemotherapy) (Navari et al., 2007). The authors suggested that olanzapine was effective in controlling chemotherapy-induced nausea and vomiting (Navari et al., 2005; Navari et al., 2007).

Behavioural and psychological symptoms of dementia

In Manitoba, the highest prevalence of antipsychotic use (across the decade of 1996 to 2006) was observed in the population aged 65 or older (reaching 4.32% in males and 6.04% in females in 2006), where dementia and Alzheimer's disease accounted for the majority of the reported diagnoses (Alessi-Severini et al., 2008a; Alessi-Severini et al., 2008b). A recent Canadian Institute for Health Information analysis of trends in the use of antipsychotics showed that the age-sex standardised rate of antipsychotic use in the elderly population of six Canadian provinces increased from 4.3% to 5% between 2001 and 2007 (The Canadian Institute for Health Information, 2009). The progressive aging of the Canadian population is associated with an increasing number of patients affected by dementia and Alzheimer's disease. Results of the Canadian Study of Health and Aging suggested that there would be approximately 60,000 new cases of dementia in Canada

each year (The Canadian Study of Health and Aging Working Group, 2000). The recent report of the Alzheimer Society of Canada states that one in eleven of Canada's seniors has Alzheimer's disease or a related dementia (Alzheimer Society of Canada, 2010). In Manitoba, the prevalence of dementia is estimated at 1.6% in the age group of 55–59 years, 7.5% in the age group of 60–69 years, 24.8% in the age group of 70–79 years, 28.6% in the group of 80–89 years and up to 37.3 % in persons aged 90 and older (Martens, 2007). The impact of dementia on medical resources and the society is growing, and there is an increasing need for effective management strategies.

Management of behavioural disturbances and psychotic symptoms associated with dementia and Alzheimer's disease is challenging. Risperidone is the only antipsychotic agent whose use is approved in Canada for patients with severe dementia; non-pharmacological strategies are recommended for psychosis and behavioural disturbances in dementia and Alzheimer's disease as first-line treatment (Gauthier et al., 2010). Taking into consideration the limited efficacy of FGAs and their extrapyramidal side effects (Barnes et al., 1982; Petrie et al., 1982) as well as the seemingly better safety profile of risperidone, physicians started prescribing the new SGAs for treating psychiatric symptoms of dementia and Alzheimer's disease. The "off-label" utilization of SGAs in the elderly population dramatically increased once they entered the market at the end of the 1990s and the use of FGAs decreased in this population group (Alessi-Severini et al., 2008a; Rochon, Stukel et al., 2005; The Canadian Institute for Health Information, 2009).

A number of RCTs of SGAs in patients with dementia have been undertaken in the last decade. The results from these RCTs (Ballard et al., 2005; Brodaty et al., 2003; De Deyn et al., 2005; De Deyn et al., 1999; De Deyn et al., 2004; Katz et al., 1999; Meehan

et al., 2002; Mintzer et al., 2007; Rocha et al., 2006; Schneider et al., 2006; Street et al., 2000; Streim et al., 2008) are summarized in Table 1. Katz et al. (1999) concluded that risperidone was efficacious in improving symptoms of psychosis in patients with severe dementia. The study results also suggested that risperidone at a higher dose, 2 mg, (Alexopoulos et al., 2004) was associated with higher risk of EPS compared to placebo. The same research group also reported deaths during the trial and stated that some of the deaths could be related to the use of SGAs. Adverse events reported by Brodaty et al. (2003) included somnolence, increased risk of stroke (five patients suffered a stroke in the risperidone-treated group) and EPS. In a study carried out by De Deyn et al. (1999) it was reported that somnolence occurred in 14 patients (12.2%) treated with risperidone and in 5 patients (4.4%) treated with placebo. The incidence of EPS was not significantly different in patients receiving risperidone (15%) and placebo (11%) (De Deyn et al., 1999).

One RCT of olanzapine showed no significant differences between any olanzapine dose and placebo in the primary outcome measures (the sum of the Agitation/Aggression, Hallucinations and Delusions items on the Neuropsychiatric Inventory – Nursing Home version) (Street et al., 2000). Adverse events reported were somnolence, abnormal gait, weight gain, anorexia and urinary incontinence. Dropouts due to adverse events were 18% in the placebo group vs. 44% in the olanzapine group. Risk of both somnolence and abnormal gait was found to be higher in the olanzapine group compared to placebo. Overall, no significant changes in EPS or cognition were reported compared to placebo (De Deyn et al., 2004; Meehan et al., 2002; Street et al., 2000).

Ballard et al. (2005) found that quetiapine did not significantly reduce agitation compared with placebo. Furthermore, quetiapine was associated with greater cognitive decline than placebo. The CATIE-AD Study Group assessed the effectiveness of risperidone, olanzapine and quetiapine in the treatment of Alzheimer's disease, and found no significant differences in time-to-discontinuation due to any reason between antipsychotic treatment and placebo, while adverse events were common in persons receiving SGAs (Schneider et al., 2006).

No RCTs of ziprasidone in elderly patients with dementia have been published. One exploratory open-label trial of ziprasidone showed significant improvements in behavioural symptoms, although only 15 out of 25 patients completed the study (Rocha et al., 2006). Four patients withdrew due to events possibly related to the drug.

Recent RCTs of aripiprazole did not show significant overall improvements in psychosis versus placebo (De Deyn et al., 2005; Mintzer et al., 2007). Several secondary efficacy measures of psychological and behavioural symptoms did show better results in aripiprazole-treated patients compared with placebo. EPS scores were low and similar in both groups. High rates of discontinuation due to adverse events for the 5 and 10 mg/d doses (18% and 25%, respectively) were noted in another recent trial (Mintzer et al., 2007). Adverse events reported in another placebo-controlled aripiprazole trial included urinary tract infection (aripiprazole vs. placebo) (8% vs. 12%), accidental injury (8% vs. 5%), somnolence (8% vs. 1%), and bronchitis (6% vs. 3%) (De Deyn et al., 2005). Streim et al. (2008) reported a higher prevalence of somnolence in the aripiprazole treatment group (14%) compared to placebo (4%).

Table 1. Randomized controlled trials of antipsychotics in dementia

Source	No. of patients/ length of study	Intervention	Outcomes	Adverse events
Katz et al. (1999)	625 patients, ≥ 55 years 12 weeks	Risperidone (0.5, 1.0, 2.0 mg/d) Placebo	BEHAVE-AD: 50% or more reduction (primary); CMAI, CGI-S (secondary). Primary: significant reduction in patients receiving 1 mg/d (45%) and 2 mg/d (50%) of risperidone. Placebo, 33%.	Significant difference in occurrence of EPS between 2 mg/d risperidone and placebo. Dose-related increases in somnolence and EPS. Three deaths considered to be drug-related. No difference in efficacy between 1 mg/d and 2 mg/d.
De Deyn et al. (1999)	229 patients, ≥ 55 years 13 weeks	Risperidone (0.5 to 4 mg/d) Placebo	BEHAVE-AD: 30% reduction (primary); CMAI, CGI-S (secondary). Primary: reductions in BEHAVE-AD score were significantly greater with risperidone than with placebo at week 12, but not at endpoint. Significant results for risperidone vs. placebo on several secondary outcomes.	No significant difference in the severity of EPS with risperidone vs. placebo. Somnolence was more common for risperidone (12.2%) than placebo (4.4%). Haloperidol was also compared to risperidone and haloperidol was associated with more severe EPS.
Street et al. (2000)	206 patients, mean age = 82.8 years 6 weeks	Olanzapine (5, 10, 15mg/d) Placebo	Sum of NPI/NH item scores for core symptoms (agitation/aggression, hallucinations and delusions) (primary) and a few secondary outcome measures. 5 and 10 mg, but not 15 mg, had a significant improvement on the core total vs. placebo.	No significant changes in EPS and no EPS event statistically different from placebo. 18% of placebo group dropouts were due to AEs vs. 44% of olanzapine group. Risk of both somnolence and abnormal gait higher in olanzapine group vs. placebo.
Meehan et al. (2002)	272 patients, mean age = 77.6 years 24 hours	Olanzapine (2.5, 5 mg) Placebo	PANSS-EC (primary); CMAI, ACES, NPI/NH (secondary). At 2 h post first injection, 2.5 and 5 mg showed significant improvement in their PANSS-EC score.	No significant differences among treatment groups in EPS (lorazepam was also studied). AEs not significantly different from placebo for any treatment.

Source	No. of patients/ length of study	Intervention	Outcomes	Adverse events
Brodaty et al. (2003)	345 patients, ≥ 55 years 12 weeks	Risperidone (mean = 0.95 mg/d) Placebo	CMAI total aggression score (primary); non-aggression CMAI subscales, BEHAVE-AD, CGI-C (secondary). Patients treated with risperidone improved significantly more than placebo on CMAI total aggression score, similar results for secondary outcomes.	Serious adverse events occurred in 8.8% in placebo group (no cerebrovascular AEs) and in 16.8% in risperidone group (5 patients had strokes, 1 transient ischemic attack). 15.9% of placebo group and 23.4% of risperidone had one or more EPS-like AE. Injury, falls and somnolence were the most common AEs.
De Deyn et al. (2004)	652 patients, ≥ 40 years 10 weeks	Olanzapine (1, 2.5, 5, 7.5 mg/d) Placebo	NPI/NH Psychosis subscale, CGI-C (primary); NPI/NH total and item subscores, BPRS total score and subscales (secondary). No significant primary outcome differences between any olanzapine dose and placebo.	Incidence of weight gain, anorexia and urinary incontinence numerically higher in olanzapine-treatment groups. General cognition showed no worsening in any treatment group, no difference among patients in motor function or anticholinergic AEs.
Ballard et al. (2005)	93 patients, > 60 years 26 weeks	Quetiapine (50–100 mg/d by week 12; 100 mg/day week 12–16) Placebo	CMAI, Cognition severe impairment battery (primary). No significant differences between treatments in the change in agitation inventory scores. Patients treated with quetiapine significantly worse severe impairment battery score than placebo.	No measures of EPS or cardiovascular events. Quetiapine-treated patients had significantly greater cognitive decline compared with placebo.
Rocha et al. (2006)	25 patients, ≥ 60 years 7 weeks	Ziprasidone (40–160 mg/d) Placebo	NPI total score (primary); CGI-S (secondary). The uncontrolled trial showed significant improvements in the primary outcome measure, as well as in the secondary outcome measure.	15 patients completed the study (4 patients withdrew due to events possibly related to the drug). 19 patients showed at least one adverse event (somnolence, gastrointestinal symptoms, parkinsonism, agitation, insomnia dizziness, lip edema).

Source	No. of patients/ length of study	Intervention	Outcomes	Adverse events
Schneider et al. (2006)	421 patients, weighted mean age = 81.2 years 36 weeks	Olanzapine (5.5 mg/day), Quetiapine (56.5 mg/day), Risperidone (1.0 mg/day) Placebo	Time to discontinuation (primary), CGI-C (secondary). There were no significant differences among treatment groups with regard to the time to discontinuation of treatment for any reason and improvement on the CGI-C scale.	There were higher rates of EPS in the olanzapine and risperidone groups (12% in each) than in the quetiapine group (2%) or the placebo group (1%). Sedation was more common in treatment groups (reported in 15 to 24% of patients) than in placebo (5%). The body weight of patients increased with antipsychotic drugs (by 0.18 to 0.45 kg per month) and decreased slightly with placebo (by-0.41 kg per month). Prolactin levels at week 12 were elevated in the risperidone group only.
De Deyn et al. (2005)	208 patients, ≥ 55–95 years 10 weeks	Aripiprazole (2 mg/d titrated upwards; 5, 10, 15 mg/d) Placebo	NPI Psychosis subscale (primary) several secondary outcome measures. NPI Psychosis subscale scores showed improvements in both groups (aripiprazole and placebo), and there was no significant difference between them. BPRS Psychosis and BPRS Core subscale scores showed significantly better results in aripiprazole-treated patients compared with placebo.	No significant differences in EPS scores found between aripiprazole and placebo. Incidence and number of discontinuations due to AEs were small (9.4% in aripiprazole, 6.9% in placebo) in the two groups.
Mintzer et al. (2007)	487 patients, 55–95 years 10 weeks	Aripiprazole (2, 5, 10 mg/d) Placebo	NPI/NH Psychosis subscale (primary) and several secondary measures. 10 mg/d group showed significantly greater improvements in the primary outcome measure compared to placebo at week 10.	Incidence of somnolence was low and not dose-dependent. Cerebrovascular AEs were found to be dose-dependent, and non-existing in placebo. High rates of discontinuation due to AEs for the 5 and 10 mg/d doses (18 and 25%, respectively) were noted.

Source	No. of patients/ length of study	Intervention	Outcomes	Adverse events
Streim et al. (2008)	256 patients, 55–95 years 10 weeks	Aripiprazole (2, 5, 10, 15 mg/d) Placebo	NPI/NH Psychosis subscale, CGI-S (primary) and several secondary outcome measures. Both primary measures showed improvements in both groups (aripiprazole and placebo), and there was no significant difference between them. Significantly greater improvements with aripiprazole vs. placebo were observed in secondary efficacy measures of psychological and behavioural symptoms.	AEs occurred in a similar proportion in each groups, except for somnolence, which was more prevalent in the aripiprazole group. EPS-related AEs were low (5% in aripiprazole, 4% in placebo) in both groups.

*ACES – Agitation-Calmness Evaluation Scale
BEHAVE-AD – Behavior Pathology in Alzheimer's Disease Rating Scale
BPRS – Brief Psychiatric Rating Scale
CGI-C – Clinical Global Improvement or Change scale
CGI-S – Clinical Global Impression scale
CMAI – Cohen-Mansfield Agitation Inventory
NPI/NH – Neuropsychiatric Inventory–Nursing Home Version (NPI-NH) Psychosis score
PANSS-EC – Positive and Negative Syndrome Scale Excited Component

Safety concerns

In the pre-clozapine decades, FGAs were occasionally given to elderly patients despite the risk of EPS and non-proven efficacy in treating psychiatric symptoms (Sink et al., 2005). While RCTs remain the gold standard for drug approval and clinical decision-making, physicians' opinion is often shaped by industry-sponsored research and marketing, especially when new drugs are brought to market. When antipsychotic therapy is indicated, clinicians often choose SGAs, yet clinical trials evaluating these agents have been short in duration and many do not provide adequate data on the risk of adverse events over long-term therapy. Epidemiological data have raised concerns over the use of antipsychotics in the elderly. Serious adverse events such as drug-induced parkinsonism, increased risk of stroke and cardiac arrhythmias, and increased mortality have been reported for both classes of antipsychotics (Trifiro et al., 2009). While SGAs have reduced the occurrence of EPS, other adverse events such as metabolic disturbances, prolongation of the QT interval, and sudden cardiac death have been observed in association with the use of this class of antipsychotics (Bullock, 2005; Straus et al., 2004; Zarate & Patel, 2001). Consequently, the safety and appropriateness of both FGA and SGA use in the elderly was brought into question.

Extrapyramidal syndromes

The link between antipsychotic use and EPS has been investigated for a long time, and concerns over both FGA and SGA use have been raised, especially in persons with dementia (Ganzini et al., 1991; Gwinn & Caviness, 1997; Mamo et al., 1999; Wirshing, 2001).

An early case-control study on antipsychotic-induced parkinsonism found a dose-response relationship (Avorn et al., 1995). Patients prescribed FGAs were more than five times more likely to begin antiparkinson medication compared to non-users of antipsychotics. The researchers suggested that extrapyramidal antipsychotic side effects often might be mistaken for idiopathic Parkinson's disease in older patients.

Rochon, Stukel et al. (2005) conducted an observational retrospective population-based cohort study on antipsychotics and induced parkinsonism. The results demonstrated that when the potency and dose of antipsychotics are considered, SGAs are not necessarily safer than FGAs in relation to the development of parkinsonism. The study found a dose-related association between the use of SGAs and the development of incident parkinsonism. At higher doses (risperidone 2 mg/day, olanzapine 10 mg/day, quetiapine 200 mg/day), individuals were more likely to experience development of parkinsonism relative to those receiving a drug at lower doses. Compared to individuals receiving SGAs, those dispensed FGAs were 30% more likely to experience the development of parkinsonism. Individuals not exposed to antipsychotics were 60% less likely to experience the development of parkinsonism compared to SGA users. Furthermore, those who received higher potency FGAs were at a 50% greater risk of developing parkinsonism compared to those receiving SGAs. Compared to persons dispensed a high-dose SGA, those dispensed an FGA were at similar risk for parkinsonism. The study suggested that parkinsonism was more common than what had been previously suspected in users of high doses of SGAs (more specifically risperidone and olanzapine).

Whereas EPS such as parkinsonism or dystonias usually develop early in the course of antipsychotic therapy, tardive dyskinesia (TD) typically takes longer to develop. An epidemiological study questioned whether SGAs have a lower risk of TD and other movement disorders than FGAs in the elderly population (Lee et al., 2005). The primary outcome was the development of TD or other drug-induced movement disorders (excluding parkinsonism). It was found that TD or other movement disorders developed in 3.0% of patients being treated with FGAs and in 3.5% of patients being treated with SGAs. The difference was not statistically significant, which suggested that drug-induced movement disorders may be a frequent complication of any antipsychotic therapy in older adults with dementia. A summary of epidemiological studies (Avorn et al., 1995; Lee et al., 2005; Rochon, Stukel et al., 2005) on antipsychotic-induced EPS can be found in Table 2.

Table 2. Observational studies on extrapyramidal syndromes

Source	Design/Population	Outcomes	Results
Avorn et al. (1995)	Case-control study using state Medicaid program	Prescription of antiparkinson medication	Compared to subjects not exposed to antipsychotics; odds ratio of 5.4 (4.8–6.1) for FGA users.
Rochon, Stukel et al. (2005)	Population-based cohort study (diagnosed with dementia)	Diagnosis of Parkinson disease or the dispensing of an antiparkinson drug	Compared to subjects treated with SGAs; hazard ratios of 1.30 (1.04–1.58) for FGAs, 0.40 (0.29–0.43) for subjects not exposed to antipsychotics. Compared to subjects treated with lower-potency SGAs; hazard ratios of 0.75 (0.48–1.15) for lower-potency FGAs, 1.44 (1.13–1.84) for higher-potency FGAs. Compared to subjects treated with low-dose SGAs; hazard ratio of 2.07 (1.42–3.02) for high-dose SGAs.
Lee et al. (2005)	Population-based cohort study (diagnosed with dementia)	Development of tardive dyskinesia or other drug-induced movement disorder other than parkinsonism	Compared to subjects treated with SGAs; hazard ratio of 0.99 (0.85–1.15) for FGAs.

Cardiovascular toxicity

Cardiovascular toxicity has long been well documented in the use of FGAs. Reports on sudden death and fatal or nonfatal arrhythmias associated with the use of antipsychotics have been numerous, especially regarding thioridazine (Hennessy et al., 2002; Timell, 2000; Reilly et al., 2002). The cardiovascular safety profile was also questioned in the new SGAs since their introduction. Cardiovascular morbidity and mortality associated with antipsychotics have been assessed in a number of observational studies. A selection of these studies is presented in Table 3. The studies report on different outcomes and antipsychotic exposures; as a consequence, it is difficult to make meaningful comparisons. Both FGAs and SGAs were found to be associated with an increased risk of sudden cardiac death (Ray et al., 2001; Ray et al., 2009). No significant differences between users of FGAs and SGAs in terms of hospitalizations for ventricular arrhythmia, congestive heart failure (Wang et al., 2007), myocardial infarction (Nakagawa et al., 2006; Wang et al., 2007) were found in some studies, although FGAs exhibited increased risks of ventricular arrhythmias and cardiac arrest in other studies (Liperoti, et al., 2005b; Wang et al., 2007).

Cerebrovascular events

In 2002, based on placebo-controlled clinical trials in dementia patients, Health Canada issued a warning regarding cerebrovascular adverse events associated with the use of risperidone (Health Canada, 2002). This warning stated that cerebrovascular adverse events such as transient ischemic attacks and stroke, including fatalities, were associated with the use of risperidone in elderly patients affected by dementia. In 2004, Health Canada followed with another warning; this time regarding cerebrovascular

adverse events of olanzapine (Health Canada, 2004). The placebo-controlled trials, which the warning was based on, showed an increased risk of cerebrovascular events and unproven efficacy of olanzapine in the treatment of dementia.

Risk of cerebrovascular events in risperidone-treated patients was reported in some RCTs (Brodaty et al., 2003; De Deyn et al., 2005), whereas others concluded that such an association could not be established (Formiga et al., 2005). In 2008, a case-control study showed a temporal relationship between antipsychotic exposure and risk of cerebrovascular events, giving further support for a causal relationship (Kleijer et al., 2009). The pattern showed that the increased risk of cerebrovascular events was concentrated in the first month of antipsychotic use, with an odds ratio of 9.9 (5.7–17.2) for antipsychotic use shorter than a week.

A summary of observational studies is given in Table 4. Two studies comparing the risk of stroke in FGAs to the agents risperidone and olanzapine, did not find any significant differences (Gill et al., 2005; Herrmann et al., 2004). Another study on stroke showed a higher risk in elderly using SGAs compared to non-exposed persons (Sacchetti et al., 2008). Exposure to antipsychotics in general was found to be associated with an overall increased risk for cerebrovascular events compared to non-exposure (Kleijer et al., 2009; Percudani et al., 2005), and a higher risk in SGA use relative to FGA use was also found (Kleijer et al., 2009; Percudani et al., 2005; Wang et al., 2007). Meanwhile, two studies failed to observe significant differences in adverse cerebrovascular events between persons exposed to either FGAs or SGAs and non-exposed (Barnett et al., 2007; Liperoti et al., 2005a). A systematic review on the subject has recently been published (Sacchetti et al., 2010).

Table 3. Observational studies on cardiovascular toxicity

Source	Design/Population	Outcomes	Results
Ray et al. (2001)	Medicaid cohort	Sudden cardiac death	Compared to subjects not exposed to antipsychotics; risk ratios of 2.39 (1.77–3.22) for moderate-dose antipsychotic use, 1.30 (0.98–1.72) for low-dose use, 1.20 (0.91–1.58) for former use.
Hennessy et al. (2004)	General Practice Research Database cohort	Diagnosis of ventricular arrhythmia, sudden death, unexplained death, and unattended death	Compared to subjects exposed to haloperidol; risk ratio of 0.9 (0.7–1.1) for thioridazine.
Liperoti et al. (2005b)	Case-control study on residents of nursing homes (diagnosed with dementia)	Hospitalization for ventricular arrhythmias and cardiac arrest	Compared to subjects not exposed to antipsychotics; odds ratios 1.86 (1.27- 2.74) for FGAs, 0.87 (0.58–1.32) for SGAs. Compared to SGAs; odds ratio of 2.13 (1.27–3.60) for FGAs.
Nakagawa et al. (2006)	Population-based case control study	Hospitalization for myocardial infarction	Compared to subjects not exposed to antipsychotics; relative risks of 0.98 (0.88–1.09) for SGAs, 0.99 (0.96–1.03) for FGAs.
Wang et al. (2007)	Prescription benefits program cohort	Hospitalization for acute myocardial infarction, diagnosis of ventricular arrhythmia, or congestive heart failure	Within 30 days, FGAs vs. SGAs; hazard ratios of 0.89 (0.59–1.33), 1.20 (1.03–1.39) and 1.04 (0.95–1.11) for acute myocardial infarction, ventricular arrhythmia, and congestive heart failure, respectively. Within 60 days, FGAs vs. SGAs; hazard ratios of 1.02 (0.75–1.40), 1.10 (0.98–1.24) and 1.00 (0.93–1.07), respectively. Within 120 days, FGAs vs. SGAs; hazard ratios of 1.16 (0.91–1.48), 1.06 (0.96–1.17) and 1.01 (0.95–1.07), respectively.
Ray et al. (2009)	Medicaid cohort	Sudden cardiac death	Compared to subjects not exposed to antipsychotics; incidence rate-ratios of 2.00 (1.69–2.35) for FGAs, 2.27 (1.89–2.73) for SGAs. Compared to former antipsychotic users; incidence rate-ratio of 1.13 (0.98–1.30) for antipsychotic use.

