

Movement Disorders in Elderly Users of Risperidone and First Generation Antipsychotic Agents: A Canadian Population-Based Study

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Abstract

Background: Despite concerns over the potential for severe adverse events, antipsychotic medications remain the mainstay of treatment of behaviour disorders and psychosis in elderly patients. Second-generation antipsychotic agents (SGAs; e.g., risperidone, olanzapine, quetiapine) have generally shown a better safety profile compared to the first-generation agents (FGAs; e.g., haloperidol and phenothiazines), particularly in terms of a lower potential for involuntary movement disorders. Risperidone, the only SGA with an official indication for the management of inappropriate behaviour in dementia, has emerged as the antipsychotic most commonly prescribed to older patients. Most clinical trials evaluating the risk of movement disorders in elderly patients receiving antipsychotic therapy have been of limited sample size and/or of relatively short duration. A few observational studies have produced inconsistent results.

Methods: A population-based retrospective cohort study of all residents of the Canadian province of Manitoba aged 65 and over, who were dispensed antipsychotic medications for the first time during the time period from April 1, 2000 to March 31, 2007, was conducted using Manitoba's Department of Health's administrative databases. Cox proportional hazards models were used to determine the risk of extrapyramidal symptoms (EPS) in new users of risperidone compared to new users of FGAs.

Results: After controlling for potential confounders (demographics, comorbidity and medication use), risperidone use was associated with a lower risk of EPS compared to FGAs at 30, 60, 90 and 180 days (adjusted hazard ratios [HR] 0.38, 95% CI: 0.22–0.67; 0.45, 95% CI: 0.28–0.73; 0.50, 95% CI: 0.33–0.77; 0.65, 95% CI: 0.45–0.94, respectively). At 360 days, the strength of the association weakened with an adjusted HR of 0.75, 95% CI: 0.54–1.05.

Conclusions: In a large population of elderly patients the use of risperidone was associated with a lower risk of EPS compared to FGAs.

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Introduction

Major physiological changes in the aging body such as variations in body composition, metabolic capacity, and receptor functionality deeply affect the pharmacokinetics and pharmacodynamics of drugs [1,2]. The common presence of multiple comorbid conditions further complicates the management of the elderly patient [1]. Because of these factors elderly subjects have historically been excluded from randomized controlled trials of pharmacotherapy [3]. As a result, medications are often prescribed to older patients despite the limited information available on their safety and effectiveness in the over-65 age group.

Antipsychotic agents (AA) are no exception and RCTs conducted in the elderly have been limited to patients with

diagnoses of schizophrenia and dementias [4–6]. Nevertheless, antipsychotic medications continue to be prescribed widely to elderly persons to control behavioural and psychotic symptoms in a variety of diagnoses [7,8].

The adverse effects of first-generation antipsychotic agents (FGAs) (e.g., haloperidol and phenothiazines), particularly cardiovascular events and movement disorders, such as extrapyramidal symptoms (EPS) and tardive dyskinesia, have been known for decades. However, concerns also have been raised on the use of the newer second-generation antipsychotic agents (SGAs) (e.g., risperidone, olanzapine, quetiapine), which were promoted as being safer than the FGAs. In fact, a significant body of literature has reported comparisons of severe adverse events in FGA- and SGA-treated elderly persons [9–23] and several warnings have also been issued by

health agencies (Health Canada, FDA, EMA) advising of the increased risk of cerebrovascular events and death in patients with dementia treated with antipsychotic agents [24–28].

Nevertheless, the practice of prescribing antipsychotics to elderly patients has continued [29–31] and risperidone, the only SGA with an official indication for behavioural disturbances of dementia in Canada as well as in Europe and the US, remains the antipsychotic agent most commonly prescribed to the over-65 age group [31]. The superiority of SGAs in terms of lower incidence of movement disorders or EPS such as acute dystonia, akathisia, parkinsonism and tardive dyskinesia, has been recently challenged [32]. The current study was designed to evaluate in a real world setting the incidence of movement disorders in the entire population of elderly residents of a Canadian province treated for various diagnoses with either risperidone or an FGA.

Methods

Ethics approval

This population-based study received ethics approval from the Health Research Ethics Board of the University of Manitoba. It was conducted in compliance with the Personal Health Information Act of Manitoba and was approved by Manitoba's Health Information Privacy Committee.

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, which has been relatively stable at approximately 1.12 million persons during the time of the study. The use of a consistent set of identifiers allows for the integration of health histories of individuals across files and time. Nearly all contacts with the provincial health care system, including physicians' visits, hospital admissions, 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. For this study the following databases were accessed: 1) Population Registry, 2) Hospital Abstracts, 3) Medical Services, 4) Drug Product Information Network (DPIN) prescription records, 5) PCH records, 6) Vital Statistics.

Records of physician reimbursement for medical care provided are submitted under a fee-for-service arrangement, and contain physician specialty and information on patient diagnosis at the 3-digit level of the International Classification of Diseases, Clinical Modification (ICD-9- and ICD-10-CM) classification system and physician specialty. Separation abstracts for hospital services include information on ICD-9- and ICD-10-CM diagnostic codes. Records of dispensed prescriptions (DPIN), which are submitted by retail pharmacies for reimbursement by provincial drug insurance plans or for drug utilization review purposes (regardless of insurance coverage), contain data on the date of dispensing, drug name, strength, dosage form, and quantity, and the 8-digit drug identification number (DIN).

Study design

The study used a retrospective cohort design in which elderly residents of Manitoba, who were dispensed their first antipsychotic medication between April 1, 2000 and March 31, 2007 constituted the cohort of incident users. The date of the first dispensation of an antipsychotic prescription was considered the index date. The time frame 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 information from 1995 onwards), and that all individuals could be followed for at least a year (up to March 31, 2008).

Outcomes

The primary outcome was a composite outcome of a diagnosis for a movement disorder, EPS or parkinsonism, and/or a dispensation of antiparkinson drugs at 360 days. Secondary outcomes were the composite outcomes of a diagnosis of movement disorder, EPS or parkinsonism, and/or a dispensation of antiparkinson drugs at 30, 60, 90, and 180 days. Taking into account that drug-induced movement disorders tend to be under-diagnosed [33], a single record in the Medical Services database was considered a diagnosis of a movement disorder.

Exclusion criteria

To ensure a complete record of patients' use of the health care system, all study subjects were required to be covered by provincial health insurance for 5 years prior to the cohort entry and during the follow-up period. As the DPIN database does not include information on medications dispensed in hospitals, patients hospitalised for longer than 25% of the year prior to the cohort entry were excluded in order to avoid a possible medication misclassification bias. Similarly, patients receiving their first antipsychotic prescription right after hospital separation were excluded if this hospitalization was longer than 30 days. As emergent EPS attributable to antipsychotic exposure was the outcome of interest, persons with prior history (5 years prior to cohort entry) of Parkinson's disease, EPS and other movement disorders and/or exposure to antiparkinson medications (i.e., dopaminergic and anticholinergic agents) as well as those with a history of brain tumours were excluded.

First-generation antipsychotics available on the Canadian market at the time of the study were included (chlorpromazine, haloperidol, flupenthixol, fluphenazine, loxapine, mesoridazine, methotrimeprazine, perphenazine, pimozide, prochlorperazine, thioridazine, trifluoperazine and zuclopenthixol). The group of FGA users was compared to the group of risperidone users.

Follow-up

All subjects included in the study were followed until an event of interest occurred, or up to one year from the index date. Individuals were censored at the time of loss of insurance coverage, a gap in prescription refill of 30 days or longer, death or the end of study. As the DPIN database does not include information on medications administered in hospitals, persons admitted to a hospital for 30 days or longer were also censored. As well, patients who switched from a FGA to a SGA (including risperidone), or from risperidone to a FGA or another SGA were censored at the time of the switch.