Table 4. Observational studies on cerebrovascular events

Source	Design/Population	Outcomes	Results
Herrmann et al. (2004)	Population-based cohort study	Hospital admission for stroke	Compared to subjects treated with FGAs; relative risk estimates of 1.1 (0.5–2.3) for olanzapine and 1.4 (0.7–2.8) for risperidone.
Liperoti et al. (2005a)	Case-control study on residents of nursing homes (diagnosed with dementia)	Hospitalization for cerebrovascular events	Compared to subjects not exposed to antipsychotics; odds ratios of 0.87 (0.67–1.12) for risperidone, 1.32 (0.83–2.11) for olanzapine, 1.57 (0.65–3.82) for other SGAs, and 1.24 (0.95–1.63) for FGAs.
Percudani et al. (2005)	Case-control study using regional databases on hospital admission and prescriptions	Cerebrovascular-related outcomes	Compared to subjects not exposed to antipsychotics; odds ratio of 1.24 (1.16–1.32) for antipsychotic use. Compared to FGAs; odds ratio of 1.42 (1.24–1.64) for SGAs. Compared to haloperidol; odds ratios of 1.44 (0.88–2.36) for clozapine, 1.26 (0.92–1.72) for olanzapine, 1.43 (1.12–1.93) for risperidone, 1.39 (0.95–2.05) for quetiapine.
Gill et al. (2005)	Population-based cohort study (diagnosed with dementia)	Hospital admission for ischaemic stroke	Compared to subjects treated with FGAs; hazard ratios of 1.01 (0.81–1.26) for SGAs, 1.04 (0.82–1.31) for risperidone, 0.91 (0.62–1.32) for olanzapine, 0.78 (0.38–1.57) for quetiapine.
Wang et al. (2007)	Prescription benefits program cohort	Diagnosis of cerebral hemorrhagic and ischemic events	Compared to subjects treated with FGAs; hazard ratios of 1.08 (0.99–1.18), 1.10 (1.02–1.19) and 1.09 (1.02–1.16) for SGAs within, 30, 60 and 120 days, respectively.
Barnett et al. (2007)	Veterans Administration cohort	Hospitalization for cerebrovascular events	Compared to subjects not exposed to antipsychotics; hazard ratios of 1.29 (0.48–3.47) for FGAs and 1.20 (0.83–1.74) for SGAs.
Sacchetti et al. (2008)	Health Search Database cohort	Incident stroke	Compared to subjects not exposed to antipsychotics; hazard ratios of 2.46 (1.07–5.65) for SGAs, 5.79 (3.07–10.9) for phenothiazines, 3.55 (1.56–8.07) for butyrophenones, 2.20 (0.98–4.90) for substituted benzamides. Compared to subjects treated with SGAs; hazard ratios of 1.44 (0.55–3.76) for butyrophenones, 2.34 (1.01–5.41) for phenothiazines, 0.89 (0.33–2.38) for substituted benzamides.
Kleijer et al. (2009)	PHARMO record database	Ischemic or haemorrhagic stroke, and transient ischemic attack	Compared to subjects not exposed to antipsychotics; odds ratio of 1.6 (1.3–2.0) for antipsychotic use. Compared to FGAs; odds ratio of 2.6 (1.3–5.0) for SGAs.

Increased mortality

In 2005, Health Canada issued a third warning on use of SGAs, this time regarding an increased risk of death associated with the use of these medications in patients with dementia (Health Canada, 2005). The warning was based on 13 placebo-controlled studies, which together showed an increased death rate in patients treated with risperidone, olanzapine and quetiapine. According to Health Canada, most deaths were related either to cardiovascular (heart failure, sudden death) or infectious causes. The epidemiological studies that followed the warning (Gill et al., 2007; Hollis et al., 2007; Hollis, Grayson et al., 2007; Kales et al., 2007; Liperoti et al., 2009; Rossom et al., 2010; Schneeweiss et al., 2007; Setoguchi et al., 2008; Trifiro et al., 2007; Wang et al., 2005) (see Table 5), having much bigger population samples, provided more comprehensive data on mortality associated with the use of antipsychotics.

Many studies have shown an increased risk of all-cause mortality in elderly taking FGAs compared to SGAs (Gill et al., 2007; Liperoti et al., 2009; Schneeweiss et al., 2007; Setoguchi et al., 2008; Wang et al., 2005), while a few other studies have reported a similar risk of death (Kales et al., 2007; Trifiro et al., 2007). Schneeweiss et al. (2007) found a dose-dependent risk of death in SGA users. Setoguchi et al. (2008) reported a greater risk of cardiovascular and respiratory deaths among FGA users. More specifically, they found that cardiovascular deaths could explain half of the excess mortality in incident FGA users. An increased risk of mortality has also been associated with both classes of antipsychotics compared to non-users (Gill et al., 2007; Trifiro et al., 2007). Gill et al. (2007) found SGAs to be associated with a significant increase in

mortality compared to non-use in both the community setting and in long-term care facilities.

A recent Finnish study on mortality in patients with schizophrenia (all age groups including the elderly) confirmed an increased risk of mortality associated with individual SGAs, and highlighted that clozapine seems to be associated with a substantially lower mortality than any other antipsychotic (Tiihonen et al., 2009). However, more evidence would be needed in order to establish the difference in risk between individual antipsychotics (Hollis et al., 2007; Rossom et al., 2010; Schneeweiss et al., 2007), which are now treated as classes in the public health advisories. Furthermore, some concerns have been raised over the fact that FGAs are not included in warnings issued by Health Canada and the FDA (Barnett et al., 2006; Schneeweiss et al., 2007; Trifiro et al., 2007; Wang et al., 2005). Based on observational data, the FDA eventually expanded their warnings to include FGAs (The Food and Drug Administration, 2008).

Pharmacoepidemiological data was also reported for patients living in long-term care facilities. Antipsychotic agents were found to be used more frequently in nursing home residents compared to community dwellers and appropriateness of such use was brought to question (Bronskill et al., 2009; Rochon, 2007). A study from the US reported that 58% of Medicare nursing home residents who were given antipsychotics exceeded maximum dose level, received duplicate therapy or had inappropriate indications (e.g., prescribing for memory problems, nonaggressive behaviours or depression without psychotic features) (Briesacher et al., 2005). A recent study showed that the Health Canada warnings had a limited effect on the prescription rates of these agents in elderly people with dementia in the province of Ontario (Valiyeva et al., 2008). In fact, the

overall use of these drugs in this patient group increased, leading the authors to call for more comprehensive and effective approaches to improve safety in vulnerable populations. The vast majority of observational studies assessing the safety of antipsychotic medication were done in patients affected by dementia and it is still unclear how generalisable the results of these studies are.

Table 5. Observational studies on all-cause mortality

Source	Design/Population	Outcomes	Results
Wang et al. (2005)	Prescription benefits program cohort	Death	Compared to subjects treated with SGAs; relative risk estimate of 1.37 (1.27–1.49).
Gill et al. (2007)	Population-based cohort study (diagnosed with dementia)	Death	Compared to subjects not exposed to antipsychotics; hazard ratio of 1.31 (1.02–1.70) for SGAs. Compared to subjects treated with SGAs; hazard ratio of 1.55 (1.19–2.02) for FGAs.
Hollis et al. (2007)	Cohort study (veterans and war widows)	Death	Compared to subjects treated with olanzapine; relative risk estimates of 2.26 (2.08–2.47) for haloperidol, 1.39 (1.15–1.67) for chlorpromazine, 1.23 (1.07–1.40) for risperidone.
Hollis et al. (2007b)	Cohort study (veterans and war widows who resided in an aged care facility)	Death	Compared to subjects treated with olanzapine; relative risk estimates of 1.67 (1.50–1.84) for haloperidol, 1.75 (1.31–2.34) for chlorpromazine. Compared to subjects treated with olanzapine, restricted to 60 days follow up; relative risk estimates of 2.17 (1.86–2.53) for haloperidol, 2.72 (1.84–4.01) for chlorpromazine.
Kales et al. (2007)	Veterans Affairs registries cohort (diagnosed with dementia)	Death	Compared to subjects treated with FGAs; relative risk estimates of 0.93 (0.75–1.16) for SGAs, 1.33 (0.94–1.86) for both FGAs and SGAs.
Schneeweiss et al. (2007)	Population-based cohort study	Death	Compared to subjects treated with SGAs; hazard ratios of 1.32 (1.23–1.42) for FGAs.
Trifirò et al. (2007)	Case-control study	Death	Compared to subjects treated with FGAs; odds ratios of 1.3 (0.7–2.4). Compared to subjects not exposed to antipsychotics; odds ratios of 2.2 (1.2–3.9) SGAs, 1.7 (1.3–2.2) for FGAs.
Setoguchi et al. (2008)	Population-based cohort study	Death	Compared to subjects treated with SGAs; hazard ratio of 1.27 (1.18–1.37) for FGAs.
Liperoti et al. (2009)	Medicaid/Medicare cohort (nursing home residents, diagnosed with dementia)	Death	Compared to subjects treated with SGAs; hazard ratio 1.26 (1.13–1.42) for FGAs. Compared to subjects treated with risperidone; hazard ratios of 1.31 (1.13–1.53) for haloperidol, 1.17 (1.00–1.38) for phenothiazines, 0.94 (0.49–1.79) for clozapine, 0.95 (0.80–1.12) for olanzapine, 1.05 (0.80–1.39) for quetiapine.

Source	Design/Population	Outcomes	Results
Rossom et al. (2010)	Veterans Health Administration cohort (diagnosed with dementia)	Death	Compared to subjects not exposed to antipsychotics; hazard ratios of 2.2 (1.7–2.9) for haloperidol, 1.3 (1.0–1.7) for olanzapine, 0.8 (0.6–1.1) for quetiapine, 1.2 (1.0–1.4) for risperidone.

Study Objectives

The current study was designed to evaluate adverse events in FGA- and SGA-treated elderly persons in order to contribute to the current knowledge on the risk of antipsychotic-associated morbidity and mortality in this vulnerable population. The entire elderly population (≥65 years of age) of the province of Manitoba, without restrictions on diagnosis, was included in the analysis.

The first objective of this study was to compare the incidence of

1. extrapyramidal syndromes,
2. cerebrovascular events,
3. cardiac events, and
4. all-cause mortality

in elderly persons taking FGAs or SGAs during the first year of treatment initiation.

The secondary objective of this study was to compare the incidence of adverse events in elderly persons treated with antipsychotics with that of those elderly persons who had never received antipsychotic therapy.

METHODS

Study design

The study was designed as a retrospective population-based cohort study. In a cohort study, a group of subjects who are free of disease at time zero are followed for a specific period of time until the onset of a certain event of interest. To achieve the first study objective, a group of subjects newly exposed to FGAs and a group of subjects newly exposed to SGAs were enrolled to be followed over time. For the secondary objective, the users of FGAs and SGAs were matched to non-exposed individuals, resulting in two independent comparisons. The incident user design that was chosen for this study has a number of advantages. First, it allows avoiding such biases as immortal time bias (Suissa, 2007; Suissa, 2008) as the analysis begins with the start of pharmacotherapy for every cohort member (Ray, 2003). Second, potential confounders can be measured just prior to the index date, which is similar to the practice in clinical trials of measuring the values of important prognostic factors just prior to randomization; as a result, the confounders cannot be influenced by the therapy. Third, the incident user design works particularly well for evaluation of short-term adverse events that occur early after pharmacotherapy initiation (Ray, 2003).

A cohort study must have a defined index date – the time of entry to the cohort. This study was an open cohort study, which means that the subjects were allowed to enter the cohort at any moment during the defined study period. The subjects were followed until the outcome of interest occurred (or death or end of study; the study was designed to have at least one year of follow-up for the last enrolled individual). The advantage of this design is that it maximizes the sample size, although, as every subject in the cohort was

followed for a different time period, statistical analysis has to account for different lengths of time that the subjects were part of the study. Clearly defined inclusion and exclusion criteria as well as outcomes of interest are essential in cohort studies (Etminan & Samii, 2004) and, for this study, are outlined below.

Data source

Data for this study were obtained from the administrative health care databases of the Manitoba Population Health Research Data Repository, housed at the Manitoba Centre for Health Policy. The databases include information on the entire population of the province and the use of a consistent set of identifiers permits the building of health histories of individuals across files and time. Nearly all contacts with the provincial health care system, including physicians, hospitals, personal care home (PCH) residence, and pharmaceutical dispensations are recorded. All registered individuals possess a 9-digit personal health identification number (PHIN), which is scrambled to protect privacy (The Manitoba Centre for Health Policy, 2009b; Roos et al., 1993; Roos & Nicol, 1999; Roos et al., 2005). The following databases were accessed: 1) population registry, 2) hospital abstracts, 3) medical services, 4) Drug Product Information Network (DPIN) prescription records, 5) personal care home records, as well as 6) vital statistics. A list of variables accessed in each database is given in Table 6.

Table 6. Administrative health care databases

Database	Variables accessed
Population Registry	PHIN, Date of birth, Postal Code
Hospital Abstracts	PHIN, Admission Date, Discharge Date, Length of Stay, Diagnosis
Medical Services	PHIN, Date of Service, Pattern of Practice Code, Diagnosis
Drug Product Information Network (DPIN)	PHIN, DIN, Date Provided, Days Supplied on Rx, Prescriber Specialty
Personal Care Home Records	PHIN, First Admission to Nursing Home
Vital Statistics	PHIN, Date of Death, Cause of Death

Records of physician reimbursement for medical care provided are submitted under a fee-for-service arrangement, and contain information on patient diagnosis at the 3-digit level of the International Classification of Diseases, Clinical Modification (ICD-9-CM) classification system and physician specialty. Separation abstracts for hospital services provided, include information on 16 ICD-9-CM diagnostic codes, of which the first is the diagnosis that is most responsible for the hospital stay. Records of dispensed prescriptions (DPIN), which are submitted by retail pharmacies for reimbursement by provincial drug insurance plans or for drug utilization review purposes, contain data on the date of dispensing, drug name, strength, dosage form, and quantity, and the 8-digit drug identification number (DIN).

Study population

A total of 81,536 persons, who were prescribed an antipsychotic agent between April 1, 2000 and March 31, 2008 and were registered with the Manitoba Population Health Research Data Repository, constituted the total user population. Among them, 39,685 persons received the first ever-recorded prescription of antipsychotics within the timeframe set for our cohort recruitment (April 1, 2000 to March 31, 2007). The timeframe of the cohort was set to ensure that all individuals who entered the cohort had no history of antipsychotic use in the five years prior to the cohort entry (as the DPIN

carries prescription dispensation information starting in 1995), and that all individuals could be followed for one year after first antipsychotic prescription dispensation (up to March 31, 2008). The final cohort of 12,434 patients was assembled on the basis of the following inclusion criteria (see flow chart in Appendix 1. Cohort definition):

1) aged 65 or older at the date of the first prescription dispensation
2) no history of antipsychotic use in 5 years prior to the cohort entry
3) Manitoba Health insurance coverage for 5 years prior to the cohort entry and during the follow-up period
4) a hospital stays for less than 25% of the year prior to the cohort entry
5) in the case of receiving the first antipsychotic prescription right after a hospital separation the length of stay had to be less than 30 days for this hospitalization

Criteria 4 and 5 above were applied in order to avoid possible medication misclassification bias, as the DPIN data does not contain information on medication administered in hospitals.

Additional exclusion criteria were applied for the EPS analysis and all-cause mortality comparisons (see below). As emergent EPS, which can be attributed to the exposure to antipsychotic medication, were the outcome of interest, persons with prior history of Parkinson's disease (ICD-9-332), extrapyramidal symptoms (ICD-9-333), other movement disorders (ICD-9-781) and/or exposure to antiparkinson medication (i.e., dopaminergic and anticholinergic agents) as well as those who had a history of brain tumour (ICD-9-191, 192, 198.3) were excluded. The SGA group exclusively in the EPS analysis was restricted to risperidone users because the agents within the SGAs class differ a lot in their receptor binding profile (with risperidone being more similar than

other SGAs to FGAs), and therefore it would make sense to run a comparison with each individual agent. However, having almost 70% of SGA users starting on risperidone, it was not possible to run meaningful comparisons for the other agents, as the sample sizes for olanzapine and quetiapine were too small. Risperidone users in the EPS comparison were censored if they switched to another SGA.

As it has been shown that physicians prefer to prescribe FGAs in terminally ill cancer patients, those individuals who would die from cancer were excluded from the mortality analysis in order to avoid such selection bias. These patients die from cancer independently from antipsychotic use and keeping them in the cohort would lead to overestimating the risk of death in FGA-treated persons.

Selection of non-exposed persons

Propensity score matching (D'Agostino, 1998) was used to identify subjects for the control group. A match of three controls per antipsychotic-exposed person was attempted (1:3 matching ratio). As the study looked at four distinct outcomes, the propensity score matching model was built only on variables that are predictors for exposure to antipsychotics (Austin et al., 2010). These variables included age, sex, PCH residence, index year, number of hospitalizations, general practitioner visits in the year prior to the index date, overall comorbidity and a diagnoses of cancer (ICD-9-140-208), dementia (ICD-9-290), Alzheimer's disease (ICD-9-331), schizophrenia (ICD-9-295), delirium (ICD-9-293), mood disorder (ICD-9-296) and other psychiatric disorders (ICD-9-297-299) in particular, as well as the total number of drugs used and treatment with antidepressants, benzodiazepines, sedatives, hypnotics and anxiolytics. The propensity score was estimated using a logistic regression model in which exposure to any

antipsychotic was regressed on the variables mentioned above. The estimated propensity score reflects the predicted probability of antipsychotic exposure from the logistic model (Austin et al., 2010).

After estimating the propensity score, the subjects were matched using nearest neighbour matching with a caliper of 0.001 of the propensity score (subjects were first randomly sorted). If no non-exposed subject had a propensity score lying within the specified caliper width of the antipsychotic-exposed subject, then a matching could not be performed and that exposed subject was not used in the subsequent analysis. A "greedy matching" algorithm was used in the matching process. This algorithm makes an optimal decision at each matching step without attempting to make the best overall decision. Consequently, if a subject was matched at a specific step, this matched pair would not be revised, even if a better match was available. The matching was done without replacement, which means that any untreated subject could serve as a match only once (Coca-Perraillon, 2007).

All baseline characteristics for the non-exposed subjects were defined in the same way as for the antipsychotic-exposed subjects. For the EPS and all-cause mortality comparisons, exclusion criteria applied to the cohorts of non-exposed subjects were the same as for antipsychotic users.

Follow-up

All subjects included in the study were followed up until an event of interest (EPS, cerebrovascular or cardiac events, or death), or the end of the study (March 31, 2008). As the DPIN database does not include information on medications administered in

hospitals, persons admitted to a hospital for 30 days or longer were censored. Patients who switched from one class of antipsychotics to another (i.e., FGAs to SGAs, and vice versa) and patients with a gap in an antipsychotic prescription refill of 30 days or longer were also censored. Persons who moved out of the province were censored at the end of their coverage information. The incidence of adverse events was evaluated at five different time points: 30-, 60-, 90-, 180- and 360 days.

Outcomes

For each individual comparison, there was a defined outcome (see Table 7 for details and specific codes used). In the EPS comparison, the outcome was a diagnosis of movement disorder or Parkinson's disease and/or dispensation of antiparkinson drugs. Taking into account the fact that drug-induced movement disorders tend to be under-diagnosed (Esper & Factor, 2008), a single record in the Medical Services database was considered sufficient to define an event. A diagnosis of any cerebrovascular disease (both stroke and transient cerebral ischemia were included) was considered to be an outcome for the cerebrovascular events comparison. For the cardiac events analyses, outcomes were defined as a diagnosis of myocardial infarction, cardiac arrhythmia or congestive heart failure (CHF). Record of death (excluding cancer-related) was the outcome in all-cause mortality analysis.

Table 7. Definition of outcomes

Outcome of Interest	Hospital Abstracts	Medical Services	Vital Statistics	DPIN
Extrapyramidal Syndromes	ICD-9-332, 333, 781	ICD-9-332, 333, 781 (at least one diagnosis)	ICD-9-332, 333, 781	Prescription of antiparkinson medication
Cerebrovascular Events	ICD-9-430-438	ICD-9-430-438 (at least 2 diagnoses)	ICD-9-430-438	n/a

Outcome of Interest	Hospital Abstracts	Medical Services	Vital Statistics	DPIN
Cardiac Events	ICD-9-410, 411, 427 (excluding 427.3), 428	n/a	ICD-9-410, 411, 427 (excluding 427.3), 428	n/a
All-cause Mortality	n/a	n/a	Record of non-cancer death	n/a

Covariates

Baseline characteristics of the antipsychotic-exposed population and the matched non-exposed subjects were evaluated. The date of the first dispensation of an antipsychotic prescription was considered to be the index date for antipsychotic-exposed persons. For non-exposed subjects, the index date was identified as the July 1 of the year used in the matching process. Age was defined on the date of the first antipsychotic prescription dispensation. The sex of each individual was retrieved from the Manitoba Health's population registry. Personal care home residence was defined as residing in a nursing home prior to the index date. Data on hospitalizations in the year prior to the index date were obtained from the Hospital Abstracts database and mean number of physician visits in the same time frame was calculated using data from the Medical Services database. Data on the number of comorbid conditions were obtained from both hospital abstracts and medical services databases. Data were accessed in the 5 years prior to the index date to build a history of comorbid conditions for each person. A condition was defined to be present if a person had at least one diagnosis in the Hospital Abstracts database and/or at least two diagnoses in the Medical Services database. As an overall measure of comorbidity, the sum of Aggregated Diagnostic Groups (ADGs), defined in the Adjusted Clinical Group (ACG) case-mix system was assigned to each subject (exposed and non-exposed) (Baldwin et al., 2006; Perkins et al., 2004; Reid et al., 1999; Reid et al., 2001; Starfield et al., 1991; The Manitoba Centre for Health Policy, 2009;

Weiner et al., 1991). The DPIN dispensation data were accessed for information on medication use. The mean number of different medication classes used in the year prior was calculated and the history of individual classes of medication use was also obtained. For diagnoses used in the covariates definition, refer to Appendix 2. Covariates definition.

Statistical analysis

Standardized differences were calculated to identify significant differences between the FGA- and SGA-treated groups in the baseline characteristics as an alternative to traditional significance testing (t-test and chi^2-test). Standardized differences reflect the mean difference as a percentage of the standard deviation. This measure of distribution is not as sensitive to the sample size as traditional tests and provides a sense of the relative magnitude of differences (Mamdani et al., 2005). Standardized differences greater than 0.1 were considered to represent a significant difference between groups. Crude event rates, for each comparison, were calculated using the number of events per 100 person-years.

To examine the effect of SGA use on the incidence of adverse events compared to FGA use, time-to-event analysis using Cox proportional hazards models was performed. Cox proportional hazards models were also built to assess an effect on incidence of adverse events of antipsychotic exposure compared to non-exposed subjects.

The Cox proportional hazards regression model (Cox, 1972) is used to study a person's hazard rate. The hazard rate is the chance of the event of interest occurring in the next instant of time for a patient yet to experience the event. If, for example, the event

is a cardiac event, such as myocardial infarction, then the hazard rate for myocardial infarction at time t, h(t), is the chance of myocardial infarction for a patient who is alive and disease-free up to time t. The Cox model assumes that the hazard rate for a given patient can be factored into a baseline hazard rate (common to all patients) and a parametric function of the covariates, which describes the patient's characteristics. Thus the hazard rate for patient i can be expressed as

$$h_i(t) = h_0(t)\exp\{\beta Z_i\}.$$

Here $h_0(t)$ is a baseline hazard rate that is estimated non-parametrically; Z_i is the ith patient's covariate and β is the risk or regression coefficient. This is called a semiparametric model since the covariate effects are modelled using a parametric model, while the baseline hazard rate, $h_0(t)$, is modelled nonparametrically (Klein et al., 2001).

The Cox proportional hazards model has two key assumptions. The first assumption is random censoring; each subject has a censoring time that is statistically independent of their failure time, i.e., individuals are not lost to follow-up for reasons related to failure time. The second key assumption in the Cox model is that of proportional hazards. In a regression type setting, this means that the survival curves for two strata must have hazard functions that are proportional over time (i.e., constant relative hazard). Log-log survival curves were used to test for the proportional hazards assumption (Smith et al., 2003).

In all analyses, adjustments were made to account for potential confounders. The covariates in the models included age, sex, PCH residence, comorbid diseases and overall comorbidity burden (ADGs). The use of other medications in one year prior to the cohort

entry was also adjusted in analyses. To assess the changes in practice adjustments were made for the index year, as the patterns of antipsychotic use changed over the study period. Variables that remained unbalanced after propensity score matching were also included in the models. The matched nature of data was taken into consideration in antipsychotic-exposed vs. non-exposed comparisons (Austin et al., 2010).

Analyses were performed using SAS statistical software for Windows, version 9.1.3 (SAS Institute, Cary, North Carolina) (see Appendix 3. Example of SAS codes and Appendix 4. Example of SAS outputs). All significance testing was two-sided, with 95% confidence intervals (CIs). All analyses were conducted from a remote access site of the Manitoba Centre for Health Policy located at the Faculty of Pharmacy, University of Manitoba.

Ethics approvals

This population-based study received ethics approval from the Research Ethics Board of the University of Manitoba. The study was conducted in full compliance with the Personal Health Information Act of Manitoba and approved by the Health Information Privacy Committee (Appendix 5. Ethics approvals).