Statistical analysis

Cox proportional hazard models were used to examine the effect of risperidone use on the incidence of EPS compared to FGA use. Adjustments were made to account for potential confounders. Covariates included in the model were age, sex, PCH residence, comorbid diseases and overall comorbidity burden. Data on the number of comorbid conditions were obtained from both hospital abstracts and medical services databases. Data were accessed from the 5 years prior to the index date to build a history of comorbid conditions for each person. As an overall measure of comorbidity, the sum of Aggregated

Diagnostic Groups (ADGs), as defined in the Johns Hopkins ACG[®] (Adjusted Clinical Group) Case-Mix System (software version 9), was assigned to each subject [34–37]. The use of other medications in one year prior to the cohort entry was also controlled for. In particular, adjustments were made for the use of medications associated with development of movement disorders (i.e., reserpine, methyl dopa, metoclopramide, lithium, valproate, amiodarone and tetrabenazine). Furthermore, adjustments were made for the index year to control for potential changes in prescribing patterns as observed in previous studies [31,38].

Standardized differences were calculated to identify significant differences between FGA- and risperidone-treated groups in baseline characteristics. 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.

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

Results

Prevalence of antipsychotic use in Manitoba was previously reported for the time period of this study [38]. The highest prevalence was observed in the elderly population (age 65 and older), reaching values of 4.3% in males and 6.0% in females [38]. These values were consistent with data reported by other jurisdictions in Canada [39], Europe [40,41] and the US [42].

Incidence rate of antipsychotic use in the elderly population of Manitoba between the fiscal year 2000–2001 and the fiscal year 2006–2007 is depicted in Figure 1. After applying all exclusion criteria a total of 8,885 persons were included in the cohort for analysis: 4,242 persons were in the FGA-exposed group and 4,643 in the risperidone-exposed group (Figure 2).

Baseline characteristics of the two groups are presented in Table 1. The number of EPS-related adverse events, mean length of follow-up and contributed person-years for FGA and risperidone

done users are given in Table 2. In both the unadjusted and the adjusted analyses the use of risperidone was associated with a lower risk of EPS adverse events at 30, 60, 90, and 180 days. At 360 days the adjusted HR was 0.75 with the 95% CI crossing 1.00 (0.54–1.05) (Figure 3).

Discussion

This study provides data on the incidence of EPS adverse events in the entire elderly population of the Canadian province of Manitoba treated with antipsychotic pharmacotherapy. More than 70% of the population initiated on a SGA was prescribed risperidone. Our results show that the use of FGAs is associated with an increased risk of EPS compared to treatment with risperidone. These results are supported by biological plausibility and are consistent with the findings of previous observational studies [43–45]. Blockade of D₂ 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 D₂ receptors) [46]. The affinity of FGAs for dopamine D₂ receptors leads to EPS. These agents bind more tightly than dopamine itself to the D₂ receptors while SGAs bind less avidly than dopamine to D₂ receptors (rapid dissociation theory) and allow normal dopamine transmission [47,48]. The reduced blockade of D₂ 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 D₂ blockade by SGAs [49]. Antipsychotic agents within the SGA class vary in their affinity to D₂ receptors and risperidone has the highest affinity [47,49].

Nevertheless, risperidone has been widely prescribed, particularly to elderly patients, with the expectation of a lower incidence of EPS compared to FGA treatment. In this study such lower risk of movement disorders has been confirmed up to approximately a year of therapy; however, a trend toward a weaker association was observed and the 95% CI of the adjusted HR at 360 days suggested a loss of statistical significance.

The interpretation of these results needs to consider the limitations of observational studies based on administrative data.

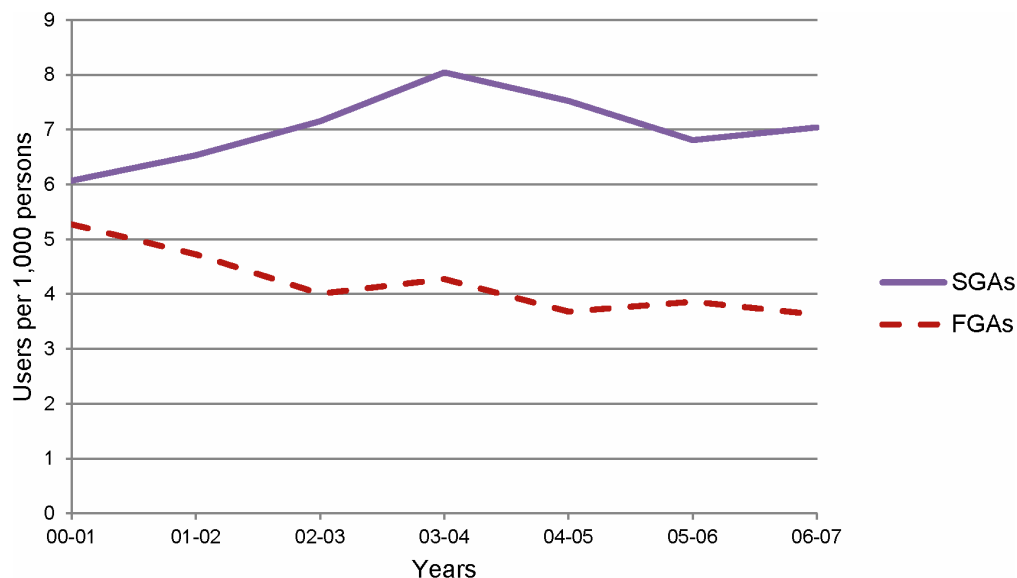


Figure 1. Incidence rates of antipsychotic use in the elderly population of Manitoba, 2001–2007.
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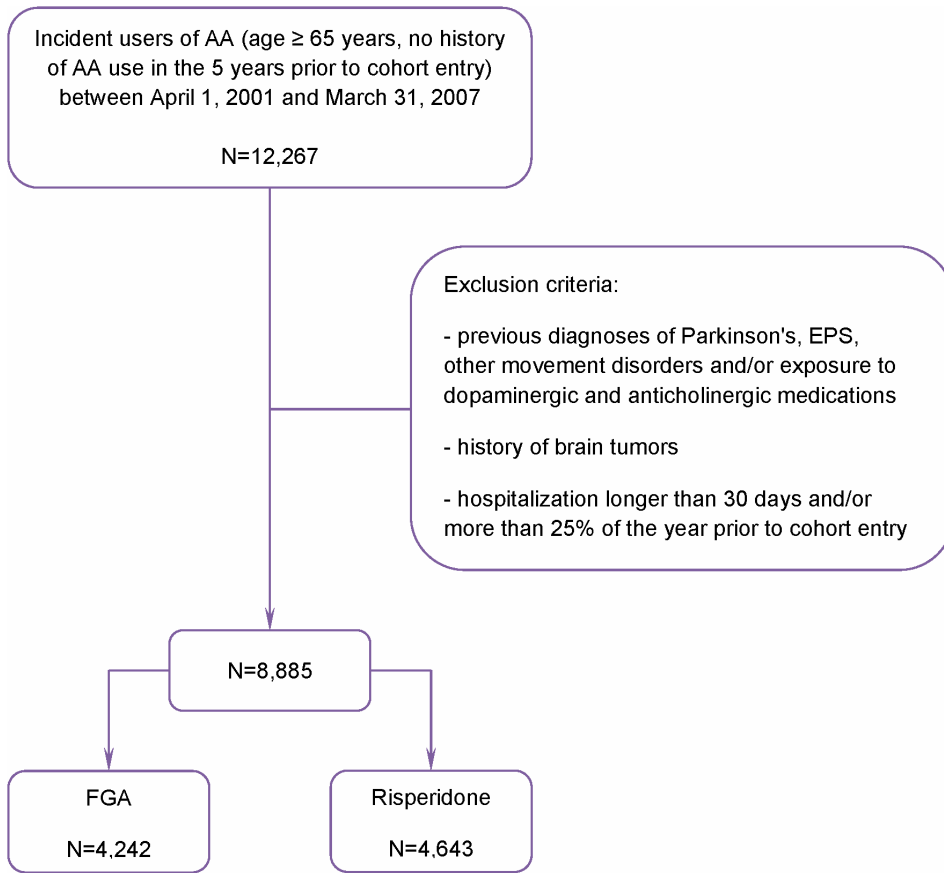