RESULTS

Eighty-one thousand and five hundred thirty-six (81,536) persons in Manitoba were prescribed antipsychotic therapy between April 1, 1995 and March 31, 2008. After applying all inclusion criteria a cohort of 12,434 persons was selected. The number of persons included into the EPS and all-cause mortality comparisons differs as additional exclusion criteria were applied. The utilization trends among incident users (the incidence rate of the elderly population overtime) are presented in Figure 1.

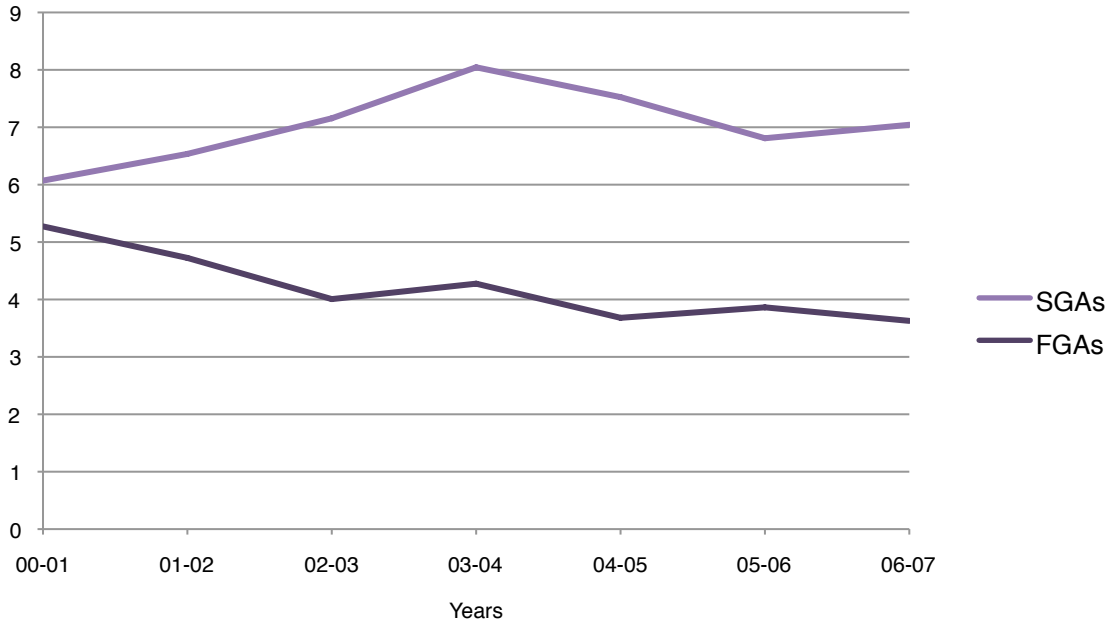

Figure 1. Utilization trends
Users per 1,000 persons.

The majority of antipsychotic users started on an SGA (Figure 2). Risperidone was the most prescribed antipsychotic overall (41.64%). Among SGA users, 66.55% started on risperidone, followed by olanzapine (22.50%) and quetiapine (10.95%). As previously mentioned, the use of clozapine is not common in this age group because of the potentially life-threatening risk of agranulocytosis. Those few persons who had a

clozapine prescription were excluded. The most commonly used FGAs were prochlorperazine (52.65% of all FGAs), haloperidol (19.87%), methotrimeprazine (8.96%), loxapine (7.71%) and chlorpromazine (6.92%).

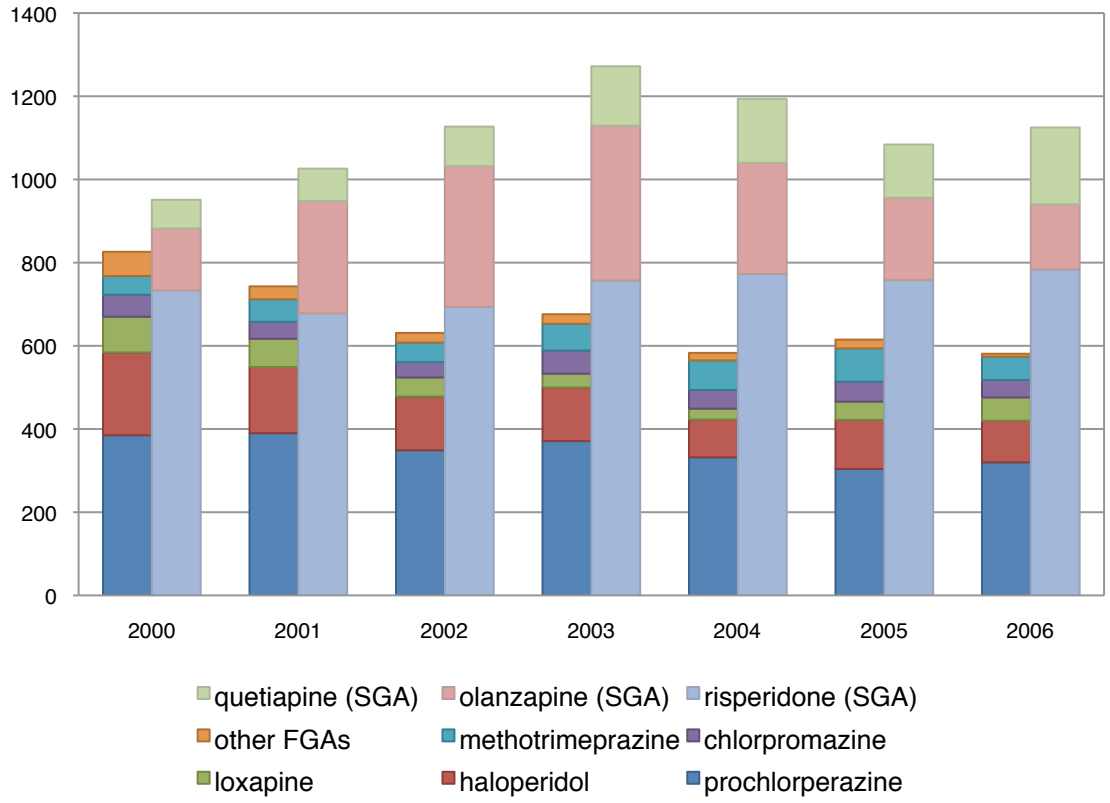

Figure 2. Utilization of antipsychotics
Number of new users of antipsychotic agents; the respective left columns are FGAs, right columns are SGAs.

Important differences in baseline characteristics were observed between FGA and SGA users. FGA users had a lower mean age (77.90 years) compared to SGA users (82.62 years). A larger proportion of SGA users were residents in a PCH (37.59% vs. 15.32%). The number of individuals with a history of hospital admission was higher in persons treated with FGAs (60.69% vs. 50.02%). Diagnoses of cerebrovascular diseases, CHF, atrial fibrillation, Parkinson's disease, dementia, Alzheimer's disease, delirium, mood disorder and other psychiatric disorders were more prevalent in persons treated

with SGAs, whereas malignant neoplasm was more common in the cohort of FGA users (this can be explained by the use of some antipsychotics as antiemetic agents used to treat nausea in cancer patients – methotrimeprazine and prochlorperazine). The use of other classes of medications was similar in both groups, except for a higher use of antidepressants (41.37% vs. 26.19%) and acetylcholinesterase inhibitors (3.23% vs. 0.56%) in SGA-treated persons.

Although the aim was to identify three non-exposed subjects for every antipsychotic-exposed individual the actual number of individuals matched to exposed subjects was less than that. While some antipsychotic-exposed persons were matched to three non-exposed persons, others had only one or two matched individuals. The matched cohort was slightly younger and differed significantly in some of the baseline characteristics.

Extrapyramidal syndromes

FGAs vs. risperidone – Extrapyramidal syndromes

Eight thousand eight hundred eighty-five (8,885) persons were selected (4,242 started on FGA therapy and 4,643 started on risperidone) for the EPS comparison. The following baseline characteristics differed significantly between the two groups (FGAs vs. risperidone): age (77.90 vs. 83.34 years), male sex (42.81% vs. 35.28%), PCH residence (15.02% vs. 40.19%), diagnoses of dementia (8.51% vs. 35.88%), Alzheimer's disease (4.79% vs. 20.59%), delirium (2.45% vs. 6.48%), mood disorder (2.78% vs. 6.16%) and other psychiatric disorders (7.54% vs. 24.12%). The mean number of medication used was significantly higher in the FGA-treated persons (12.48 vs. 11.31). An additional covariate was defined for this comparison – use of other medications

associated with development of movement disorders, which included such agents as reserpine, methyldopa, metoclopramide, lithium, valproate, amiodarone and tetrabenazine (Susatia & Fernandez, 2009; Van Gerpen, 2002). Use of these medications was much higher in FGA users (18.81% vs. 5.69%). The baseline characteristics of the cohorts are presented in Table 8.

Table 8. Baseline characteristics of FGA and risperidone users – EPS

Characteristics	First Generation Antipsychotics n = 4,242	Risperidone n = 4,643	Standardized Difference
Age, years (mean ± SD)	77.90 ± 7.97	83.34 ± 7.72	0.694*
Age distribution (n, %)			
65–74	1,682 (39.65)	710 (15.29)	
75–84	1,730 (40.78)	1,900 (40.92)	
> 85	830 (19.57)	2,033 (43.79)	
Sex, male	1,816 (42.81)	1,638 (35.28)	0.155*
Personal Care Home	637 (15.02)	1,866 (40.19)	0.587*
Year of entry to cohort			
2000–2001	764 (18.01)	663 (14.28)	
2001–2002	676 (15.94)	621 (13.37)	
2002–2003	573 (13.51)	618 (13.31)	
2003–2004	623 (14.69)	680 (14.65)	
2004–2005	540 (12.73)	692 (14.90)	
2005–2006	544 (12.82)	676 (14.56)	
2006–2007	522 (12.31)	693 (14.93)	
Hospitalization in past year	2,560 (60.35)	2,222 (47.86)	0.253*
Frequency of GP visits (mean ± SD)	16.02 ± 12.74	16.42 ± 12.89	0.031
History of Comorbidity (n, %)			
Dementia	361 (8.51)	1,666 (35.88)	0.698*
Alzheimer's Disease	203 (4.79)	956 (20.59)	0.489*
Schizophrenia	22 (0.52)	52 (1.12)	0.067
Delirium	104 (2.45)	301 (6.48)	0.196*
Mood Disorder	118 (2.78)	286 (6.16)	0.164*
Other Psychiatric Disorder	320 (7.54)	1,120 (24.12)	0.466*
Stroke	100 (2.36)	202 (4.35)	0.111*
History of Medication Use			
Number of medications used (mean ± SD)	12.48 ± 7.60	11.31 ± 6.94	0.161*
Anticonvulsants (n, %)	371 (8.75)	427 (9.20)	0.016
Benzodiazepines	1,811 (42.69)	2,059 (44.35)	0.033
Antidepressants	1,073 (25.29)	1,739 (37.45)	0.264*
Sedatives & Hypnotics	794 (18.72)	760 (16.37)	0.062
Anxiolytics	1,463 (34.49)	1,667 (35.90)	0.030

Characteristics	First Generation Antipsychotics n = 4,242	Risperidone n = 4,643	Standardized Difference
Acetylcholinesterase inhibitors	19 (0.45)	139 (2.99)	0.197*
Other medications associated with development of movement disorders	798 (18.81)	264 (5.69)	0.409*

*Standardized difference > 0.1 represents a significant difference

The number of events, average length of follow-up and contributed person-years for comparing FGA users and risperidone users are given in Table 9.

Table 9. Incidence of EPS within 360 days since treatment initiation

Cohort	No. of events	Mean duration of follow-up, days ± SD	Contributed person-years	Crude event rate, per 100 p-y
FGAs	74	88 ± 123	1,016.79	7.27
Risperidone	111	195 ± 140	2,472.50	4.49

The use of FGAs was associated with higher risks of EPS in the unadjusted analysis. After adjusting for variables listed in Table 8, users of FGAs were found to be at higher risk compared to users of risperidone. The results of unadjusted and adjusted analyses are presented in Figure 3.

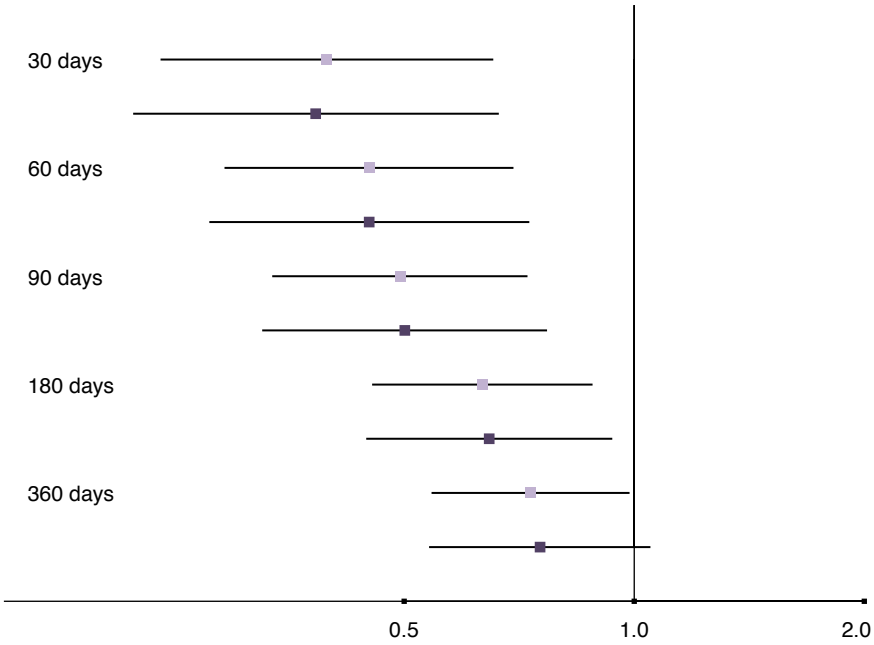

Figure 3. Hazard ratios for risperidone vs. FGAs – EPS
FGAs constitutes reference group. 95% CIs; unadjusted HRs in light coloured square markers, adjusted in dark. Values are given in Appendix 6. Hazard ratios.

Exposed vs. non-exposed – Extrapyramidal syndromes

Eight thousand one hundred twenty-four (8,124) out of 8,885 antipsychotic-exposed subjects were matched to non-exposed individuals. The baseline characteristics of FGA-exposed, risperidone-exposed and matched cohorts of non-exposed persons are given in Table 10.

Table 10. Baseline characteristics of antipsychotic-exposed and non-exposed cohorts – EPS

Characteristics	First Generation Antipsychotics n = 4,014	Matched non-users n = 9,433	Risperidone n = 4,110	Matched non-users n = 9,161
Age, years (mean, SD)	77.79 ± 7.94	76.86 ± 7.38	82.91 ± 7.69	80.32 ± 8.07
Age distribution (n, %)				
65–74	1,617 (40.28)	3,975 (42.14)	672 (16.35)	2,409 (26.30)
75–84	1,632 (40.66)	3,886 (41.20)	1,738 (42.29)	3,874 (42.29)
> 85	765 (19.06)	1,572 (16.66)	1,700 (41.36)	2,878 (31.42)
Sex, male	1,724 (42.95)	3,914 (41.49)	1,460 (35.52)	3,512 (38.34)
Personal Care Home	553 (13.78)	957 (10.15)	1,443 (35.11)	2,005 (21.89)

Characteristics	First Generation Antipsychotics n = 4,014	Matched non-users n = 9,433	Risperidone n = 4,110	Matched non-users n = 9,161
Year of entry to cohort				
2000–2001	724 (18.04)	1,677 (17.78)	615 (14.96)	1,361 (14.86)
2001–2002	646 (16.09)	1,501 (15.91)	547 (13.31)	1,224 (13.36)
2002–2003	541 (13.48)	1,256 (13.31)	546 (13.28)	1,212 (13.23)
2003–2004	588 (14.65)	1,394 (14.78)	598 (14.55)	1,306 (14.26)
2004–2005	508 (12.66)	1,221 (12.94)	605 (14.72)	1,355 (14.79)
2005–2006	512 (12.76)	1,212 (12.85)	584 (14.21)	1,316 (14.37)
2006–2007	495 (12.33)	1,172 (12.42)	615 (14.96)	1,387 (15.14)
Hospitalization in past year	2,369 (59.02)	4,394 (46.58)	1,856 (45.16)	3,723 (40.64)
Frequency of GP visits (mean ± SD)	15.40 ± 12.27	14.54 ± 11.28	15.23 ± 12.02	14.66 ± 11.37
History of Comorbidity (n, %)				
Dementia	327 (8.15)	228 (2.42)	1,328 (32.31)	630 (6.88)
Alzheimer's Disease	178 (4.43)	144 (1.53)	790 (19.22)	371 (4.05)
Schizophrenia	22 (0.55)	17 (0.18)	47 (1.14)	28 (0.31)
Delirium	85 (2.12)	130 (1.38)	228 (5.55)	259 (2.83)
Mood Disorder	105 (2.62)	45 (0.48)	236 (5.74)	212 (2.31)
Other Psychiatric Disorder	282 (7.03)	111 (1.18)	913 (22.26)	303 (3.31)
Stroke	92 (2.29)	130 (1.38)	161 (3.92)	178 (1.94)
History of Medication Use				
Number of medications used (mean ± SD)	11.86 ± 6.94	11.30 ± 7.25	10.64 ± 6.46	10.61 ± 6.96
Anticonvulsants (n, %)	337 (8.40)	554 (5.87)	355 (8.64)	589 (6.43)
Benzodiazepines	1,654 (41.21)	3,832 (40.62)	1,728 (42.04)	4,003 (43.70)
Antidepressants	950 (23.67)	2,198 (23.30)	1,431 (34.82)	3,323 (36.27)
Sedatives & Hypnotics	733 (18.26)	1,567 (16.61)	656 (15.96)	1,659 (18.11)
Anxiolytics	1,321 (32.91)	3,037 (32.20)	1,372 (33.38)	3,030 (33.07)
Acetylcholinesterase inhibitors	17 (0.42)	14 (0.15)	127 (3.09)	24 (0.26)
Other medications associated with development of movement disorders	719 (17.91)	722 (7.65)	221 (5.38)	553 (6.04)

The number of events, average length of follow-up and contributed person-years for FGA users vs. non-exposed and risperidone users vs. non-exposed are presented in Table 11 and Table 12, respectively.

Table 11. Incidence of EPS within 360 days since FGA treatment initiation

Cohort	No. of events	Mean duration of follow-up, days ± SD	Contributed person-years	Crude event rate, per 100 p-y
FGAs	68	87 ± 123	961.59	7.07
Non-exposed	159	332 ± 79	8,580.57	1.85

Table 12. Incidence of EPS within 360 days since risperidone treatment initiation

Cohort	No. of events	Mean duration of follow-up, days ± SD	Contributed person-years	Crude event rate, per 100 p-y
Risperidone	93	195 ± 139	2,197.34	4.23
Non-exposed	195	329 ± 82	8,256.45	2.36

Both FGA users and risperidone users were found to be at an increased risk of EPS compared to non-exposed subjects in the unadjusted models. In analyses adjusted for baseline characteristics (Table 10) both FGA and risperidone exposures were associated with a higher incidence of EPS. Hazard ratios for FGA users compared to non-exposed and risperidone users compared to non-exposed are shown in Figure 4 and Figure 5, respectively.

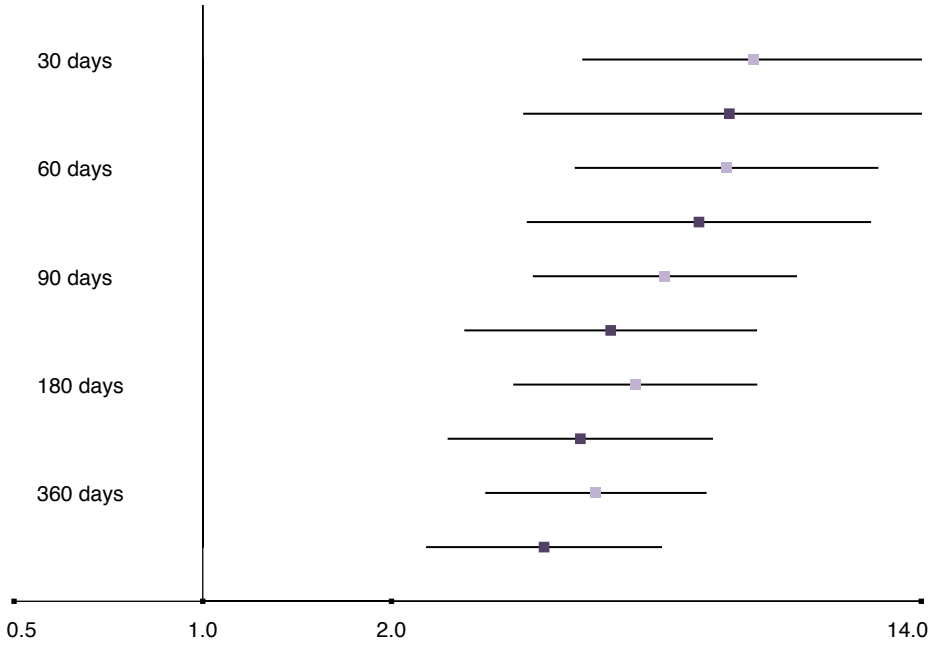

Figure 4. Hazard ratios for FGAs vs. non-exposed – EPS
Non-exposed constitutes reference group. 95% CIs; unadjusted HRs in light coloured square markers, adjusted in dark. Values are given in Appendix 6. Hazard ratios.

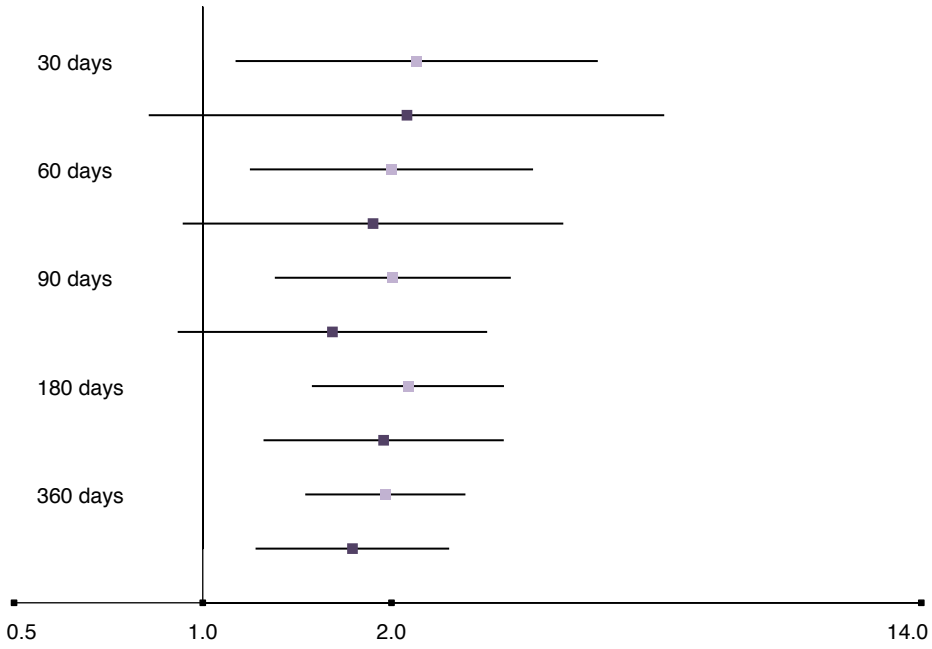

Figure 5. Hazard ratios for risperidone vs. non-exposed – EPS
Non-exposed constitutes reference group. 95% CIs; unadjusted HRs in light coloured square markers, adjusted in dark. Values are given in Appendix 6. Hazard ratios.

Cerebrovascular and cardiac events

FGAs vs. SGAs – Cerebrovascular and cardiac events

Twelve thousand four hundred thirty-four (12,434) persons were selected for cerebrovascular and cardiac events comparisons (4,655 started on FGA therapy and 7,779 started on SGAs). The baseline characteristics of the cohorts are presented in Table 13.

Table 13. Baseline characteristics of FGA and SGA users – Cerebrovascular and cardiac events

Characteristics	First Generation Antipsychotics n = 4,655	Second Generation Antipsychotics n = 7,779	Standardized Difference
Age years (mean, SD)	77.90 ± 7.98	82.62 ± 7.80	0.597*
Age distribution (n, %)			
65–74	1,854 (39.83)	1,394 (17.92)	
75–84	1,888 (40.56)	3,263 (41.95)	
> 85	913 (19.61)	3,122 (40.13)	
Sex, male	1,996 (42.88)	2,917 (37.50)	0.110*
Personal Care Home	713 (15.32)	2,924 (37.59)	0.522*
Year of entry to cohort			
2000–2001	826 (17.74)	951 (12.23)	
2001–2002	743 (15.96)	1,026 (13.19)	
2002–2003	631 (13.56)	1,127 (14.49)	
2003–2004	676 (14.52)	1,272 (16.35)	
2004–2005	583 (12.52)	1,194 (15.35)	
2005–2006	615 (13.21)	1,084 (13.93)	
2006–2007	581 (12.48)	1,125 (14.46)	
Hospitalization in past year	2,825 (60.69)	3,891 (50.02)	0.216*
Frequency of GP visits (mean ± SD)	16.24 ± 12.81	16.87 ± 12.85	0.049
History of Comorbidity (n, %)			
Stroke	117 (2.51)	312 (4.01)	0.084
Other cerebrovascular disease	748 (16.07)	1,889 (24.28)	0.206*
Hypertension	2,721 (58.45)	4,587 (58.97)	0.010
Congestive Heart Failure	894 (19.21)	1,930 (24.81)	0.136*
Atrial Fibrillation	374 (8.03)	903 (11.61)	0.120*
Other Arrhythmias	202 (4.34)	375 (4.82)	0.023
Myocardial infarction	361 (7.76)	692 (8.90)	0.041
Other ischemic disease	1,266 (27.20)	2,355 (30.27)	0.068
Peripheral vascular disease	218 (4.68)	453 (5.82)	0.051
Rheumatic heart disease	49 (1.05)	83 (1.07)	0.001
Other heart disease	395 (8.49)	767 (9.86)	0.048

Characteristics	First Generation Antipsychotics n = 4,655	Second Generation Antipsychotics n = 7,779	Standardized Difference
Diabetes mellitus	948 (20.37)	1,600 (20.57)	0.005
Chronic pulmonary disease	1,509 (32.42)	2,310 (29.70)	0.059
Malignant neoplasm	1,959 (42.08)	1,240 (15.94)	0.602*
Parkinson's disease	103 (2.21)	472 (6.07)	0.194*
Dementia	406 (8.72)	2,530 (32.52)	0.616*
Alzheimer's disease	226 (4.85)	1,489 (19.14)	0.451*
Schizophrenia	34 (0.73)	89 (1.14)	0.043
Delirium	122 (2.62)	542 (6.97)	0.205*
Mood disorder	144 (3.09)	601 (7.73)	0.206*
Other psychiatric disorder	375 (8.06)	1,860 (23.91)	0.443*
History of Medication Use			
Number of medications used (mean ± SD)	12.74 ± 7.73	11.79 ± 7.08	0.127*
Anticonvulsants (n, %)	475 (10.20)	894 (11.49)	0.041
Benzodiazepines	2,053 (44.10)	3,651 (46.93)	0.057
Antidepressants	1,219 (26.19)	3,218 (41.37)	0.325*
Sedatives & Hypnotics	887 (19.05)	1,461 (18.78)	0.007
Anxiolytics	1,660 (35.66)	2.899 (37.27)	0.033
Acetylcholinesterase inhibitors	26 (0.56)	251 (3.23)	0.197*
Anticoagulants	823 (17.68)	1,590 (20.44)	0.070
Diuretics	1,925 (41.35)	3,483 (44.77)	0.069
Beta-blockers	1,072 (23.03)	1,753 (22.54)	0.012
Calcium channel blockers	1,036 (22.26)	1,693 (21.76)	0.012
Angiotensin II receptors blockers	453 (9.73)	624 (8.02)	0.060
Angiotensin converting enzyme inhibitors	1,322 (28.40)	2,326 (29.90)	0.033
Lipid-lowering agents	860 (18.47)	1,203 (15.46)	0.080
Antidiabetic agents	688 (14.78)	1,088 (13.99)	0.023
Hormone replacement therapies	291 (6.25)	327 (4.20)	0.092

*Standardized difference > 0.1 represents a significant difference

Cerebrovascular events

The number of events, average length of follow-up and contributed person-years for FGA and SGA users are given in Table 14.

Table 14. Incidence of cerebrovascular events within 360 days since treatment initiation

Cohort	No. of events	Mean duration of follow-up, days ± SD	Contributed person-years	Crude event rate, per 100 p-y
FGAs	197	86 ± 121	1093.19	18.02
SGAs	809	193 ± 141	4101.07	19.72

Treatment with SGAs was associated with a higher risk of cerebrovascular events in unadjusted analyses. After adjustments for variables listed in Table 13 were made, no significant differences were found between FGA and SGA users. The results of the analyses are presented in Figure 6.

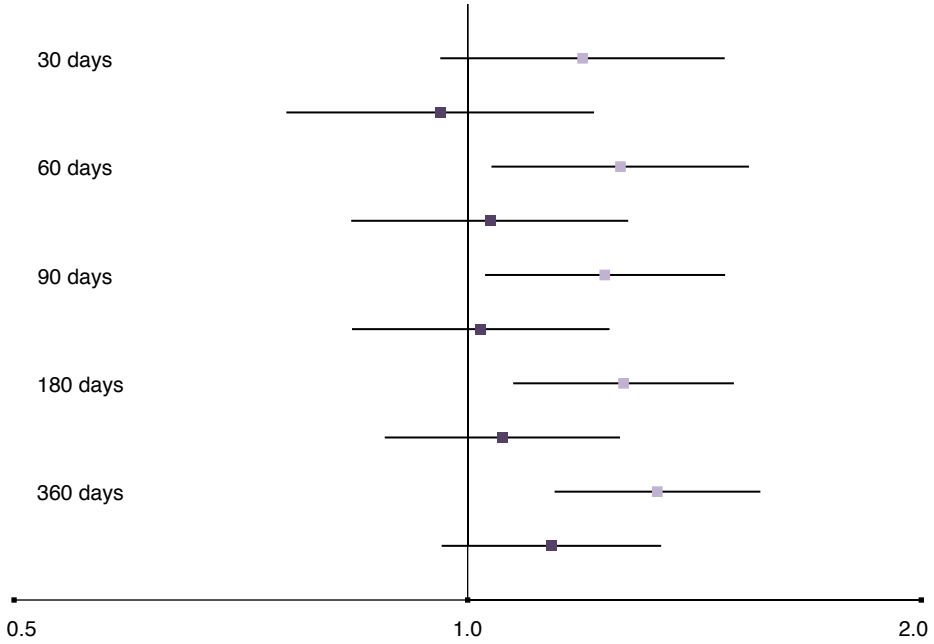

Figure 6. Hazard ratios for SGAs vs. FGAs – Cerebrovascular events
FGAs constitutes reference group. 95% CIs; unadjusted HRs in light coloured square markers, adjusted in dark. Values are given in Appendix 6. Hazard ratios.

Myocardial infarction

The number of events, average length of follow-up and contributed person-years for FGA and SGA users are given in Table 15.

Table 15. Incidence of myocardial infarction within 360 days since treatment initiation

Cohort	No. of events	Mean duration of follow-up, days ± SD	Contributed person-years	Crude event rate, per 100 p-y
FGAs	26	90 ± 124	1,145.71	2.23
SGAs	125	205 ± 140	4,359.50	2.87

In both unadjusted and adjusted analyses, hazard ratios were higher for the SGA-exposed group, but the confidence intervals, with the exception of the adjusted 360-day model, overlapped 1.0. The results of the analyses are presented in Figure 7.

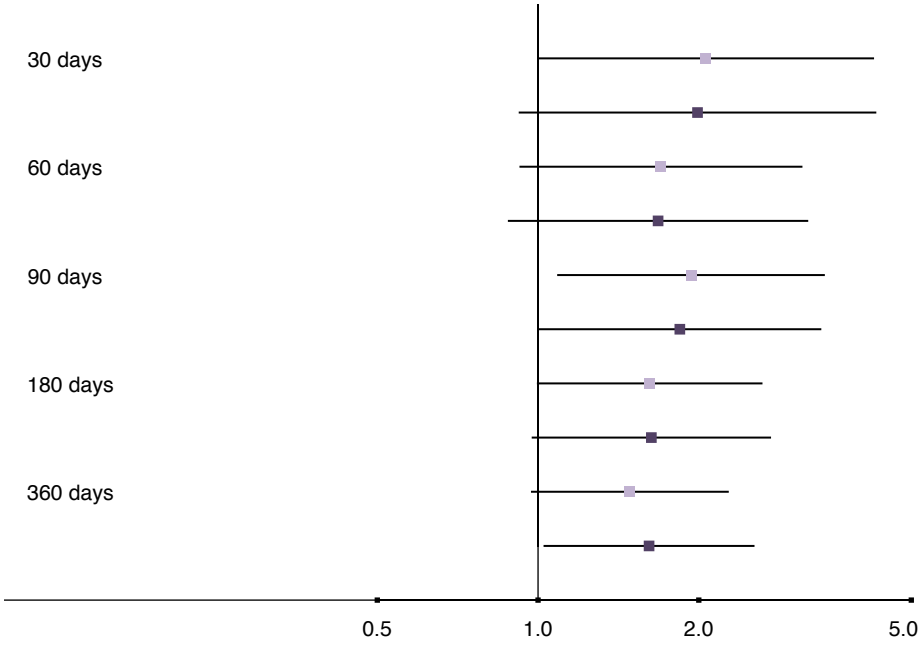

Figure 7. Hazard ratios for SGAs vs. FGAs – Myocardial infarction
FGAs constitutes reference group. 95% CIs; unadjusted HRs in light coloured square markers, adjusted in dark. Values are given in Appendix 6. Hazard ratios.

Cardiac arrhythmia

The number of events, average length of follow-up and contributed person-years for FGA and SGA users are given in Table 16.

Table 16. Incidence of cardiac arrhythmia within 360 days since treatment initiation

Cohort	No. of events	Mean duration of follow-up, days ± SD	Contributed person-years	Crude event rate, per 100 p-y
FGAs	7	90 ± 124	1,149.81	0.61
SGAs	21	206 ± 140	4,384.00	0.48

Cardiac arrhythmia diagnoses were rare events in our study. Confidence intervals for unadjusted and adjusted analyses were wide and overlapped 1.0. No statistically significant differences in risk of cardiac arrhythmia were found between the two groups. Hazard ratios are presented in Figure 8.

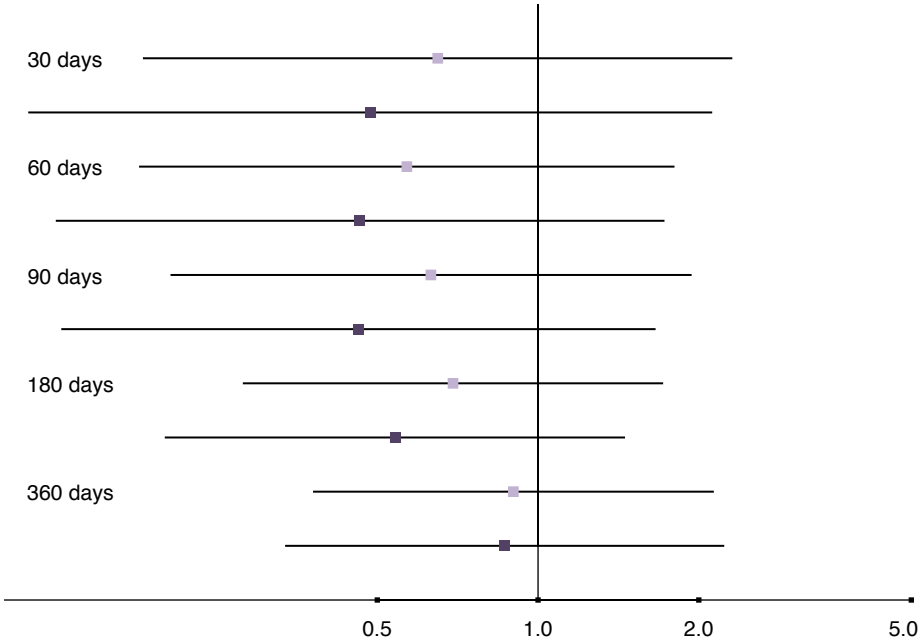

Figure 8. Hazard ratios for SGAs vs. FGAs – Cardiac arrhythmia
FGAs constitutes reference group. 95% CIs; unadjusted HRs in light coloured square markers, adjusted in dark. Values are given in Appendix 6. Hazard ratios.

Congestive heart failure

The number of events, average length of follow-up and contributed person-years for FGA and SGA users are given in Table 17.

Table 17. Incidence of CHF within 360 days since treatment initiation

Cohort	No. of events	Mean duration of follow-up, days ± SD	Contributed person-years	Crude event rate, per 100 p-y
FGAs	118	89 ± 123	1,131.10	10.43
SGAs	406	202 ± 140	4,311.90	9.42

No statistically significant differences were found in unadjusted and adjusted analyses between FGA and SGA users. Unadjusted and adjusted hazard ratios are shown in Figure 9.

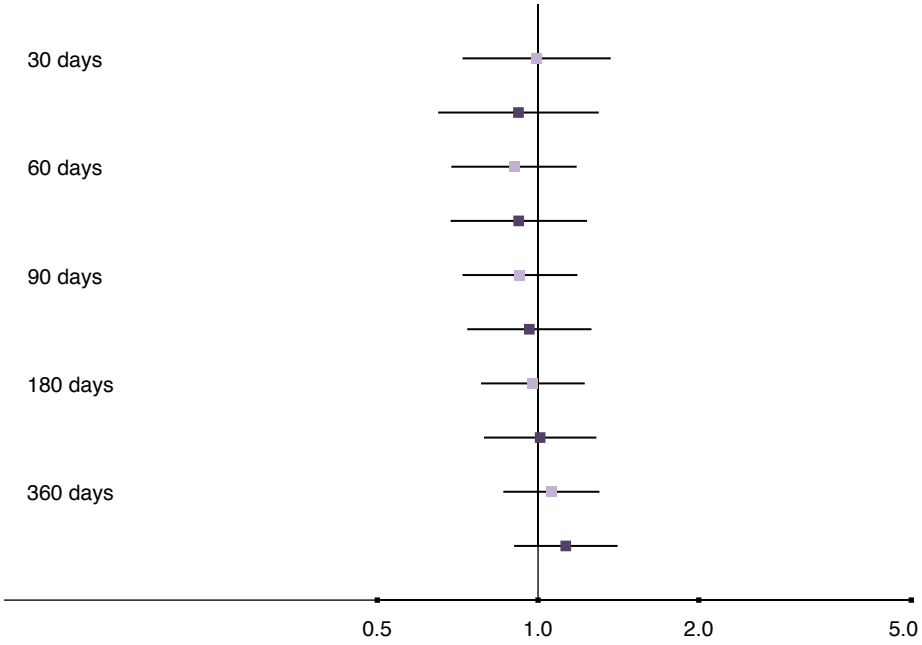

Figure 9. Hazard ratios for SGAs vs. FGAs – CHF
FGAs constitutes reference group. 95% CIs; unadjusted HRs in light coloured square markers, adjusted in dark. Values are given in Appendix 6. Hazard ratios.

Exposed vs. non-exposed – Cerebrovascular and cardiac events

Eleven thousand five hundred sixty-nine (11,569) out of 12,434 antipsychotic-exposed subjects were matched to non-exposed individuals. The baseline characteristics of FGA-exposed, SGA-exposed and matched cohorts of non-exposed persons are given in Table 18.

Table 18. Baseline characteristics of antipsychotic-exposed and non-exposed cohorts – Cerebrovascular and cardiac events

Characteristics	First Generation Antipsychotics n = 4,445	Matched non-users n = 10,813	Second Generation Antipsychotics n = 7,124	Matched non-users n = 16,373
Age years (mean, SD)	77.83±7.97	76.95±7.40	82.24±7.76	80.46±8.04
Age distribution (n, %)				
65–74	1,792 (40.31)	4,507 (41.68)	1,356 (19.03)	4,177 (25.51)
75–84	1,797 (40.43)	4,466 (41.30)	3,059 (42.94)	6,955 (42.48)
> 85	856 (19.26)	1,840 (17.02)	2,709 (38.03)	5,241 (32.01)
Sex, male	1,909 (42.95)	4,476 (41.39)	2,689 (37.75)	6,322 (38.61)
Personal Care Home	631 (14.20)	1,236 (11.43)	2,388 (33.52)	4,001 (24.44)
Year of entry to cohort				
2000–2001	789 (17.75)	1,886 (17.44)	895 (12.56)	2,040 (12.46)
2001–2002	716 (16.11)	1,727 (15.97)	941 (13.21)	2,163 (13.21)
2002–2003	601 (13.52)	1,459 (13.49)	1,042 (14.63)	2,357 (14.40)
2003–2004	646 (14.53)	1,568 (14.50)	1,160 (16.28)	2,647 (16.17)
2004–2005	553 (12.44)	1,382 (12.78)	1,077 (15.12)	2,478 (15.13)
2005–2006	583 (13.12)	1,416 (13.10)	987 (13.85)	2,289 (13.98)
2006–2007	557 (12.53)	1,375 (12.72)	1,022 (14.35)	2,399 (14.65)
Hospitalization in past year	2,642 (59.44)	5,162 (47.74)	3,430 (48.15)	6,695 (40.89)
Frequency of GP visits (mean ± SD)	15.67±12.33	14.86±11.48	16.00±12.26	15.18±11.79
History of Comorbidity (n, %)				
Stroke	109 (2.45)	174 (1.61)	268 (3.76)	345 (2.11)
Other cerebrovascular disease	692 (15.57)	813 (7.52)	1,660 (23.30)	1,440 (8.79)
Hypertension	2,572 (57.86)	2,851 (26.37)	4,142 (58.14)	4,226 (25.81)
Congestive Heart Failure	808 (18.18)	1,484 (13.72)	1,663 (23.34)	2,281 (13.93)
Atrial Fibrillation	336 (7.56)	1,092 (10.10)	767 (10.77)	1,689 (10.32)
Other Arrhythmias	185 (4.16)	524 (4.85)	318 (4.46)	826 (5.04)
Myocardial infarction	336 (7.56)	968 (8.95)	606 (8.51)	1,395 (8.52)
Other ischemic disease	1,176 (26.46)	1.980 (18.31)	2,083 (29.24)	2,737 (16.72)
Peripheral vascular disease	194 (4.36)	538 (4.98)	385 (5.40)	819 (5.00)
Rheumatic heart disease	46 (1.03)	63 (0.58)	72 (1.01)	81 (0.49)
Other heart disease	367 (8.26)	570 (5.27)	647 (9.08)	911 (5.56)
Diabetes mellitus	888 (19.98)	1,638 (15.15)	1,426 (20.02)	2,075 (12.67)
Chronic pulmonary disease	1,415 (31.83)	1,370 (12.67)	2,082 (29.23)	1,865 (11.39)
Malignant neoplasm	1,827 (41.10)	2,665 (24.65)	1,126 (15.81)	1,028 (6.28)
Parkinson's disease	96 (2.16)	272 (2.52)	425 (5.97)	645 (3.94)
Dementia	369 (8.30)	319 (2.95)	2,129 (29.88)	1,192 (7.28)
Alzheimer's disease	204 (4.59)	195 (1.80)	1,293 (18.15)	696 (4.25)
Schizophrenia	34 (0.76)	22 (0.20)	84 (1.18)	93 (0.57)
Delirium	107 (2.41)	159 (1.47)	427 (5.99)	521 (3.18)
Mood disorder	129 (2.90)	59 (0.55)	534 (7.50)	452 (2.76)

Characteristics	First Generation Antipsychotics n = 4,445	Matched non-users n = 10,813	Second Generation Antipsychotics n = 7,124	Matched non-users n = 16,373
Other psychiatric disorder	333 (7.50)	141 (1.30)	1,590 (22.32)	600 (3.66)
History of Medication Use				
Number of medications used (mean ± SD)	12.20±7.14	11.57±7.32	11.31±6.78	10.91±7.06
Anticonvulsants (n, %)	432 (9.72)	698 (6.46)	792 (11.12)	1,153 (7.04)
Benzodiazepines	1,904 (42.83)	4,441 (41.07)	3,228 (45.31)	7,274 (44.43)
Antidepressants	1,111 (24.99)	2,640 (24.42)	2,794 (39.22)	6,162 (37.64)
Sedatives & Hypnotics	827 (18.61)	1,829 (16.91)	1,303 (18.29)	3,025 (18.48)
Anxiolytics	1,522 (34.24)	3,513 (32.49)	2,535 (35.58)	5,546 (33.87)
Acetylcholinesterase inhibitors	24 (0.54)	16 (0.15)	233 (3.27)	50 (0.31)
Anticoagulants	757 (17.03)	2,238 (20.70)	1,399 (19.64)	3,444 (21.03)
Diuretics	1,796 (40.40)	5,032 (46.54)	3,095 (43.44)	7,532 (46.00)
Beta-blockers	994 (22.36)	3,207 (29.66)	1,577 (22.14)	4,299 (26.26)
Calcium channel blockers	976 (21.96)	3,044 (28.15)	1,527 (21.43)	4,142 (25.30)
Angiotensin II receptors blockers	427 (9.61)	1,412 (13.06)	575 (8.07)	1,779 (10.87)
Angiotensin converting enzyme inhibitors	1,239 (27.87)	3,726 (34.46)	2,075 (29.13)	5,245 (32.03)
Lipid-lowering agents	814 (18.31)	3,060 (28.30)	1,109 (15.57)	3,793 (23.17)
Antidiabetic agents	643 (14.47)	1,935 (17.90)	975 (13.69)	2,370 (14.48)
Hormone replacement therapies	268 (6.03)	916 (8.47)	306 (4.30)	896 (5.47)

Cerebrovascular events

The number of events, average length of follow-up and contributed person-years for FGA users vs. non-exposed and SGA users vs. non-exposed are presented in Table 19 and Table 20, respectively.

Table 19. Incidence of cerebrovascular events within 360 days since FGA treatment initiation

Cohort	No. of events	Mean duration of follow-up, days ± SD	Contributed person-years	Crude event rate, per 100 p-y
FGAs	184	86 ± 121	1,049.69	17.53
Non-exposed	429	321 ± 94	9,497.75	4.52

Table 20. Incidence of cerebrovascular events within 360 days since SGA treatment initiation

Cohort	No. of events	Mean duration of follow-up, days ± SD	Contributed person-years	Crude event rate, per 100 p-y
SGAs	735	193 ± 141	3,755.53	19.57
Non-exposed	1,625	318 ± 96	14,252.19	11.40

In both unadjusted and adjusted models, treatment with FGAs was associated with a significant increase in the risk of cerebrovascular events compared to non-exposed subjects. A similar trend was present in SGA-treated individuals compared to non-exposed. Hazard ratios for the FGA vs. non-exposed and the SGA vs. non-exposed comparisons are shown in Figure 10 and Figure 11, respectively.

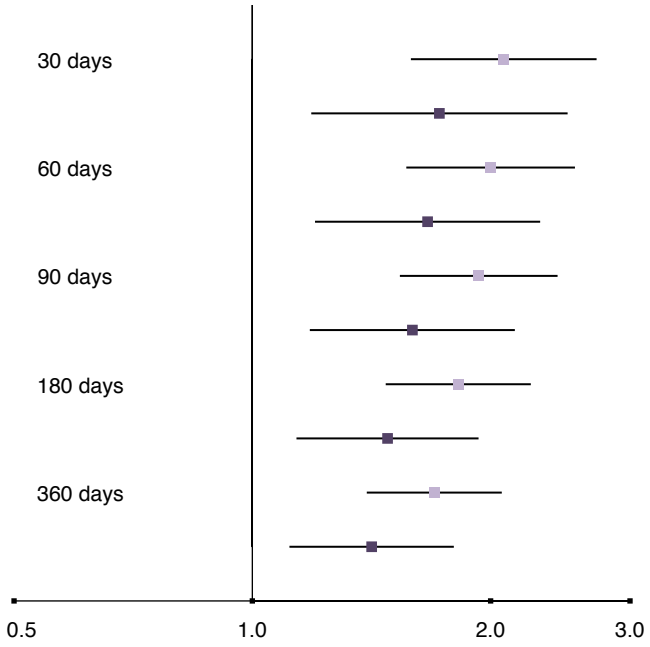

Figure 10. Hazard ratios for FGAs vs. non-exposed – Cerebrovascular events
Non-exposed constitutes reference group. 95% CIs; unadjusted HRs in light coloured square markers, adjusted in dark. Values are given in Appendix 6. Hazard ratios.