Figure 2. Study cohort.
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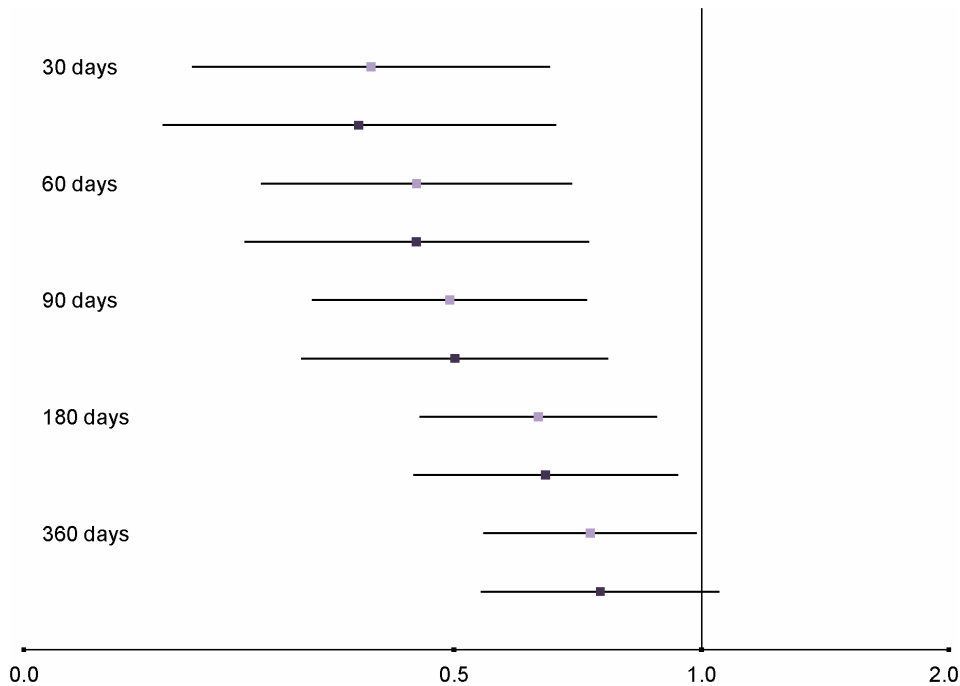


Figure 3. Hazard ratios for risperidone vs. FGAs. FGAs constitute the reference group. 95% CIs; unadjusted HRs in light colour square markers, adjusted in dark.
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Table 1. Baseline characteristics of FGA and risperidone users.

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 (%)			
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
PCH residence	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 (%)			
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 (%)	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
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

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However, a number of steps were taken to account for potential confounding. The key covariates that are associated with outcome or exposure were identified and adjustments were made in the analysis. Age, sex, residence in a PCH and comorbidities were

used to control for a possible selection bias. The index year was included into the adjusted models to account for possible changes in medical practice over the time frame of this study. The time frame of the study cohort did not include the time period of 1998

Table 2. 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

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to 2000 when much of the shift between FGA and SGA use happened.

No attempt was made to evaluate the effect of dose on incidence of EPS in this population, as small dose adjustments that commonly and continuously occur in clinical practise are not accurately captured by an observational study design that utilizes exclusively administrative data. Nevertheless, it is well known that EPS are dose-related and high doses of risperidone are expected to cause movement effects similar to those caused by FGAs.

Furthermore, 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 provide a real-world observation that the use of risperidone is associated with lower risk for potentially debilitating EPS adverse events in elderly subjects compared to the traditional antipsychotic medications. The advantage of this study is the fact that the entire elderly population of a Canadian province was included without restrictions due to insurance coverage or limited access. The results can be generalizable to other populations as they are not affected by sampling errors or recall bias. In conclusion, the information can be useful to clinicians, decision makers, patients and caregivers in choosing the most effective treatment for psychotic symptoms particularly in patients who might be at greater risk for certain adverse events such as movement disorders.

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