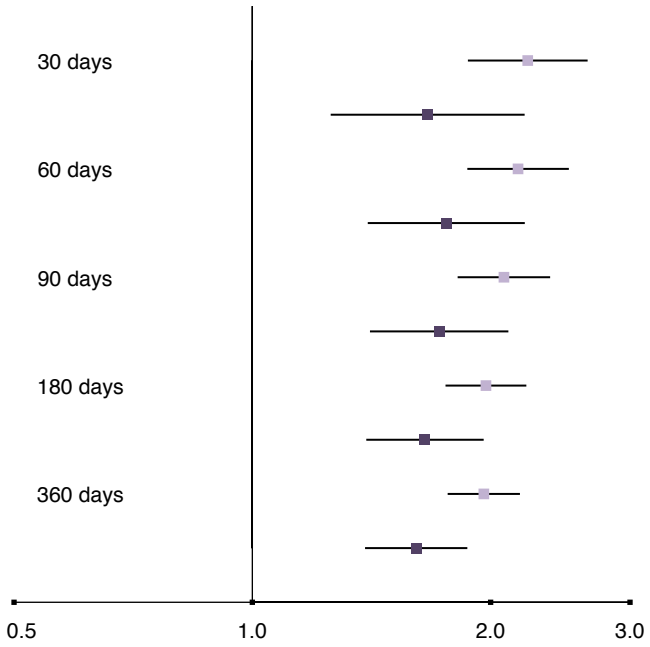

Figure 11. Hazard ratios for SGAs vs. non-exposed – Cerebrovascular events
Non-exposed constitutes reference group. 95% CIs; unadjusted HRs in light coloured square markers, adjusted in dark. Values are given in Appendix 6. Hazard ratios.

Myocardial infarction

The number of events, average length of follow-up and contributed person-years for FGA users vs. non-exposed and SGA users vs. non-exposed are presented in Table 21 and Table 22, respectively.

Table 21. Incidence of myocardial infarction within 360 days since FGA treatment initiation

Cohort	No. of events	Mean duration of follow-up, days ± SD	Contributed person-years	Crude event rate, per 100 p-y
FGAs	23	90 ± 124	1,098.37	2.09
Non-exposed	61	330 ± 83	9,757.20	0.63

Table 22. Incidence of myocardial infarction within 360 days since SGA treatment initiation

Cohort	No. of events	Mean duration of follow-up, days ± SD	Contributed person-years	Crude event rate, per 100 p-y
SGAs	110	205 ± 140	3,990.86	2.76
Non-exposed	245	328 ± 83	14,713.08	1.67

No significant differences in the risk of myocardial infarction were found between FGA-treated persons and matched non-exposed subjects, while SGA users were at higher risk of myocardial infarction in the 30-, 60- and 180-day models. Hazard ratios for the FGA vs. non-exposed and SGA vs. non-exposed comparisons are shown in Figure 12 and Figure 13, respectively.

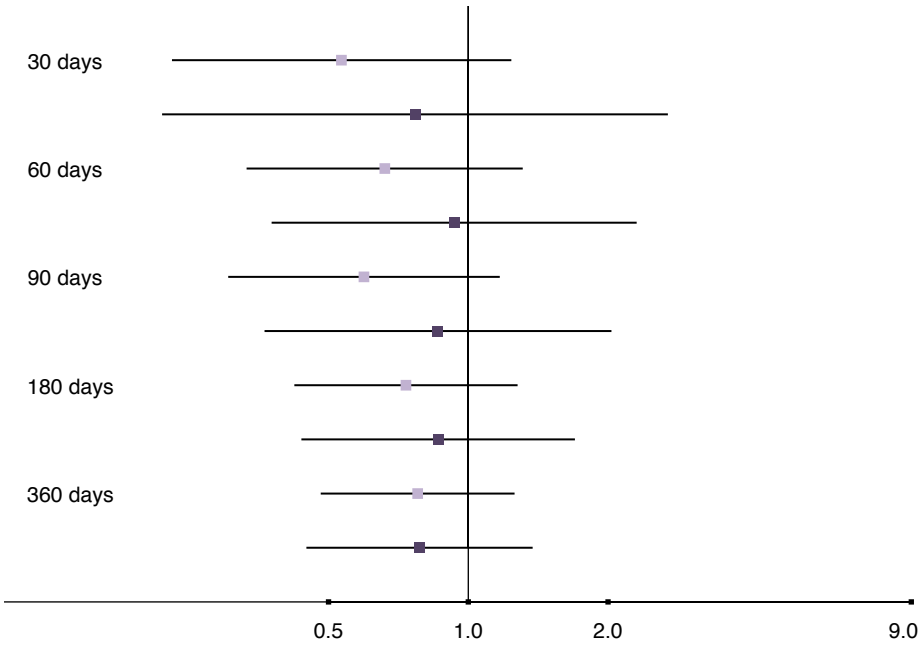

Figure 12. Hazard ratios for FGAs vs. non-exposed – Myocardial infarction
Non-exposed constitutes reference group. 95% CIs; unadjusted HRs in light coloured square markers, adjusted in dark. Values are given in Appendix 6. Hazard ratios.

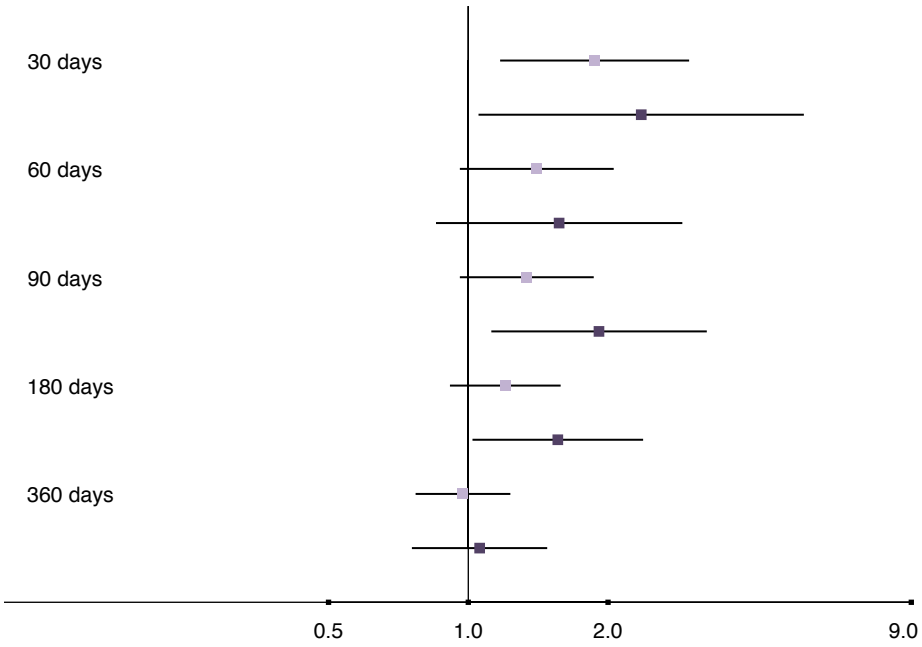

Figure 13. Hazard ratios for SGAs vs. non-exposed – Myocardial infarction
Non-exposed constitutes reference group. 95% CIs; unadjusted HRs in light coloured square markers, adjusted in dark. Values are given in Appendix 6. Hazard ratios.

Cardiac arrhythmia

The number of events, average length of follow-up and contributed person-years for FGA users vs. non-exposed and SGA users vs. non-exposed are presented in Table 23 and Table 24, respectively.

Table 23. Incidence of cardiac arrhythmia within 360 days since FGA treatment initiation

Cohort	No. of events	Mean duration of follow-up, days ± SD	Contributed person-years	Crude event rate, per 100 p-y
FGAs	7	91 ± 125	1,101.96	0.64
Non-exposed	16	332 ± 80	9,828.97	0.16

Table 24. Incidence of cardiac arrhythmia within 360 days since SGA treatment initiation

Cohort	No. of events	Mean duration of follow-up, days ± SD	Contributed person-years	Crude event rate, per 100 p-y
SGAs	18	205 ± 140	4,012.72	0.45
Non-exposed	45	330 ± 80	14,812.11	0.30

As already mentioned, cardiac arrhythmias were not commonly noted in the administrative data. Hazard ratios for adjusted analyses within 90 days were not applicable because of unstable estimation; i.e., convergence was not attained with the multivariable model. None of unadjusted models showed significant differences between either FGA- or SGA-treated subjects and matched non-exposed individuals. The adjusted 180- and 360-day models did not show significant differences between the compared groups. Hazard ratios for the FGA vs. non-exposed and the SGA vs. non-exposed comparisons are shown in Figure 14 and Figure 15, respectively.

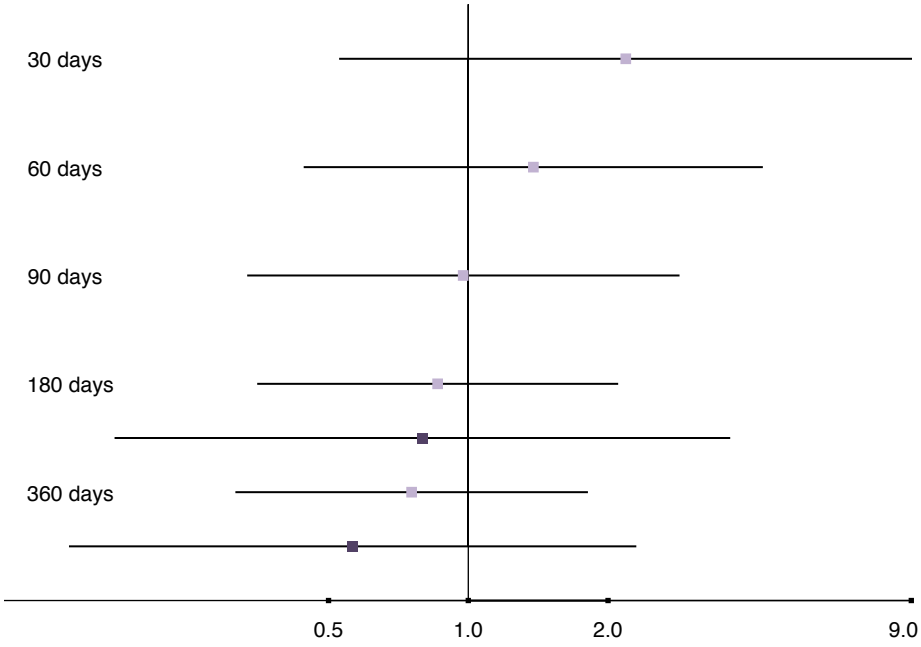

Figure 14. Hazard ratios for FGAs vs. non-exposed – Cardiac arrhythmia
Non-exposed constitutes reference group. 95% CIs; unadjusted HRs in light coloured square markers, adjusted in dark. Values are given in Appendix 6. Hazard ratios.

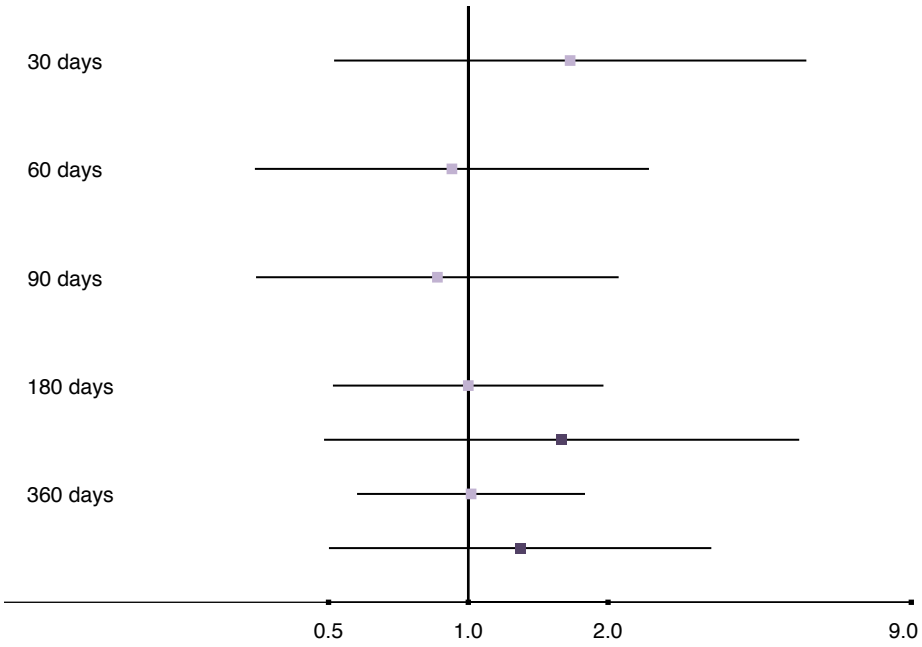

Figure 15. Hazard ratios for SGAs vs. non-exposed – Cardiac arrhythmia
Non-exposed constitutes reference group. 95% CIs; unadjusted HRs in light coloured square markers, adjusted in dark. Values are given in Appendix 6. Hazard ratios.

Congestive heart failure

The number of events, average length of follow-up and contributed person-years for FGA users vs. non-exposed and SGA users vs. non-exposed are presented in Table 25 and Table 26, respectively.

Table 25. Incidence of CHF within 360 days since FGA treatment initiation

Cohort	No. of events	Mean duration of follow-up, days ± SD	Contributed person-years	Crude event rate, per 100 p-y
FGAs	110	89 ± 124	1,084.06	10.15
Non-exposed	262	326 ± 87	9,664.39	2.7

Table 26. Incidence of CHF within 360 days since SGA treatment initiation

Cohort	No. of all-cause deaths	Mean duration of follow-up, days ± SD	Contributed person-years	Crude event rate, per 100 p-y
SGAs	358	203 ± 140	3,950.57	9.06
Non-exposed	795	325 ± 87	14,589.08	5.45

Compared to matched non-exposed subjects, both classes of antipsychotics had higher hazard ratios. The differences between groups in both comparisons were not significant in the 360-day models. Hazard ratios for the FGA vs. non-exposed and the SGA vs. non-exposed comparisons are shown in Figure 16 and Figure 17, respectively.

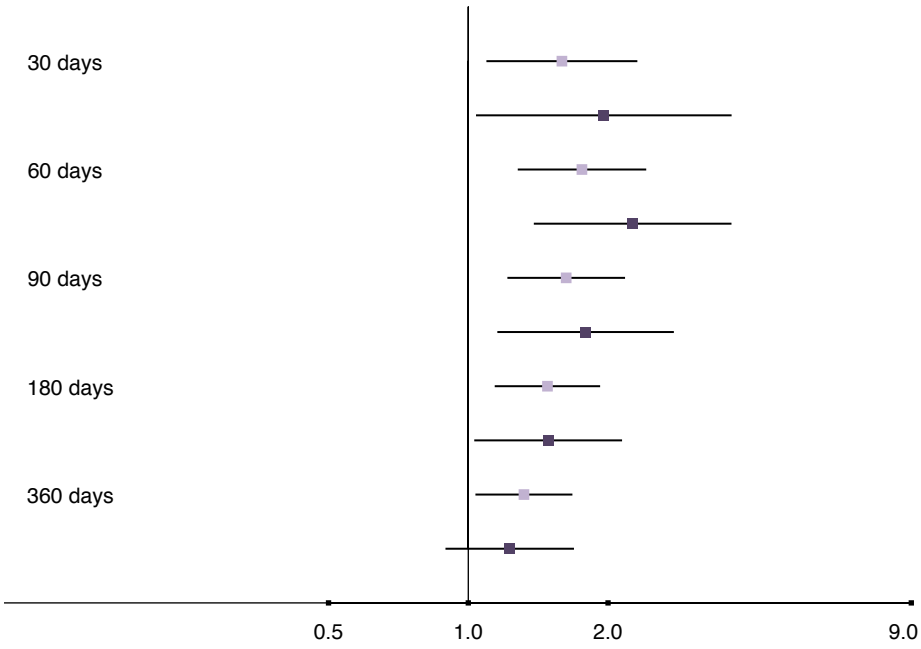

Figure 16. Hazard ratios for FGAs vs. non-exposed – CHF
Non-exposed constitutes reference group. 95% CIs; unadjusted HRs in light coloured square markers, adjusted in dark. Values are given in Appendix 6. Hazard ratios.

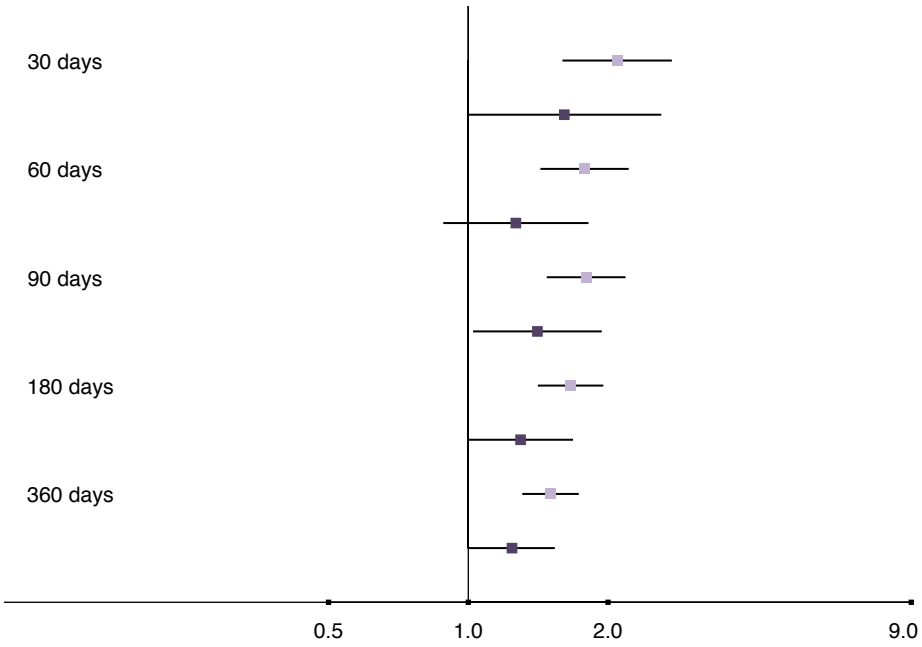

Figure 17. Hazard ratios for SGAs vs. non-exposed – CHF
Non-exposed constitutes reference group. 95% CIs; unadjusted HRs in light coloured square markers, adjusted in dark. Values are given in Appendix 6. Hazard ratios.

All-cause mortality

FGAs vs. SGAs – All-cause mortality

Eleven thousand nine hundred eighty-six (11,986) persons were selected for the all-cause mortality comparison (4,652 started on FGA therapy and 7,769 started on SGAs). Important differences between FGA and SGA users were the same as in the cohorts selected for the EPS, cerebrovascular and cardiac comparisons. The baseline characteristics of the cohorts are presented in Table 27.

Table 27. Baseline characteristics of FGA and SGA users – All-cause mortality

Characteristics	First Generation Antipsychotics n = 4,300	Second Generation Antipsychotics n = 7,686	Standardized Difference
Age, years (mean, SD)	77.88 ± 8.00	82.62 ± 7.80	0.600*
Age distribution (n, %)			
65–74	1,716 (39.91)	1,376 (17.90)	
75–84	1,746 (40.60)	3,231 (42.04)	
> 85	838 (19.49)	3,079 (40.06)	

Characteristics	First Generation Antipsychotics n = 4,300	Second Generation Antipsychotics n = 7,686	Standardized Difference
Sex, male	1,803 (41.93)	2,855 (37.15)	0.098
Personal Care Home	673 (15.65)	2,881 (37.48)	0.510*
Year of entry to cohort			
2000–2001	791 (18.40)	940 (12.23)	
2001–2002	707 (16.44)	1,016 (13.22)	
2002–2003	577 (13.42)	1,114 (14.49)	
2003–2004	624 (14.51)	1,256 (16.34)	
2004–2005	525 (12.21)	1,180 (15.35)	
2005–2006	552 (12.84)	1,072 (13.95)	
2006–2007	524 (12.19)	1,108 (14.42)	
Hospitalization in past year (n, %)	2,528 (58.79)	3,823 (49.74)	0.510*
Frequency of GP visits (mean ± SD)	16.01 ± 12.67	16.85 ± 12.87	0.066
History of Comorbidity (%)			
Stroke	114 (2.65)	310 (4.03)	0.077
Other cerebrovascular disease	705 (16.40)	1,873 (24.37)	0.199*
Hypertension	2,523 (58.67)	4,532 (58.96)	0.006
Congestive Heart Failure	826 (19.21)	1,900 (24.72)	0.133*
Atrial Fibrillation	350 (8.14)	888 (11.55)	0.115*
Other Arrhythmias	188 (4.37)	371 (4.83)	0.022
Myocardial infarction	333 (7.74)	683 (8.89)	0.041
Other ischemic disease	1,171 (27.23)	2,335 (30.83)	0.070
Peripheral vascular disease	199 (4.63)	442 (5.75)	0.051
Rheumatic heart disease	47 (1.09)	82 (1.07)	0.003
Other heart disease	368 (8.56)	761 (9.90)	0.046
Diabetes mellitus	883 (20.53)	1,579 (20.54)	0.000
Chronic pulmonary disease	1,390 (32.33)	2,273 (29.57)	0.060
Connective tissue disease	109 (2.53)	162 (2.11)	0.028
Ulcer disease	276 (6.42)	363 (4.72)	0.074
Liver disease	64 (1.49)	76 (0.99)	0.045
Hemiplegia or paraplegia	63 (1.47)	144 (1.87)	0.032
Renal disease	234 (5.44)	442 (5.75)	0.013
Malignant neoplasm	1,620 (37.67)	1,166 (15.17)	0.528*
Parkinson's disease	99 (2.30)	467 (6.08)	0.189*
Dementia	389 (9.05)	2,506 (32.60)	0.606*
Alzheimer's disease	222 (5.16)	1,481 (19.27)	0.441*
Schizophrenia	33 (0.77)	89 (1.16)	0.040
Delirium	114 (2.65)	529 (6.88)	0.200*
Mood disorder	138 (3.21)	600 (7.81)	0.203*
Other psychiatric disorder	355 (8.26)	1,839 (23.93)	0.437*

Characteristics	First Generation Antipsychotics n = 4,300	Second Generation Antipsychotics n = 7,686	Standardized Difference
History of Medication Use			
Number of medications used (mean ± SD)	12.43 ± 7.64	11,75 ± 7.07	0.092
Anticonvulsants (n, %)	429 (9.98)	879 (11.44)	0.047
Benzodiazepines	1,841 (42.81)	3,605 (46.90)	0.082
Antidepressants	1,131 (26.30)	3,184 (41.43)	0.324*
Sedatives & Hypnotics	815 (18.95)	1,444 (18.79)	0.004
Anxiolytics	1,464 (34.05)	2,857 (37.17)	0.065
Acetylcholinesterase inhibitors	26 (0.60)	249 (3.24)	0.193*
Anticoagulants	748 (17.40)	1,568 (20.40)	0.077
Diuretics	1,764 (41.02)	3,437 (44.72)	0.075
Beta-blockers	993 (23.09)	1,737 (22.60)	0.012
Calcium channel blockers	969 (22.53)	1,677 (21.82)	0.017
Angiotensin II receptors blockers	422 (9.81)	615 (8.00)	0.064
Angiotensin converting enzyme inhibitors	1,237 (28.77)	2,298 (29.90)	0.025
Lipid-lowering agents	809 (18.81)	1,194 (15.53)	0.087
Antidiabetic agents	643 (14.95)	1,076 (14.00)	0.027
Hormone replacement therapies	278 (6.47)	321 (4.18)	0.102*

*Standardized difference > 0.1 represents a significant difference

The number of events, average length of follow-up and contributed person-years for FGA and SGA users are given in Table 28.

Table 28. Mortality within 360 days since treatment initiation

Cohort	No. of all-cause deaths	Mean duration of follow-up, days ± SD	Contributed person-years	Crude event rate, per 100 p-y
FGAs	205	95 ± 127	1,123.31	18.25
SGAs	646	207 ± 140	4,366.24	14.80

In both unadjusted models and models adjusted for the baseline characteristics (Table 27) the use of FGAs was associated with significantly higher risk of death compared to treatment with SGAs. The results of the time-to-event analysis are presented in Figure 18.

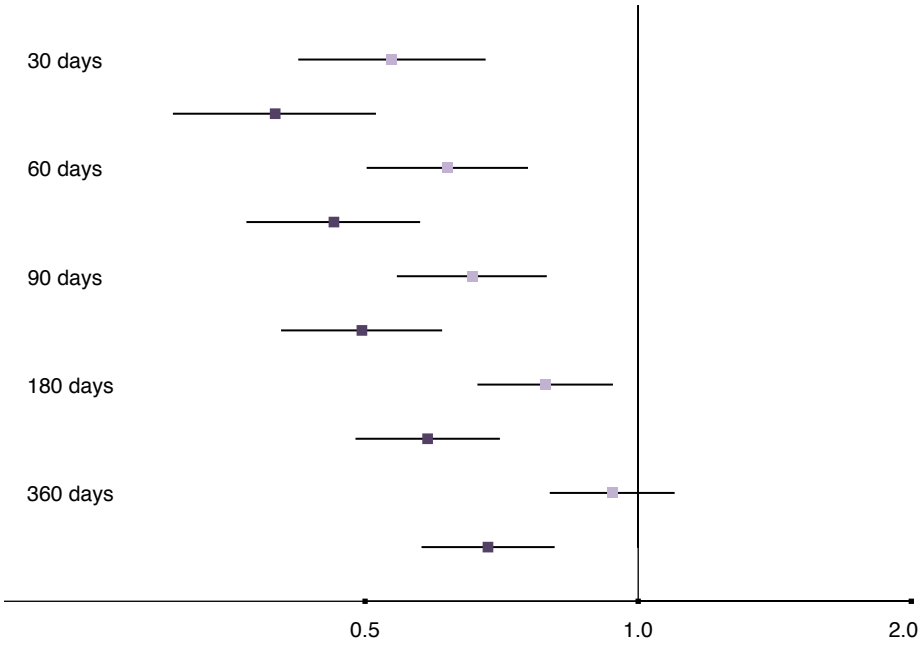

Figure 18. Hazard ratios for SGAs vs. FGAs – All-cause mortality
FGAs constitutes reference group. 95% CIs; unadjusted HRs in light coloured square markers, adjusted in dark. Values are given in Appendix 6. Hazard ratios.

Exposed vs. non-exposed – All-cause mortality

Eleven thousand seventy-six (11,076) out of 11,986 antipsychotic-exposed subjects were matched to non-exposed individuals. The baseline characteristics of FGA-exposed, SGA-exposed and matched cohorts of non-exposed persons are given in Table 29.

Table 29. Baseline characteristics of antipsychotic-exposed and non-exposed cohorts – All-cause mortality

Characteristics	First Generation Antipsychotics n = 4,076	Matched non-exposed n = 9,822	Second Generation Antipsychotics n = 7,000	Matched non-exposed n = 15,920
Age, years (mean, SD)	77.78 ± 7.98	76.88 ± 7.41	82.23 ± 7.76	80.41 ± 8.04
Age distribution (n, %)				
65–74	1,655 (40.60)	4,151 (42.26)	1,334 (19.06)	4,102 (25.77)
75–84	1,642 (40.28)	4,018 (40.19)	3,015 (43.07)	6,756 (42.44)
> 85	779 (19.11)	1,653 (16.83)	2,651 (37.87)	5,062 (31.80)
Sex, male	1,718 (42.15)	4,032 (41.05)	2,622 (37.46)	6,113 (38.40)
Personal Care Home	582 (14.28)	1,061 (10.80)	2,328 (33.26)	3,843 (24.14)

Characteristics	First Generation Antipsychotics n = 4,076	Matched non-exposed n = 9,822	Second Generation Antipsychotics n = 7,000	Matched non-exposed n = 15,920
Year of entry to cohort				
2000–2001	747 (18.33)	1,763 (17.95)	880 (12.57)	1,979 (12.43)
2001–2002	675 (16.56)	1,605 (16.34)	929 (13.27)	2,103 (13.21)
2002–2003	544 (13.35)	1,312 (13.36)	1,023 (14.61)	2,291 (14.39)
2003–2004	587 (14.40)	1,409 (14.35)	1,137 (16.24)	2,576 (16.18)
2004–2005	502 (12.32)	1,256 (12.79)	1,057 (15.10)	2,397 (15.06)
2005–2006	517 (12.68)	1,245 (12.68)	971 (13.87)	2,236 (14.05)
2006–2007	504 (12.37)	1,232 (12.54)	1,003 (14.33)	2,338 (14.69)
Hospitalization in past year	2,337 (57.34)	4,507 (45.89)	3,341 (47.73)	6,449 (40.51)
Frequency of GP visits (mean ± SD)	15.40 ± 12.14	14.42 ± 11.20	15.94 ± 12.24	15.10 ± 11.76
History of Comorbidity (n, %)				
Stroke	101 (2.48)	147 (1.50)	266 (3.80)	334 (2.10)
Other cerebrovascular disease	642 (15.75)	697 (7.10)	1,635 (23.36)	1,395 (8.76)
Hypertension	2,366 (58.05)	2,499 (25.44)	4,067 (58.10)	4,079 (25.62)
Congestive Heart Failure	736 (18.06)	1,299 (13.23)	1,622 (23.17)	2,200 (13.82)
Atrial Fibrillation	306 (7.51)	947 (9.64)	746 (10.66)	1,626 (10.21)
Other Arrhythmias	169 (4.15)	445 (4.53)	308 (4.40)	797 (5.01)
Myocardial infarction	307 (7.53)	864 (8.80)	592 (8.46)	1,342 (8.43)
Other ischemic disease	1,077 (26.42)	1,760 (17.92)	2,048 (29.26)	2,647 (16.63)
Peripheral vascular disease	173 (4.24)	470 (4.79)	374 (5.34)	788 (4.95)
Rheumatic heart disease	41 (1.01)	55 (0.56)	71 (1.01)	75 (0.47)
Other heart disease	334 (8.19)	496 (5.05)	637 (9.10)	880 (5.53)
Diabetes mellitus	818 (20.07)	1,424 (14.50)	1,401 (20.01)	2,001 (12.57)
Chronic pulmonary disease	1,288 (31.60)	1,185 (12.06)	2,036 (29.09)	1,789 (11.24)
Connective tissue disease	98 (2.40)	147 (1.50)	140 (2.00)	246 (1.55)
Ulcer disease	246 (6.04)	266 (2.71)	310 (4.43)	401 (2.52)
Liver disease	57 (1.40)	83 (0.85)	69 (0.99)	154 (0.97)
Hemiplegia or paraplegia	55 (1.35)	103 (1.05)	128 (1.83)	224 (1.41)
Renal disease	203 (4.98)	384 (3.91)	382 (5.46)	585 (3.67)
Malignant neoplasm	1,493 (36.63)	2,133 (21.72)	1,048 (14.97)	885 (5.56)
Parkinson's disease	91 (2.23)	238 (2.42)	419 (5.99)	634 (3.98)
Dementia	344 (8.44)	268 (2.73)	2,093 (29.90)	1,153 (7.24)
Alzheimer's disease	199 (4.88)	168 (1.71)	1,280 (18.29)	673 (4.23)
Schizophrenia	33 (0.81)	19 (0.19)	84 (1.20)	91 (0.57)
Delirium	91 (2.23)	131 (1.33)	411 (5.87)	493 (3.10)
Mood disorder	123 (3.02)	51 (0.52)	529 (7.56)	442 (2.78)
Other psychiatric disorder	312 (7.65)	114 (1.16)	1,560 (22.29)	577 (3.62)

Characteristics	First Generation Antipsychotics n = 4,076	Matched non-exposed n = 9,822	Second Generation Antipsychotics n = 7,000	Matched non-exposed n = 15,920
History of Medication Use				
Number of medications used (mean ± SD)	11.86 ± 7.04	11.23 ± 7.20	11,25 ± 6.76	10.87 ± 7.06
Anticonvulsants (n, %)	391 (9.59)	622 (6.33)	772 (11.03)	1,115 (7.00)
Benzodiazepines	1,688 (41.41)	3,944 (40.15)	3,162 (45.17)	7,063 (44.37)
Antidepressants	1,024 (25.12)	2,340 (23.82)	2,745 (39.21)	5,989 (37.62)
Sedatives & Hypnotics	754 (18.50)	1,606 (16.35)	1,275 (18.21)	2,950 (18.53)
Anxiolytics	1,321 (32.41)	3,118 (31.75)	2,481 (35.44)	5,371 (33.74)
Acetylcholinesterase inhibitors	23 (0.56)	14 (0.14)	231 (3.30)	49 (0.31)
Anticoagulants	678 (16.63)	1,983 (20.19)	1,370 (19.57)	3,338 (20.97)
Diuretics	1,627 (39.92)	4,500 (45.82)	3,031 (43.30)	7,322 (45.99)
Beta-blockers	915 (22.45)	2,905 (29.58)	1,551 (22.16)	4,190 (26.32)
Calcium channel blockers	902 (22.13)	2,770 (28.20)	1,504 (21.49)	4,037 (25.36)
Angiotensin II receptors blockers	398 (9.76)	1,312 (13.36)	563 (8.04)	1.744 (10.95)
Angiotensin converting enzyme inhibitors	1,149 (28.19)	3,360 (34.21)	2,035 (29.07)	5,104 (32.06)
Lipid-lowering agents	761 (18.67)	2,796 (28.47)	1,094 (15.63)	3,718 (23.35)
Antidiabetic agents	596 (14.62)	1,729 (17.60)	961 (13.73)	2,295 (14.42)
Hormone replacement therapies	252 (6.18)	850 (8.65)	299 (4.27)	869 (5.46)

The number of events, average length of follow-up and contributed person-years for FGA users vs. non-exposed and SGA users vs. non-exposed are presented in Table 30 and Table 31, respectively.

Table 30. Mortality within 360 days since FGA treatment initiation

Cohort	No. of events	Mean duration of follow-up, days ± SD	Contributed person-years	Crude event rate, per 100 p-y
FGAs	182	96 ± 127	1,068.27	17.04
Non-exposed	639	339 ± 69	9,121.67	7.01

Table 31. Mortality within 360 days since SGA treatment initiation

Cohort	No. of events	Mean duration of follow-up, days ± SD	Contributed person-years	Crude event rate, per 100 p-y
SGAs	528	208 ± 140	3,978.25	13.27
Non-exposed	1,600	333 ± 77	14,535.81	11.01

Compared to matched non-exposed subjects, FGA users were at much higher risks of death, while no significant differences were found between SGA-treated and non-exposed individuals with exception of the 360-day model, where the SGA users were at significantly lower risk of death compared with non-exposed. Hazard ratios for the FGA vs. non-exposed and the SGA vs. non-exposed comparisons are shown in Figure 19 and Figure 20, respectively.

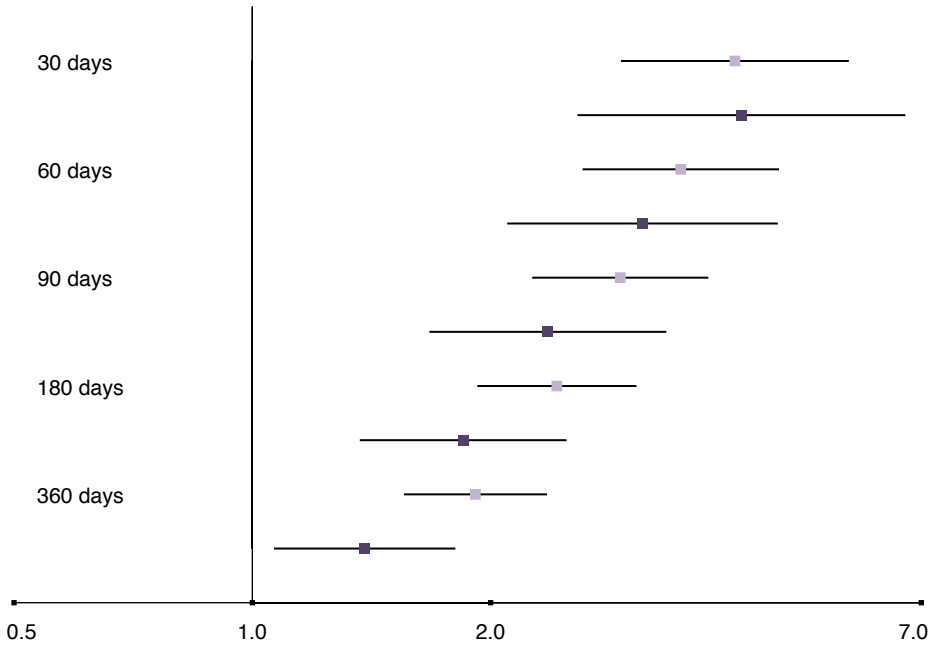

Figure 19. Hazard ratios for FGAs vs. non-exposed – All-cause mortality
Non-exposed constitutes reference group. 95% CIs; unadjusted HRs in light coloured square markers, adjusted in dark. Values are given in Appendix 6. Hazard ratios.

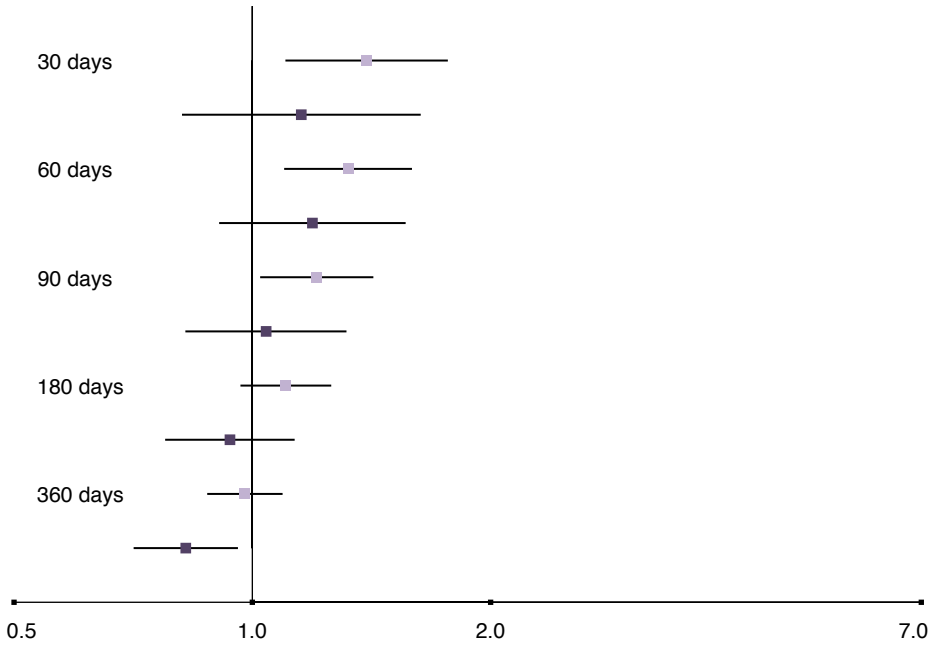

Figure 20. Hazard ratios for SGAs vs. non-exposed – All-cause mortality
Non-exposed constitutes reference group. 95% CIs; unadjusted HRs in light coloured square markers, adjusted in dark. Values are given in Appendix 6. Hazard ratios.

DISCUSSION

This population-based study was designed to determine the risk of adverse events in all elderly residents of Manitoba initiated on antipsychotic medications, and to contribute to the current knowledge on the subject. Comprehensive evaluation of major adverse events associated with the use of both classes of antipsychotics was carried out and risks of EPS, cerebrovascular and cardiac events and all-cause mortality were compared between FGA- and SGA-treated individuals. For further investigation, a cohort of non-exposed persons was selected to be a reference group in assessment of risks of adverse events in antipsychotic-treated individuals.

Selection of the study cohort

This retrospective population-based cohort study included all elderly persons in Manitoba (≥65 years of age) initiated on antipsychotics without restriction on diagnosis. The universal health care system in the province of Manitoba makes it possible to carry out studies on the total population without limiting cohorts to enrollees of insurance programs (e.g., Medicaid users in the US). The timeframe of the study subjects' enrolment was from April 1, 2000 to March 31, 2007. The reason for starting observations in 2000 is that the DPIN data goes back only to 1995, and the interest of this study was to select incident users of antipsychotics with no history of antipsychotic use in the five years prior to cohort entry. Ensuring that every subject in the cohort had Manitoba Health coverage during five years prior to the cohort entry, as well as during the follow-up time, allowed for obtaining virtually all information on health care system use by these individuals.

Information on medications administered in hospitals is missing from Manitoba's administrative databases. A preliminary analysis showed that a number of patients in the cohort had likely started antipsychotic pharmacotherapy in a hospital (i.e., the date of the first recorded prescription in the DPIN database was the same as the date of hospital separation). In order to avoid possible misclassification bias, patients hospitalized for longer than 30 days prior to the cohort entry were excluded. Again, as the databases do not have information on specific agents administered in hospitals, those persons, who had been hospitalized in total for longer than 25% of the year prior to cohort entry, were excluded. Similarly, to avoid possible exposure misclassification bias, individuals admitted to a hospital for longer than 30 days were censored at the time of hospital admission. Considering that switching from one class of antipsychotics to another (i.e., FGAs to SGAs and vice versa) can be done to control adverse events, study subjects were censored at the time of switching.

The total number of elderly persons selected for the study was 12,434. This cohort was used in the cerebrovascular and cardiac events comparisons. For EPS and all-cause mortality analyses, additional exclusion criteria were applied. Individuals with preexisting movement disorders were taken out from the cohort used for the EPS comparison, as any recorded EPS for these persons would more likely be related to the preexisting disorder rather than to antipsychotic exposure. Preexisting movement disorders were defined as a diagnosis of Parkinson's disease or EPS and/or a prescription of antiparkinson medications (anticholinergic agents, levodopa) in the five years prior to cohort entry. Amantadine was not included in the list of antiparkinson medications as it is commonly used for influenza rather than treatment of EPS (Tamblyn, 1997). For the

complete list of antiparkinson medication used in this study please refer to Appendix 7. Antiparkinson medications. As FGAs (and haloperidol specifically) have been preferred by physicians in terminally ill patients with cancer, (Breitbart & Strout, 2000; Bruera & Neumann, 1998; Caraceni & Simonetti, 2009; Centeno et al., 2004) the cohort for the all-cause mortality did not include cancer-related deaths, because these deaths cannot be attributed to antipsychotic exposure and keeping those individuals, who would eventually die from cancer, in the cohort would bias the study results and overestimate the risk of mortality in FGA users.

The population of Manitoba is relatively small (around 1.15 million people in 2006) (Statistics Canada, 2006) and the focus of this study, the elderly population of the province, remained stable over the study period (around 160,000 in 2006) (Manitoba Health, 2006). Even though the prevalence of antipsychotic use was relatively high during the study time frame (Alessi-Severini et al., 2008a), the overall number of persons selected into the cohort was not large and stratification to subgroups with specific diagnoses or specific agent pharmacotherapy was problematic as meaningful comparisons were not possible due to the lack of statistical power in some groups.

Study design

This observational study was conducted using administrative databases and, therefore, carries the advantages and disadvantages of such design. The advantages include the assessment of antipsychotic-associated adverse events in a 'real-world' setting, including a broader population and longer follow-up periods. Population-based cohort studies are necessary when RCTs are unethical, as, for example, in the assessment of life-threatening adverse events in vulnerable individuals. The ability to simultaneously

investigate an effect of exposure on multiple outcomes provides an advantage over case-control studies; however, there are some potential pitfalls in assessing risks of rare outcomes, as in this case a cohort design might not be efficient or sufficient (Mann, 2003). The main disadvantage of observational studies is the lack of randomization, as the investigator has no control over patients' allocation to one treatment group or another. Patients could have been preferentially selected to receive one treatment over another and factors that determined the decision to prescribe could confound the assessment of the effect of the intervention (Rochon et al., 2005). This type of bias is called selection bias and can affect a study's validity if appropriate measures to control for it are not taken. Confounding is another important issue in observational studies. A confounder is an independent variable, which predicts the outcome of interest and differs between study groups. Selection of appropriate comparison groups, identification of potential confounders, and use of proper statistical techniques in the analysis control for the selection bias and confounding. Antipsychotics are used for both acute (management of an acute psychosis) and long-term (behavioural and psychological symptoms of dementia, and bipolar disorder) indications. As a result, an analysis of new users might include disproportionate numbers of short-term users as well as patients not complying with pharmacotherapy. Accounting for preexisting conditions and comorbidities and survival analysis methods are used to address this issue (Ray, 2003).

Confounding

This study carries limitations of possible confounding as any observational study based on administrative data. However, a number of steps were taken in this study to account for potential confounding. The key covariates that are associated with outcome

or exposure were identified and adjustments were made in the regression analysis. Age, sex, residence in a PCH and comorbidities were used to capture the possible selection bias. The overall comorbidity was the most challenging covariate to measure, as it has to reflect the overall health status of the individual. The Adjusted Clinical Group (Baldwin et al., 2006; Perkins et al., 2004; Reid et al., 1999; Reid et al., 2001; Starfield et al., 1991; The Manitoba Centre for Health Policy, 2009; Weiner et al., 1991) system was chosen to measure comorbidity, considering that this method was developed to include all available diagnoses (both ambulatory and hospital). Previous studies based on administrative databases in Manitoba have shown that the ACG method performs well in measuring morbidity of individuals (Reid et al., 1999; Reid et al., 2001). For each individual, the ACG system assigns up to 32 different Ambulatory Diagnosis Groups (ADGs) by clustering diagnoses coded in hospital separation abstracts and physician claims over a year prior to the cohort entry. Diagnostic codes are grouped intro clinically meaningful categories based on their expected clinical outcomes. The sum of the ADGs was calculated for each individual and included as a covariate in the regression analysis.

The time frame of the study cohort did not include the time period of 1998 to 2000 when much of the shift between FGA and SGA use happened. Further, the time period of study subjects' selection overlapped with the dates of the Health Canada warnings which could have affected the prescribing practices. However, there are reasons to believe that the warnings had only marginal effects on antipsychotic utilization (Valiyeva et al., 2008). The index year was included into the adjusted models to account for possible changes in practice over the time frame of this study.

Nonetheless, there is always a possibility that some important confounders remained unaccounted for and could have affected the study results. For example, important clinical data and lifestyle factors such as smoking, alcohol consumption, obesity that are expected to have an effect on cerebrovascular and cardiac outcomes and all-cause mortality could not be measured. However, it has been proposed that some of the measured variables (such as cardiovascular diseases, diabetes and treatment with lipid-lowering drugs) could serve as proxies for unmeasured confounders (such as obesity) (Kraemer et al., 2001).

Statistical analysis

Regression and propensity score matching are frequently used statistical techniques for adjusting for differences between the comparison groups.

Cox proportional hazards model

Cox proportional hazards model accounts for censoring, simultaneously adjusting for confounders, and estimate the risks. Stratification in the Cox regression allows for fitting the model for comparison of matched groups (Austin et al., 2010). All covariates considered to be confounders were included in the Cox models, regardless of differences in these covariates reaching statistical significance between the comparison groups, as the absence of statistical significance does not imply that the imbalance is small enough to be ignored (Haro et al., 2006).

Propensity score matching

Propensity score matching is among the options for selecting a group of non-exposed subjects. In this study, propensity score matching allowed for selecting the group of non-exposed individuals that had a similar chance to be prescribed antipsychotic

medications; hence it addressed the selection bias, which is a major issue in selecting a proper control group for antipsychotic users. Propensity score matching is a two-stage process: first, the method summarizes observed covariate information using logistic regression and then, assigns a propensity score to each individual. A propensity score is a probability to be assigned to a particular treatment, conditional on a number of observed covariates. There is a number of ways to select covariates for propensity score estimation: the model can be built on a) covariates associated with the exposure, b) covariates associated with the outcome, c) covariates associated with both the exposure and the outcome. As this study assessed multiple outcomes, models were built based only on covariates associated with exposure (Austin et al., 2010). Once the propensity scores were calculated, subjects were matched based on their score, and comparisons among subjects within each matched cluster were carried out. Eventually, adjustments were made in the Cox proportional hazards regression to account for imbalances in covariates (including those that were used in the matching model) between the antipsychotic-exposed and non-exposed groups.

A potential limitation can be seen in not including all possible predictors of outcomes; however, such an approach has been suggested as a possible way of selecting a comparison group in observational studies assessing multiple outcomes (Austin et al., 2010). Including predictors of exposure to antipsychotics does not entirely account for potential selection bias, i.e., patients at high risk of adverse events do not receive medication that is associated with incidence of such adverse events. An alternative way would be to build an independent propensity score matching model for each outcome which would include risk factors of investigated adverse events and would better address

the selection bias. However, adjustments to account for risk factors were made in regression analyses, therefore, the used matching model's limitations were not ignored and the impact of potential confounders was accounted for in analyses.

Extrapyramidal syndromes

FGAs vs. risperidone

Risperidone has been shown to be more similar to FGAs than to SGAs in terms of risk of EPS, and therefore it might be preferable to look at these agents separately rather than pooling them together for the purpose of comparing EPS events; however, in our study, we observed that the majority of elderly users of SGAs were started on risperidone (nearly 70% of all SGAs users) and the groups treated with olanzapine or quetiapine were too small for valid comparisons. For this reason, the cohort of SGAs was restricted to risperidone users and the results of this comparison cannot, obviously, be extrapolated to persons taking quetiapine or olanzapine.

The findings of the EPS comparison demonstrated that treatment with risperidone is associated with lower risks of EPS compared to treatment with FGAs (within 360 days – adjusted HR 0.753, 95% CI 0.539–1.050). These results are supported by biological plausibility and are consistent with the findings of previous observational studies (Avorn et al., 1995; Lee et al., 2005; Rochon, Stukel et al., 2005). Blockade of D_2 receptors in the brain plays the major role in the mechanism of antipsychotic action; however, it is also associated with occurrence of EPS (specifically because of occupancy of nigrostriatal D_2 receptors). The affinity of FGAs for dopamine D_2 receptors leads to EPS. These agents bind more tightly than dopamine itself to the D_2 receptors (Seeman, 2002). SGAs bind less avidly than dopamine to D_2 receptors (rapid dissociation theory) and allow normal

dopamine transmission (Thanvi & Treadwell, 2009). The reduced blockade of D_2 receptors has also been linked to antagonism of 5-HT_{2A} serotonin receptors. Serotonin regulates dopamine release and the presence of serotonin in nigrostriatal dopamine pathway inhibits the release of dopamine, subsequently reversing some of D_2 blockade by SGAs (Stahl, 2003). Antipsychotic agents within the SGA class vary in their affinity to D_2 receptors (risperidone has the highest affinity, and shares some properties of the FGA class) (He & Richardson, 1995; Seeman, 2002). The onset of drug-induced parkinsonism is delayed for days to weeks after use of antipsychotics, whereas dopamine receptor blockade occurs within minutes of exposure to these agents. EPS, such as parkinsonism or dystonias, usually develop early in the course of antipsychotic treatment, while TD typically takes longer to develop. However, in elderly populations, TD can occur rapidly during the first year of total antipsychotic use (Lee et al., 2005). Older age and being female are among risk factors for EPS (Caligiuri et al., 2000).

Management of EPS includes adjusting the dose, switching to another agent, or discontinuation of antipsychotic therapy. Another option is to add an antiparkinson agent without discontinuation of antipsychotic therapy, although this choice places frail elderly persons at additional risks associated with the use of antiparkinson drugs. Anticholinergic agents have their own toxicity and the use of levodopa is not recommended in antipsychotic-induced parkinsonism because it delivers higher concentrations of dopamine to the blocked receptors, which results in reduced antipsychotic efficacy and adds potentially serious side effects (e.g., hallucinations and psychotic behaviour) without effectively treating drug-induced EPS (Avorn et al., 1995).

The analysis conducted in this study relies on the accuracy of administrative data and proper coding by clinicians. While such measures as switching from one agent to another, changing dose or stopping antipsychotic therapy taken to control for EPS, can be identified using administrative data, there is no data on the reasons for such changes in pharmacotherapy. Therefore, there is the possibility of underestimating EPS as only individuals with EPS severe enough to be diagnosed and treated with antiparkinson medications were captured. This issue was partly addressed by allowing for just one diagnosis in the medical services database to be counted as an event. Dose-related association between antipsychotic use and incidence of EPS have previously been found for both FGAs and SGAs (Lee et al., 2005; Rochon, Stukel et al., 2005). No dose assessments were done in this study, which could be a potential limitation. To note, the group receiving FGAs was taking more of other medications associated with the development of EPS (e.g., metoclopramide), although all necessary adjustments were made to control for it. Other limitations of using administrative data are lack of clinical context and difficulty of assessing causality. It is, therefore, possible that antipsychotics unmasked already existing Parkinson's disease in some subjects.

It is important to remember that there is always a possibility for confounding by indication in observational studies. It might be that physicians were giving risperidone to those individuals who were expected to be at higher risks for EPS. Accounting for possible confounders addressed this issue, although an unmeasured confounder could have affected the results.

Exposed vs. non-exposed

Relative to matched non-exposed individuals, both classes of antipsychotics showed higher risks of EPS (360 days – FGAs adjusted HR 3.503, 95% CI 2.271–5.403; risperidone HR 1.733, 95% CI 1.214–2.472). More than a 3-fold increase in the risk of EPS in persons treated with FGAs and a nearly 2-fold increase in persons treated with risperidone is not unexpected and accordant with biological mechanisms of antipsychotics action. The risks of EPS development were the highest for FGA-treated persons within short-term use (30 days – HR 6.918, 95% CI 3.244–14.756). Risperidone users at the same time interval were also at higher risk of EPS; however, the difference was not as dramatic as for FGA users and lacked statistical significance (HR 2.117, 95% CI 0.820–5.446).

Cerebrovascular and cardiac events

FGAs vs. SGAs

Concerns over cerebrovascular adverse events associated with risperidone and olanzapine were raised in 2002 and 2004, respectively, and warnings were issued by Health Canada (Wooltorton, 2002; Wooltorton, 2004). In a post-hoc analysis of 11 placebo-controlled RCTs (6 with risperidone and 5 with olanzapine) the relative risk of cerebrovascular events was 3.2 (1.4–7.2) and 1.8 (0.5–6.3) for risperidone and olanzapine, respectively (Herrmann & Lanctot, 2005). A pooled analysis of RCTs documented a nearly three-fold increase in incidence of cerebrovascular events with risperidone and olanzapine compared to placebo. However, some, but not all (Sacchetti et al., 2008), observational studies did not support the findings of these RCTs (Barnett et al., 2007; Liperoti et al., 2005a).

The findings of this study's cerebrovascular events analysis showed that FGA users have similar risks of stroke and transient ischemic attack compared to SGA users (adjusted HR 1.136, 95% CI 0.961–1.344), which is consistent with other observational studies (Gill et al., 2005; Herrmann et al., 2004; Wang et al., 2007) showing no difference between the two classes of antipsychotics in the risk of cerebrovascular events.

Among cardiac events, there was no significant difference found in the incidence of cardiac arrhythmias (HR 0.865, 95% CI 0.336–2.232) and congestive heart failure (HR 1.127, 95% CI 0.902–1.409), though treatment with SGAs was associated with increased risks of myocardial infarction relative to FGAs (HR 1.614, 95% CI 1.024–2.543). The outcome definition in cardiac events comparisons was restricted to only events that led to hospitalization, because the use of 3 digits ICD-9-codes in the Medical Services database did not allow the retrieving of specific 4-digit diagnoses. Hospitalizations with a diagnosis of cardiac arrhythmia were rare events resulting in rather wide confidence intervals and, subsequently, the inability to draw a meaningful conclusion in this analysis.

The finding that there is no difference between the two classes of antipsychotics in incidence of congestive heart failure is consistent with the results of another study (Wang et al., 2007). However, it has not been reported before that the use of SGAs is associated with higher risk of myocardial infarction compared to treatment with FGAs. Some discrepancies between the results of this study and the current evidence, as reported by others, can be partly explained by the time frame of the cohort selection (2000–2007). The FGAs known to be the most cardiotoxic, thioridazine and mesoridazine, were withdrawn in 2000, making it possible that the FGA-initiators in this study cohort were in

fact started on safer FGAs compared to cohorts of previous studies (starting in late 1990s and going up to the first warning in 2002).

Exposed vs. non-exposed

This study found that users of both classes of antipsychotics are at increased risk of cerebrovascular events compared to non-exposed subjects (FGAs adjusted HR 1.415, 95% CI 1.114–1.797; SGAs HR 1.611, 95% CI 1.388–1.869). These results are in line with the findings of the RCTs and demonstrate that elderly persons starting on any class of antipsychotics are at higher risk of cerebrovascular events compared to non-exposed subjects.

The findings of the cardiac events comparison were not entirely consistent with results of other studies. It has not been found previously that SGA users are at higher risk of myocardial infarction compared to FGAs or non-exposed. Compared to non-exposed subjects, users of both FGAs and SGAs were found to be at higher risk of congestive heart failure (FGAs HR 1.228, 95% CI 0.893–1.689; SGAs HR 1.242, 95% CI 1.003–1.536). No differences between antipsychotic-exposed and non-exposed were found in comparisons of cardiac arrhythmia (FGAs HR 0.564, 95% CI 1.138–2.301; SGAs HR 1.293, 95% CI 0.501–3.338). Users of SGAs, but not FGAs, were at higher risk of myocardial infarction over the 90-day follow-up period compared to non-exposed (FGAs HR 0.860, 95% CI 0.364–2.034; SGAs HR 1.912, 95% CI 1.121–3.264).

There are some possible pharmacological mechanisms that might lead to increased risks of cerebrovascular and cardiac events among antipsychotic users. The QT interval prolongation has been well documented in antipsychotic users. Some FGAs were even

withdrawn from the market due to their cardiac toxicity (e.g., thioridazine, mesoridazine). However, there is no way to assess changes in the QT interval using administrative data. Risk factors such as history of cardiac disease and concomitant treatment with medication that also prolong the QT interval, pose an individual at greater risk of cardiac events and were, therefore, adjusted for. Both classes of antipsychotics have been associated with an increased risk of venous thromboembolism (Liperoti et al., 2005). Suggested mechanisms for thromboembolism have included enhanced platelet aggregation and the presence of anticardiolipin antibodies (Zornberg & Jick, 2000). Affinity of antipsychotic medications to α_1-adrenoceptors is associated with cardiac events, such as tachycardia or orthostatic hypotension and that might lead to stroke (Eigenbrodt et al., 2000). Muscarinic antagonist activity of some antipsychotic agents (olanzapine, loxapine) might lead to increase in blood pressure and heart rate, which are known risk factors for cardiovascular disorders (Ayer et al., 2007). Sedation and EPS could lead to venous stasis and/or dehydration and haemoconcentration and, eventually, to cerebrovascular events (Herrmann & Lanctot, 2005). Pathological pathways might also involve susceptibility of dementia-affected persons to stroke (i.e., confounding by indication). This study cohort, however, was not restricted by any diagnosis, and adjustments included a history of dementia and use of acetylcholinesterase inhibitors. The affinity of antipsychotic agents to H_1-histamine, 5-HT_{2C}-serotonin, and M3-muscarinic receptors possibly leads to metabolic disturbances in antipsychotic users (Jindal & Keshavan, 2008). Taking into account the fact that risks of cerebrovascular and cardiac events were apparent in short time intervals since antipsychotic pharmacotherapy initiation (30 days – FGAs HR 1.723, 95% CI 1.187–

2.502; SGAs HR 1.665, 95% CI 1.256–2.208), it is unlikely that induced weight gain or diabetes played a major role in the incidence of cardiac events.

All-cause mortality

Selection bias may have played the biggest role in the all-cause mortality comparison and the results of this comparison should be interpreted cautiously keeping this limitation in mind. As already mentioned, there is a preference for FGAs in the treatment of terminally ill patients (Breitbart & Strout, 2000; Bruera & Neumann, 1998; Caraceni & Simonetti, 2009; Centeno et al., 2004). Although adjustment for history of cancer was made and cancer deaths were excluded, there is still a possibility of overestimating the risk in FGA-treated individuals, as an opportunity for the outcome misclassification exists (the diagnosis at death was not coded as cancer and therefore counted as an event, while this condition was the one responsible for death).

FGAs vs. SGAs

Results of the all-cause mortality analyses showed that persons treated with FGAs were at higher risk compared to the SGA-treated cohort (adjusted HR 0.683, 95% CI 0.577–0.809) and further confirmed the greater risk of mortality in FGA users as has previously been demonstrated (Gill et al., 2007; Hollis et al., 2007; Hollis, Grayson et al., 2007; Schneeweiss et al., 2007; Setoguchi et al., 2008; Wang et al., 2005).

Some of the possible biological explanations for increased mortality can be seen in the mechanisms involved in the increased risks of cerebrovascular and cardiac events as previously mentioned. First, antipsychotics may prolong the QT interval, predisposing patients to arrhythmias and sudden cardiac death (Hennessy et al., 2004; Ray et al., 2001;

Ray et al., 2009). Second, sedation and accelerated cognitive decline caused by exposure to antipsychotics may increase the risk for aspiration syndromes and choking (Ruschena et al., 2003; Warner, 2004). Pneumonia was shown to be a common cause of death among elderly people treated with antipsychotics (Wang et al., 2005; Setoguchi et al., 2008). Third, several studies have found a link between SGA use and venous thromboembolism (Zornberg & Jick, 2000; Liperoti et al., 2005). Therefore, pulmonary embolism can contribute to mortality in older patients. Fourth, the risk for cerebrovascular events is associated with antipsychotic use, as this study has shown. Finally, antipsychotics may contribute to events that are not initially recognized as the first step in a sequence that brings premature death, such as falls leading to hip fractures (Jalbert et al., 2010).

Exposed vs. non-exposed

The findings suggested that the use of FGAs is associated with higher risks of death relative to non-exposure (adjusted HR 1.387, 95% CI 1.065–1.805). No differences between SGA users and non-exposed individuals were found at different time intervals within the first year of follow-up. At 360 days the difference between SGA users and non-exposed subjects reached statistical significance (HR 0.824, 95% CI 0.708–0.959); however, the effect is marginal and requires further confirmation. The results, showing no difference in mortality between SGA users and non-exposed individuals, differ from the results of some previous observational studies (Gill et al., 2007; Ray et al., 2009). Quetiapine, however, was reported not to be associated with higher risk of mortality in a recent study (Rossom et al., 2010).

Conclusions

Post-marketing pharmacosurveillance provides essential information on medication safety. In recent years, concerns have been raised regarding the use of antipsychotic medications in elderly populations but observational studies have reported contrasting results on the risks of specific adverse events.

This study provides the most recent data available on mortality, cardiac and cerebrovascular adverse events as well as the incidence of EPS in the entire elderly population of Manitoba treated with antipsychotic pharmacotherapy.

The results of this study show that the use of FGAs seems to be associated with a higher risk of EPS and mortality compared to treatment with SGAs, while SGA users were found to be at a higher risk of myocardial infarction. Compared to non-exposed individuals both classes of antipsychotics were found to be associated with harmful adverse events and neither FGAs nor SGAs seem to have a superior overall safety profile.

This study did not address the benefits of using antipsychotic pharmacotherapy, especially because quality of life cannot be assessed in observational studies that are based on administrative data. Yet the findings of this research highlight the importance of giving careful consideration to all risks associated with the use of these medications before prescribing antipsychotic pharmacotherapy to frail elderly persons. The information provided will be useful to clinicians, patients, caregivers as well as to decision-makers.

Further studies comparing non-pharmacological approaches to currently prevailing pharmacological treatments are warranted. Furthermore, the benefits of choosing

antipsychotic pharmacotherapy should be evaluated by assessing changes in quality of life and well-being of patients in prospective clinical trials.

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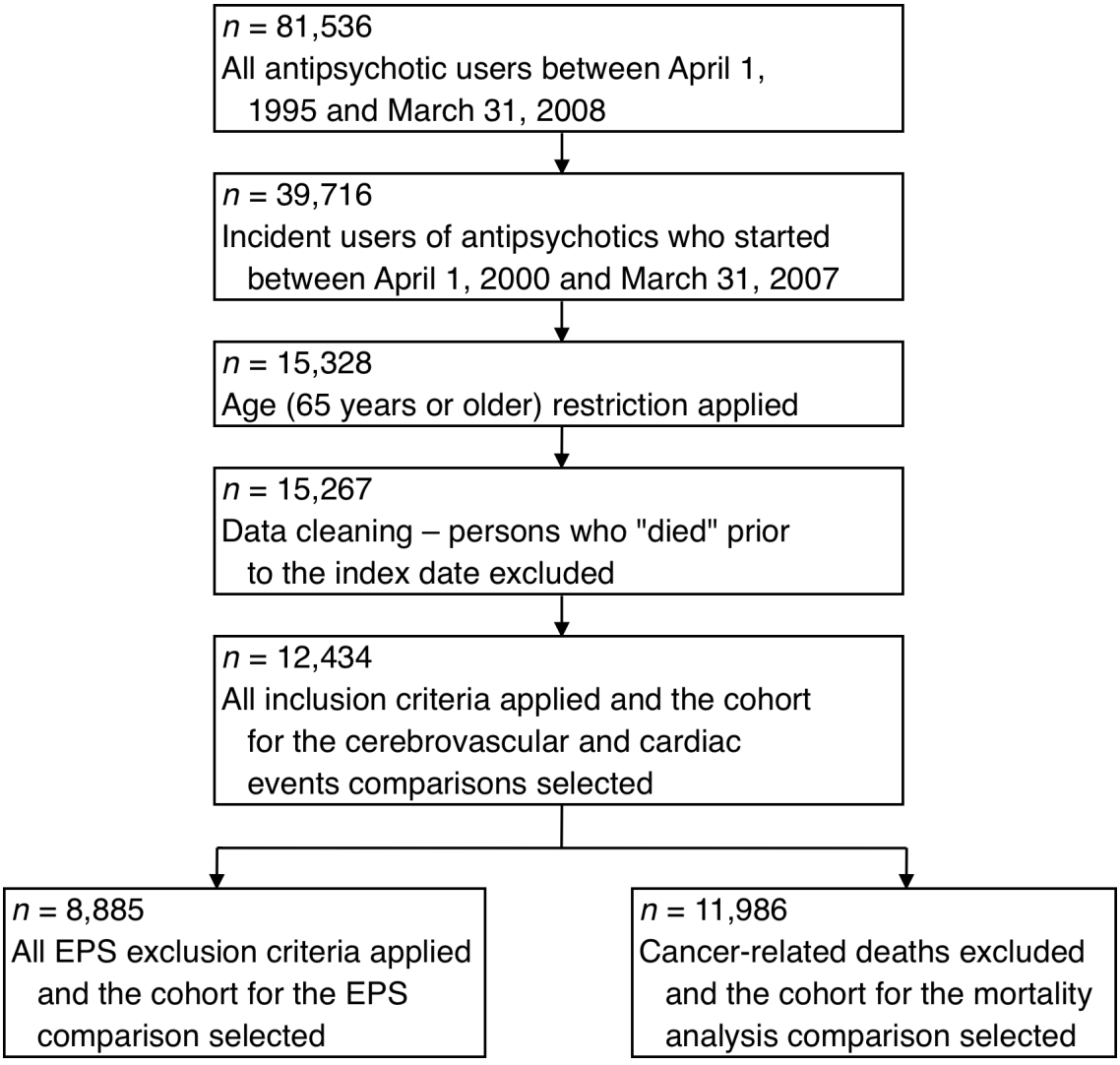
Appendix 1. Cohort definition



Appendix 2. Covariates definition

Covariate	Hospital Abstracts	Medical Services
Congestive Heart Failure	'39891', '40201', '40211', '40291', '40401', '40403', '40411', '40413', '40491', '40493', '4254', '4255', '4257', '4258', '4259', '428'	'428'
Peripheral Vascular Disease	'0930', '4373', '440', '441', '4431', '4432', '4438', '4439', '4471', '5571', '5579', 'V434'	'440', '441'
Stroke	'43491', '43411', '430', '431', '432', '43401'	'430', '431', '432'
Cerebrovascular Disease	'36234', '433', '43400', '43410', '43490','435', '436', '437', '438'	'433', '435', '436', '437', '438'
Dementia	'290', '2941'	'290'
Chronic Pulmonary Disease	'4168', '4169', '490', '491', '492', '493', '494', '495', '496', '500', '501', '502', '503', '504', '505', '5064', '5081', '5088'	'490', '491', '492', '493', '494', '495', '496', '500', '501', '502', '503', '504', '505'
Connective Tissue-Rheumatic Disease	'725', '4465', '7100', '7101', '7102', '7103', '7140', '7141', '7142', '7148'	'725'
Peptic Ulcer Disease	'531', '532', '533', '534'	'531', '532', '533', '534'
Liver Disease	'07022', '07023', '07032', '07033', '07044', '07054', '0706', '0709', '570', '571', '5733', '5734', '5738', '5739', 'V427', '4560', '4561', '4562', '5722', '5723', '5724', '5728'	'570', '571'
Diabetes	'250'	'250'
Paraplegia and Hemiplegia	'3341', '342', '343', '3440', '3441', '3442', '3443', '3444', '3445', '3446', '3449'	'342', '343'
Renal Disease'	'40301', '40311', '40391', '40402', '40403', '40412', '40413', '40492', '40493', '582', '585', '586', '5830', '5831', '5832', '5834', '5836', '5837', '5880', 'V420', 'V451', 'V56'	'582', '585', '586'
Cancer	'140', '141', '142', '143', '144', '145', '146', '147', '148', '149', '150', '151', '152', '153', '154',' 155', '156', '157', '158', '159', '160', '161', '162', '163', '164', '165', '170', '171', '172', '174', '175', '176', '179', '180', '181', '182', '183', '184', '185', '186', '187', '188', '189', '190', '191', '192', '193', '194', '195', '200', '201', '202', '203', '204', '205', '206', '207', '208', '196', '197', '198', '199'	'140', '141', '142', '143', '144', '145', '146', '147', '148', '149', '150', '151', '152', '153', '154',' 155', '156', '157', '158', '159', '160', '161', '162', '163', '164', '165', '170', '171', '172', '174', '175', '176', '179', '180', '181', '182', '183', '184', '185', '186', '187', '188', '189', '190', '191', '192', '193', '194', '195', '200', '201', '202', '203', '204', '205', '206', '207', '208', '196', '197', '198', '199'
Cardiac arrhythmias	'4270', '4271', '4272', '4274', '4275', '4276', '4277', '4278', '4279'	n/a
Atrial fibrillation	'4273'	n/a
Hypertension	'401', '402', '404', '403', '405'	'401', '402', '403', '404', '405'

Covariate	Hospital Abstracts	Medical Services
Rheumatic Heart Disease	'393', '394', '395', '396', '397', '398'	'393', '394', '395', '396', '397', '398'
Myocardial Infarction	'410', '412'	'410', '412'
Other ischemic heart disease	'411', '413', '414'	'411', '413', '414'
Endocarditis	'421'	'421'
Other cardiovascular disorder	'420', '422', '423', '424', '425', '426', '429'	'420', '422', '423', '424', '425', '426', '429'
Parkinson's disease	'332'	'332'
Any movement disorder	'332', '333', '7810'	'332', '333'
Alzheimer's disease	'331'	'331'
Schizophrenia	'295'	'295'
Mood disorder	'296'	'296'
Delirium	'2930', '2910', '2911', '29389', '29281', '30011', '2939', '2931', '2920'	'293'
Other psychiatric disorder	'297', '298', '299'	'297', '298', '299'

Appendix 3. Example of SAS codes

Cox proportional hazards model for FGAs vs. SGAs analysis

```
title 'unadjusted cox ph for MI within 30 days';
proc tphreg data=data3;
        class atypical (ref='0');
        model studyperiod30*status30(0)=atypical/risklimits;
run;
title 'adjusted cox ph for MI within 30 days;
proc tphreg data=data3;
        class atypical (ref='0') sex(ref='1');
        model studyperiod30*status30(0)=atypical age sex PCH noadm totalperphin adjyear
        adgsum d_431 d_433 d_401_405 d_428 d_4273 d_427 d_410 d_421
        d_411_414 d_440 d_393_398 d_420_429 d_250 d_490 d_140 d_332 d_290 d_331 d_295
        d_2930 d_296 d_297 drugs_per_year anticonvs benzo antidepr
        sedatives_hypnotics anxiolytics cholinester anticoagulants diuretics
        betablockers ca_blockers angio_2_antagon angioconvert HMG_COA antidiab
        hrt/risklimits;
run;
```

Cox proportional hazards model for antipsychotic-exposed vs. non-exposed analysis

```
title 'unadjusted cox ph for MI within 30 days';
proc tphreg data=data3;
        class atypical (ref='2');
        model studyperiod30*status30(0)=atypical/risklimits;
        strata case_phin;
run;
title 'adjusted cox ph for MI within 30 days';
proc tphreg data=data3;
        class atypical (ref='2') sex(ref='1');
        model studyperiod30*status30(0)=atypical age pch sex adgsum drugs_per_year
        totalperphin adjyear noadm d_410 d_428 d_440
        d_433 d_290 d_490 d_725 d_342 d_582 d_431 d_427 d_4273 d_401_405
        d_331 d_295 d_296 d_2930 d_297 d_140 hrt d_421 d_393_398 d_411_414  d_420_429
betablockers HMG_COA anticoagulants angioconvert diuretics  cholinester
ca_blockers angio_2_antagon antidiab/risklimits;
        strata case_phin;
run;
```

Appendix 4. Example of SAS outputs

Cox proportional hazards model (unadjusted) - 30 days - Cerebrovascular Events Comparison

The TPHREG Procedure

Model Information

Data Set	WORK.DATA3
Dependent Variable	studyperiod30
Censoring Variable	status30
Censoring Value(s)	0
Ties Handling	BRESLOW

Number of Observations Read	12434
Number of Observations Used	12434

Class Level Information

Class	Value	Design Variables
atypical	0	0
	1	1

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
12434	414	12020	96.67

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	7666.920	7664.353
AIC	7666.920	7666.353
SBC	7666.920	7670.379

The TPHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	2.5665	1	0.1092
Score	2.5089	1	0.1132
Wald	2.5024	1	0.1137

Type 3 Tests

Effect	DF	Wald Chi-Square	Pr > ChiSq
atypical	1	2.5024	0.1137

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Variable Label
atypical	1	1	0.17534	0.11084	2.5024	0.1137	1.192	0.959	1.481	atypical 1

Cox proportional hazards model (adjusted) - 30 days - Cerebrovascular Events Comparison

The TPHREG Procedure

Model Information

Data Set	WORK.DATA3
Dependent Variable	studyperiod30
Censoring Variable	status30
Censoring Value(s)	0
Ties Handling	BRESLOW

Number of Observations Read	12434
Number of Observations Used	12434

Class Level Information

Class	Value	Design Variables
atypical	0	0
	1	1
sex	1	0
	2	1

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
12434	414	12020	96.67

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

The TPHREG Procedure

Model Fit Statistics

Criterion	Without Covariates	With Covariates

-2 LOG L	7666.920	7075.073
AIC	7666.920	7167.073
SBC	7666.920	7352.263

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	591.8472	46	<.0001
Score	810.8299	46	<.0001
Wald	565.5337	46	<.0001

Type 3 Tests

Effect	DF	Wald Chi-Square	Pr > ChiSq
atypical	1	0.1223	0.7265
age	1	5.0741	0.0243
sex	1	11.4723	0.0007
pch	1	5.8044	0.0160
noadm	1	0.2528	0.6151
totalperphin	1	0.8483	0.3570
adjyear	1	13.7992	0.0002
adgsum	1	0.7930	0.3732
d_431	1	22.9185	<.0001
d_433	1	213.6827	<.0001
d_401_405	1	0.0487	0.8254
d_428	1	2.7666	0.0962
d_4273	1	0.0427	0.8362
d_427	1	0.9401	0.3323
d_410	1	0.4832	0.4870
d_421	1	0.0012	0.9724
d_411_414	1	1.6837	0.1944
d_440	1	0.4276	0.5131
d_393_398	1	0.1609	0.6884
d_420_429	1	0.0080	0.9285
d_250	1	2.6010	0.1068
d_490	1	0.0936	0.7597
d_140	1	1.9175	0.1661
d_332	1	1.0510	0.3053
d_290	1	0.3684	0.5439
d_331	1	6.5067	0.0107
d_295	1	0.8030	0.3702

d_2930	1	1.1172	0.2905
d_296	1	0.6684	0.4136
d_297	1	1.8311	0.1760
drugs_per_year	1	5.9524	0.0147
anticonvs	1	1.3714	0.2416
benzo	1	3.4111	0.0648
antidepr	1	1.1635	0.2807
sedatives_hypnotics	1	3.0306	0.0817
anxiolytics	1	2.7110	0.0997
cholinester	1	0.0030	0.9565
anticoagulants	1	21.9710	<.0001
diuretics	1	0.5703	0.4501
betablockers	1	0.0016	0.9683
ca_blockers	1	0.0018	0.9662
angio_2_antagon	1	3.5836	0.0584
angioconvert	1	2.6767	0.1018
HMG_COA	1	5.9061	0.0151
antidiab	1	1.5456	0.2138
hrt	1	2.1206	0.1453

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
atypical	1	1	-0.04187	0.11972	0.1223	0.7265	0.959	0.758	1.213
age		1	0.01708	0.00758	5.0741	0.0243	1.017	1.002	1.032
sex	2	1	-0.35987	0.10625	11.4723	0.0007	0.698	0.567	0.859
pch		1	0.28859	0.11979	5.8044	0.0160	1.335	1.055	1.688
noadm		1	0.01334	0.02652	0.2528	0.6151	1.013	0.962	1.067
totalperphin		1	0.00445	0.00483	0.8483	0.3570	1.004	0.995	1.014
adjyear		1	-0.10008	0.02694	13.7992	0.0002	0.905	0.858	0.954
adgsum		1	0.01890	0.02122	0.7930	0.3732	1.019	0.978	1.062
d_431		1	0.66794	0.13952	22.9185	<.0001	1.950	1.484	2.564
d_433		1	1.77328	0.12131	213.6827	<.0001	5.890	4.644	7.471
d_401_405		1	0.02649	0.12008	0.0487	0.8254	1.027	0.812	1.299
d_428		1	-0.22008	0.13232	2.7666	0.0962	0.802	0.619	1.040
d_4273		1	0.02984	0.14436	0.0427	0.8362	1.030	0.776	1.367
d_427		1	-0.21905	0.22592	0.9401	0.3323	0.803	0.516	1.251
d_410		1	0.11011	0.15840	0.4832	0.4870	1.116	0.818	1.523
d_421		1	-9.45935	273.21328	0.0012	0.9724	0.000	0.000	2.83E228
d_411_414		1	0.15164	0.11687	1.6837	0.1944	1.164	0.926	1.463
d_440		1	-0.12238	0.18715	0.4276	0.5131	0.885	0.613	1.277
d_393_398		1	-0.18554	0.46259	0.1609	0.6884	0.831	0.335	2.057
d_420_429		1	-0.01366	0.15223	0.0080	0.9285	0.986	0.732	1.329
d_250		1	0.27082	0.16793	2.6010	0.1068	1.311	0.943	1.822
d_490		1	0.03391	0.11085	0.0936	0.7597	1.034	0.832	1.286

d_140	1	-0.18478	0.13344	1.9175	0.1661	0.831	0.640	1.080
d_332	1	-0.25024	0.24410	1.0510	0.3053	0.779	0.483	1.256
d_290	1	-0.07330	0.12075	0.3684	0.5439	0.929	0.733	1.177
d_331	1	-0.42730	0.16752	6.5067	0.0107	0.652	0.470	0.906
d_295	1	-0.52396	0.58471	0.8030	0.3702	0.592	0.188	1.863
d_2930	1	0.18592	0.17590	1.1172	0.2905	1.204	0.853	1.700
d_296	1	0.17011	0.20807	0.6684	0.4136	1.185	0.788	1.782
d_297	1	-0.17423	0.12875	1.8311	0.1760	0.840	0.653	1.081
drugs_per_year	1	-0.02809	0.01151	5.9524	0.0147	0.972	0.951	0.994
anticonvs	1	0.17820	0.15216	1.3714	0.2416	1.195	0.887	1.610
benzo	1	-0.34813	0.18849	3.4111	0.0648	0.706	0.488	1.022
antidepr	1	-0.12103	0.11220	1.1635	0.2807	0.886	0.711	1.104
sedatives_hypnotics	1	0.28442	0.16338	3.0306	0.0817	1.329	0.965	1.831
anxiolytics	1	0.27974	0.16990	2.7110	0.0997	1.323	0.948	1.845
cholinester	1	-0.02120	0.38832	0.0030	0.9565	0.979	0.457	2.096
anticoagulants	1	0.53052	0.11318	21.9710	<.0001	1.700	1.362	2.122
diuretics	1	-0.08594	0.11380	0.5703	0.4501	0.918	0.734	1.147
betablockers	1	0.00492	0.12374	0.0016	0.9683	1.005	0.789	1.281
ca_blockers	1	0.00511	0.12067	0.0018	0.9662	1.005	0.793	1.273
angio_2_antagon	1	0.31690	0.16740	3.5836	0.0584	1.373	0.989	1.906
angioconvert	1	0.18561	0.11345	2.6767	0.1018	1.204	0.964	1.504
HMG_COA	1	0.32706	0.13458	5.9061	0.0151	1.387	1.065	1.805
antidiab	1	-0.24480	0.19691	1.5456	0.2138	0.783	0.532	1.152
hrt	1	-0.52817	0.36270	2.1206	0.1453	0.590	0.290	1.200

Analysis of Maximum Likelihood Estimates

Parameter		Variable Label
atypical	1	atypical 1
age		
sex	2	Sex 2
pch		PCH
noadm		total No. of hsp admissions
totalperphin		Total No. of GP Visits
adjyear		Index Year
adgsum		Sum of ADGs (Num)
d_431		Stroke
d_433		Cerebro Vascular Disease
d_401_405		Hypertension
d_428		Congestive Heart Failure
d_4273		Atrial Fibrillation
d_427		Cardiac Dysrhythmias
d_410		Myocardial Infarction
d_421		Endocarditis
d_411_414		Other Ischemic Heart Disease
d_440		Peripheral Vascular Disease

d_393_398	Rheumatic Heart Disease
d_420_429	Other Cardiovascular Disorder
d_250	Diabetes
d_490	Chronic Pulmonary Disease
d_140	Cancer
d_332	PD
d_290	Dementia
d_331	Alzheimers
d_295	Schizophrenia
d_2930	Delirium
d_296	Mood Disorder
d_297	Other Pscyhiatric Disorder
drugs_per_year	Total No. of Drugs Used
anticonvs	anticonvulsants drugs
benzo	benzodiazepines
antidepr	antidepressants
sedatives_hypnotics	sedatives and hypnotics
anxiolytics	anxiolytics
cholinester	anti-dementia agents
anticoagulants	anticoagulants
diuretics	diuretics
betablockers	betablockers
ca_blockers	calcium channels blockers
angio_2_antagon	angiotensin-2-antagonists
angioconvert	angioconverting agents
HMG_COA	statins
antidiab	antidiabetic agents
hrt	hormone replacement therapy

Appendix 5. Ethics approvals

Pledge of confidentiality – The Personal Health Information Act

Research Ethics Board approval – Reference Number H2009:223

Health Information Privacy Committee approval – File Number 2009/2010-25

Manitoba Centre for Health Policy approval – Project Number 2009-027

UNIVERSITY OF MANITOBA

PLEDGE OF CONFIDENTIALITY
PERSONAL HEALTH INFORMATION

I have read and understood the University of Manitoba ("the University") policy on security and confidentiality of personal health information as described in The FIPPA and PHIA Policy, which is in accordance with ***The Personal Health Information Act*** (Manitoba).

I have read and understood the University procedures on security and confidentiality of personal health information as described in The FIPPA and PHIA Procedures, including procedures relating to collection, access, use, disclosure, retention and storage, and destruction of personal health information.

In consideration of my association, appointment, employment, or contract with the University ("my relationship"), and as an integral part of the terms and conditions of my relationship, I hereby agree, pledge and undertake that I will not at any time, during my relationship with the University, access or use personal health information, or reveal or disclose to any persons within or outside the University, any personal health information except as may be required in the course of my duties and responsibilities, in accordance with applicable Laws, and pursuant to University and departmental policies governing proper release of the information.

I understand that my obligations concerning the protection of confidentiality relate to all personal health information in the custody or under the control of the University that I may gain access to, directly or indirectly, as a result of my relationship.

I understand that the obligations outlined above will continue after my relationship with the University of Manitoba ends.

I understand that unauthorized use or disclosure of personal health information may result in disciplinary action being taken, and legal action at the discretion of the University.

IRINA VASILYEVA	[redacted]
Name of Individual Making Pledge (Print)	Signature of Individual Making Pledge
Faculty of Pharmacy	25.09.09
Faculty/Department/Program/Office/Unit/Site	Date Signed
[redacted]	Oct. 25/09
Access & Privacy Coordinator *University of Manitoba*	*Date Signed*

FIPPA Form 21, Rev. March, 2009

UNIVERSITY OF MANITOBA

BANNATYNE CAMPUS
Research Ethics Boards

P126-770 Bannatyne Avenue
Winnipeg, Manitoba
Canada R3E 0W3
Tel: (204) 789-3255
Fax: (204) 789-3414

APPROVAL FORM

Principal Investigator: Ms. I. Vasilyeva
Supervisor: Dr. S. Alessi-Severini

Ethics Reference Number: H2009:223
Date of Approval: August 4, 2009
Date of Expiry: August 4, 2010

Protocol Title: Antipsychotic-induced adverse events in the elderly population of Manitoba (Linked to H2006:145)

The following is/are approved for use:

- **Revised Proposal submitted July 30, 2009**
- **Data Fields (Attachment 1) submitted July 30, 2009**

The above underwent expedited review and was **approved as submitted** on August 4, 2009 by Dr. John Arnett, Ph.D., C. Psych., Health Research Ethics Board, Bannatyne Campus, University of Manitoba on behalf of the committee per your letter dated July 30, 2009. The Research Ethics Board is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement, and the applicable laws and regulations of Manitoba. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the *Food and Drug Regulations of Canada*.

This approval is valid for one year only. A study status report must be submitted annually and must accompany your request for re-approval. Any significant changes of the protocol and informed consent form should be reported to the Chair for consideration in advance of implementation of such changes. The REB must be notified regarding discontinuation or study closure.

This approval is for the ethics of human use only. For the logistics of performing the study, approval must be sought form the relevant institution, if required.

Sincerely yours,

John Arnett, Ph.D., C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus

Please quote the above Ethics Reference Number on all correspondence.
Inquiries should be directed to REB Secretary
Telephone: (204) 789-3255 / Fax: (204) 789-3414

UNIVERSITY
OF MANITOBA

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APPROVAL FORM

Principal Investigator: Ms. I. Vasilyeva
Supervisor: Dr. S. Alessi-Severini

Ethics Reference Number: H2009:223
Date of Approval: August 4, 2010
Date of Expiry: August 4, 2011

Protocol Title: Antipsychotic-induced adverse events in the elderly population of Manitoba (Linked to H2006:145)

The following is/are approved for use:

- **Annual Approval**

The above was approved by Dr. John Arnett, Ph.D., C. Psych., Chair, Health Research Ethics Board, Bannatyne Campus, University of Manitoba on behalf of the committee per your submission dated July 13, 2010. The Research Ethics Board is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement, and the applicable laws and regulations of Manitoba. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the *Food and Drug Regulations of Canada.*

This approval is valid until the expiry date only. A study status report must be submitted annually and must accompany your request for re-approval. Any significant changes of the protocol and informed consent form should be reported to the Chair for consideration in advance of implementation of such changes. The REB must be notified regarding discontinuation or study closure.

This approval is for the ethics of human use only. For the logistics of performing the study, approval must be sought from the relevant institution, if required.

Sincerely yours,

John Arnett, PhD., C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus

Please quote the above Ethics Reference Number on all correspondence.
Inquiries should be directed to the REB Secretary **Telephone**: (204) 789-3255 / Fax: (204) 789-3414

Manitoba
Health and Healthy Living
Health Information Privacy Committee
4045 – 300 Carlton Street
Winnipeg MB R3B 3M9
Phone: (204) 786-7204
FAX: (204) 944-1911

October 13, 2009

Irina Vasilyeva
Faculty of Pharmacy
Apotex Centre – 750 McDermot Avenue
Winnipeg, MB R3E 0T5

File No. 2009/2010 - 25

Dear Ms. Vasilyeva:

Re: Antipsychotic-induced Adverse Events in the Elderly Populations of MB

Thank you for submitting the requested documentation and providing clarification for the above project. The Health Information Privacy Committee has now ***approved*** your request for data for this project.

Any significant changes to the proposed study design should be reported to the Chair for consideration in advance of their implementation. Also, please be reminded that *all manuscripts and presentation materials resulting from this study must be submitted for review at least 30 days prior to being submitted for publication or presentation.*

Please note that a Researcher Agreement will need to be completed before work on this project can commence. This will be initiated by the MCHP. If you have any questions or concerns, please do not hesitate to contact Lisa LaBine, Committee Coordinator at 786-7204.

Yours truly,

For:
R. Walker, MD FRCPC
Chair, Health Information Privacy Committee

Please quote the file number on all correspondence

cc. D. Malazdrewicz
S. Alessi-Severini

Manitoba
spirited energy

Manitoba Centre for Health Policy

Dept. of Community Health Sciences, Faculty of Medicine, University of Manitoba

4th Floor, Room 408
727 McDermot Ave.
Winnipeg, Manitoba
Canada R3E 3P5
Ph (204) 789 3819
Fax (204) 789 3910

December 1, 2009

Irina Vasilyeva
Apotex Centre
750 McDermot Avenue
Winnipeg, MB R3E 0T5

Dear Irina:

Re: **"Antipsychotic-Induced Adverse Events in the Elderly Population of Manitoba"**
MCHP project number: "2009-027"

Enclosed is a copy for your records of the fully executed Researcher Agreement, representing approval to proceed with the above research project at the Manitoba Centre for Health Policy (MCHP) using Manitoba Health data. It is important that the requirements outlined in this agreement be shared with all members of your project team, specifically Section 5 obligations respecting use and disclosure and Section 6 regarding reports, monitoring and enforcement. It is also important that all correspondence with MCHP relating to this project reference the MCHP project number.

We look forward to facilitating access to the Population Health Research Data Repository for your project. To proceed, please contact Charles Burchill (Manager, Program and Analysis System) at charles_burchill@cpe.umanitoba.ca. Sophie Buternowsky, Senior Grants Accountant, at MCHP will be contacting you regarding invoicing for your project. We would also be glad to assist you in meeting ongoing project requirements for maintaining access to the data, as outlined at our website:
http://umanitoba.ca/faculties/medicine/units/mchp/resources/access/index.html

Should you have any questions about the process, please do not hesitate to contact me at (204) 975-7770.

Sincerely,

[redacted]
JoAnne Baribeau
Repository Access Coordinator

Cc Ruth Bond, Manager, Data Repository
Charles Burchill, Manager, Program and Analysis System
Sophie Buternowsky, Senior Grants Accountant
Dr. Silvia Alessi-Severini

UNIVERSITY OF MANITOBA

Appendix 6. Hazard ratios

Extrapyramidal syndromes – hazard ratios

Model	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Risperidone vs. FGAs		
30 days	0.396 (0.240–0.654)	0.383 (0.221–0.665)
60 days	0.450 (0.291–0.695)	0.450 (0.278–0.729)
90 days	0.494 (0.336–0.725)	0.501 (0.326–0.769)
180 days	0.633 (0.454–0.882)	0.646 (0.446–0.936)
360 days	0.732 (0.543–0.986)	0.753 (0.539–1.050)
FGAs vs. non-exposure		
30 days	7.557 (4.030–14.172)	6.918 (3.244–14.756)
60 days	6.846 (3.920–11.959)	6.187 (3.288–11.642)
90 days	5.460 (3.361–8.869)	4.474 (2.613–7.660)
180 days	4.896 (3.128–7.664)	4.002 (2.458–6.515)
360 days	4.238 (2.822–6.362)	3.503 (2.271–5.403)
Risperidone vs. non-exposure		
30 days	2.193 (1.128–4.267)	2.117 (0.820–5.446)
60 days	2.000 (1.189–3.364)	1.869 (0.929–3.759)
90 days	2.010 (1.303–3.100)	1.610 (0.912–2.842)
180 days	2.125 (1.493–3.023)	1.943 (1.250–3.021)
360 days	1.955 (1.457–2.624)	1.733 (1.214–2.472)

Cerebrovascular events – hazard ratios

Model	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
SGAs vs. FGAs		
30 days	1.192 (0.959–1.481)	0.959 (0.758–1.213)
60 days	1.263 (1.037–1.537)	1.035 (0.837–1.278)
90 days	1.233 (1.027–1.482)	1.020 (0.838–1.242)
180 days	1.269 (1.072–1.502)	1.054 (0.881–1.262)
360 days	1.336 (1.142–1.564)	1.136 (0.961–1.344)
FGAs vs. non-exposure		
30 days	2.078 (1.586–2.722)	1.723 (1.187–2.502)
60 days	2.000 (1.565–2.556)	1.665 (1.200–2.310)
90 days	1.932 (1.536–2.430)	1.593 (1.182–2.146)
180 days	1.820 (1.474–2.248)	1.482 (1.137–1.931)
360 days	1.698 (1.395–2.066)	1.415 (1.114–1.797)
SGAs vs. non-exposure		
30 days	2.228 (1.872–2.652)	1.665 (1.256–2.208)
60 days	2.166 (1.869–2.511)	1.758 (1.399–2.209)
90 days	2.079 (1.817–2.378)	1.722 (1.408–2.106)
180 days	1.973 (1.754–2.219)	1.652 (1.393–1.960)
360 days	1.961 (1.765–2.178)	1.611 (1.388–1.869)

Myocardial infarction – hazard ratios

Model	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
SGAs vs. FGAs		
30 days	2.061 (0.998–4.258)	1.989 (0.920–4.300)
60 days	1.698 (0.923–3.127)	1.678 (0.878–3.206)
90 days	1.934 (1.086–3.444)	1.843 (1.001–3.392)
180 days	1.618 (0.995–2.632)	1.630 (0.973–2.731)
360 days	1.486 (0.970–2.276)	1.614 (1.024–2.543)
FGAs vs. non-exposure		
30 days	0.533 (0.230–1.238)	0.768 (0.219–2.691)
60 days	0.661 (0.333–1.310)	0.932 (0.377–2.305)
90 days	0.596 (0.304–1.169)	0.860 (0.364–2.034)
180 days	0.734 (0.422–1.277)	0.861 (0.437–1.697)
360 days	0.778 (0.481–1.258)	0.785 (0.448–1.376)
SGAs vs. non-exposure		
30 days	1.871 (1.171–2.990)	2.358 (1.052–5.282)
60 days	1.404 (0.959–2.057)	1.569 (0.852–2.891)
90 days	1.337 (0.959–1.863)	1.912 (1.121–3.264)
180 days	1.201 (0.913–1.581)	1.559 (1.021–2.380)
360 days	0.974 (0.770–1.232)	1.058 (0.756–1.479)

Cardiac arrhythmia – hazard ratios

Model	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
SGAs vs. FGAs		
30 days	0.649 (0.182–2.311)	0.485 (0.111–2.119)
60 days	0.568 (0.179–1.801)	0.464 (0.125–1.725)
90 days	0.630 (0.205–1.939)	0.461 (0.128–1.660)
180 days	0.693 (0.280–1.715)	0.540 (0.200–1.455)
360 days	0.899 (0.379–2.134)	0.865 (0.336–2.232)
FGAs vs. non-exposure		
30 days	2.184 (0.527–9.053)	
60 days	1.381 (0.442–4.310)	
90 days	0.975 (0.334–2.851)	
180 days	0.859 (0.351–2.103)	0.798 (0.173–3.666)
360 days	0.755 (0.315–1.810)	0.564 (0.138–2.301)
SGAs vs. non-exposure		
30 days	1.657 (0.514–5.348)	
60 days	0.922 (0.347–2.450)	
90 days	0.858 (0.349–2.108)	
180 days	1.000 (0.511–1.955)	1.589 (0.489–5.162)
360 days	1.014 (0.576–1.784)	1.293 (0.501–3.338)

Congestive heart failure – hazard ratios

Model	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
SGAs vs. FGAs		
30 days	0.993 (0.722–1.368)	0.919 (0.650–1.299)
60 days	0.902 (0.688–1.181)	0.920 (0.686–1.235)
90 days	0.925 (0.722–1.185)	0.963 (0.737–1.259)
180 days	0.978 (0.782–1.223)	1.009 (0.792–1.286)
360 days	1.059 (0.861–1.303)	1.127 (0.902–1.409)
FGAs vs. non-exposure		
30 days	1.591 (1.094–2.313)	1.958 (1.039–3.691)
60 days	1.757 (1.278–2.417)	2.259 (1.384–3.689)
90 days	1.625 (1.214–2.176)	1.789 (1.155–2.772)
180 days	1.481 (1.140–1.923)	1.486 (1.030–2.144)
360 days	1.318 (1.036–1.676)	1.228 (0.893–1.689)
SGAs vs. non-exposure		
30 days	2.093 (1.595–2.745)	1.610 (0.995–2.605)
60 days	1.780 (1.430–2.216)	1.266 (0.883–1.815)
90 days	1.794 (1.476–2.181)	1.409 (1.024–1.939)
180 days	1.661 (1.412–1.954)	1.296 (0.999–1.681)
360 days	1.504 (1.307–1.730)	1.242 (1.003–1.536)

All-cause mortality – hazard ratios

Model	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
SGAs vs. FGAs		
30 days	0.535 (0.422–0.679)	0.398 (0.307–0.514)
60 days	0.616 (0.502–0.756)	0.462 (0.370–0.575)
90 days	0.656 (0.542–0.793)	0.496 (0.404–0.608)
180 days	0.790 (0.665–0.938)	0.586 (0.488–0.704)
360 days	0.936 (0.799–1.097)	0.683 (0.577–0.809)
FGAs vs. non-exposure		
30 days	4.071 (2.923–5.670)	4.148 (2.575–6.683)
60 days	3.477 (2.613–4.627)	3.112 (2.099–4.612)
90 days	2.916 (2.257–3.768)	2.363 (1.674–3.334)
180 days	2.425 (1.924–3.057)	1.847 (1.367–2.494)
360 days	1.913 (1.554–2.356)	1.387 (1.065–1.805)
SGAs vs. non-exposure		
30 days	1.394 (1.101–1.766)	1.153 (0.815–1.632)
60 days	1.321 (1.097–1.591)	1.191 (0.908–1.562)
90 days	1.206 (1.023–1.422)	1.041 (0.823–1.315)
180 days	1.102 (0.966–1.258)	0.937 (0.776–1.131)
360 days	0.978 (0.877–1.092)	0.824 (0.708–0.959)

Appendix 7. Antiparkinson medications

Dopamine agents: selegine, carbidopa/levodopa, bromocriptine, pergolide

Anticholinergic agents: benztropine, biperiden, procyclidine, trihexyphenidyl, ethopropazine

Non-ergot agents: pramipexole, ropinirole, tolcapone, entacapone