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Patterns of Antipsychotic use Among Community-Dwelling Elderly Patients with Dementia: Impact of Regulatory Warnings

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Abstract

Purpose: In Canada, regulatory warnings on cerebrovascular effects of risperidone and olanzapine in the elderly population with dementia were issued, respectively, in 2002 and 2004, and those on mortality associated with all atypical antipsychotics (APs) in 2005. These warnings led to a decrease in the prescription of APs, but effects on patterns of usage remain poorly examined. We conducted a study to assess the association between warnings and patterns of AP use in a population of community-dwelling elderly with dementia.

Methods: A retrospective cohort of 10,969 community-dwelling elderly (age 66+) with dementia who were new users of APs between 1st January 2000 and 31st December 2009 was assembled through the Quebec drug claims database (RAMQ). Association between regulatory warnings and rate of initiation of AP treatment was evaluated through interrupted time series analysis. Effects of the 2005 warning on cerebrovascular history in treated patients, and AP usage patterns (dosage, duration) were assessed, respectively through multivariate logistic regression and multiple linear regression analysis.

Results: The proportion of AP treatments initiated with risperidone decreased over time while that of quetiapine increased and of olanzapine remained stable. Controlling for covariates, the cerebrovascular risk profile of treated patients did not change after the 2005 warning (OR=1.05, 95%CI: 0.90 – 1.22). A small decrease in mean prescribed daily dose for risperidone was observed after the 2005 warning (-0.05 mg, p<0.001) while an increase was observed for olanzapine (+0.34 mg, p=0.009) and quetiapine (+1.27 mg, p=0.40). No change in treatment duration was observed (p=0.19).

Conclusion: Although regulatory warnings led to a decrease in the use of atypical APs, these products are still widely prescribed off-label in the elderly population with dementia. Channelling of APs toward patients with lower cerebrovascular risks and changes in prescription practices were not apparent after the warnings.

Keywords: Atypical antipsychotics; Dementia; Elderly; Regulatory warnings; Drug safety communication; Risk minimization intervention; Pharmacoepidemiology

Introduction

Approximately 50 to 80% of patients with dementia experience some behavioural and psychological symptoms of dementia (BPSD) [1], which include agitation, psychosis and mood disorders [2]. Antipsychotics (APs) are commonly prescribed for the management of these conditions with a prevalence of use of approximately 15% among US veterans [3]. Antipsychotics are divided into two classes: conventional and atypical. The latter are the most frequently prescribed, accounting for 82.5% of AP prescriptions in elderly patients in Canada in 2002 [4]. Concerns about the safety of atypical APs emerged following the publication of randomized controlled trials (RCTs) conducted in elderly patients with dementia, whereby an increased risk of cerebrovascular events associated with the use of risperidone and olanzapine was reported [5,6]. Following the RCT publications, three safety warnings were issued by Health Canada regarding the use of APs in the elderly population with dementia: the first two addressed the increased risk of cerebrovascular events associated with the use of risperidone and olanzapine (October 2002 and March 2004, respectively) [7,8], and the third focused on the increased mortality associated with the use of atypical APs (June 2005) [9]. In 2008, the US Food and Drug Administration (FDA) extended the black box warning to conventional APs [10-12]. In Canada, only risperidone is indicated for the treatment of BPSD, according to the product monograph. It is specified that the optimal dosage in this population should be 0.5 mg twice daily, and health care professionals are advised to assess the benefits and risks of the treatment, particularly with respect to cerebrovascular and cardiovascular risk factors [13]. This is not the case in the US where any AP use in elderly patients with dementia is considered to be off-label [14]. Despite these regulatory interventions, APs remain frequently prescribed for the management of BPSD [15].

Several studies have been published in the literature on the effectiveness of regulatory warnings on the use of APs in the elderly population with dementia. The study published in 2008 by Valiyeva et

al., showed that, in Ontario, each of the three warnings was associated with a relative decrease in atypical AP dispensing while the overall prescription rate of APs increased by 20% from 2002 to 2007 among elderly with dementia [16]. According to a recent study, the use of atypical APs in older patients with dementia began to decrease in 2003 and the black box warning issued by the FDA in 2005 accelerated this decline [3]. It was also found that AP use decreased especially in patients older than 80 years and with several comorbidities, although the impact of the warnings in this sub-population was not statistically significant [3].

With the general recommendation to prescribing physicians to evaluate the benefits and risks of APs in the elderly with dementia, our hypothesis is that, following the regulatory warnings, users of APs have less cerebrovascular and cardiovascular risk factors than elderly patients who initiated a treatment prior to the warnings. Another hypothesis is that regulatory warnings have influenced prescribing practices through a reduction in prescribed dosage and/or treatment duration.

Our study aimed at assessing the association between the 2005 warning and the characteristics of users, especially with respect to cerebrovascular risk factors. A secondary objective was to evaluate trends in prescribing practices, namely type of AP prescribed at treatment initiation, daily dosage, and treatment duration. The 2005 warning was selected as the main intervention of interest because, according to literature findings, this warning appeared to have had the greatest influence on AP use [3,16].

Methods

Study design

A retrospective cohort study was conducted among community-dwelling elderly with dementia who were covered by the Quebec public drug program and who initiated an AP treatment. The Quebec public drug program covers the great majority of elderly residents of the province (approximately 98%). Dementia was ascertained through cholinesterase inhibitor (ChI) dispensings in the drug claims database (RAMQ) from 1st January 2000 to 31st December 2009. Since the reliability of diagnostic codes for dementia in physician billings is questionable, ascertainment through ChI dispensings has been shown to be sensitive [17]. New AP use was defined as absence of AP dispensing in the 12 months prior to the current AP dispensing. Date of entry in the cohort was the date of first AP dispensing during the study period. Inclusion criteria consisted of being at least 66 years of age at cohort entry, and to have at least one year of prescription history. Patients were followed until death, institutionalization, or end of the study period (31st December 2009), whichever came first.

Data sources

Data sources for the study consisted of three RAMQ databases: the beneficiary database, the drug claims database, and the medical services claims database. The beneficiary database includes information on age group, sex and dates of coverage by the public drug program. The RAMQ drug claims database includes information on all dispensings of prescribed drugs included in the provincial formulary of reimbursed medications. Only drugs acquired in an outpatient setting are recorded; drugs acquired in-hospital, over-the-counter, or out-of-pocket are not recorded. For each dispensing, the following information is recorded: drug name, number of units dispensed, dosage per unit, prescribed duration, and date of dispensing. In Quebec, medical coverage is universal i.e., it includes all residents regardless of age and income. The medical services claims database includes all services billed by physicians on a fee-for-service. All services rendered in an inpatient or outpatient settings, including emergency departments, are recorded. The database includes the following information: type of service or procedure (coded according to the Canadian classification of diagnostic, therapeutic, and surgical procedures), date of service, location (private practice, emergency department, hospital, long-term care unit, or institution) and diagnostic code (ICD-9). Linkage between these databases is possible through an anonymized Health Insurance Number, which is a unique patient identifier that remains unchanged over time.

Study outcomes

The effect of the regulatory warnings was assessed using three main study outcomes: rate of AP treatment initiation (i.e., new use), characteristics of new AP users, and patterns of AP use. Rate of AP treatment initiation was defined as the proportion of individuals in the source population of patients with dementia who initiated an AP treatment during each month covered by the study period. Type of AP was the product dispensed at cohort entry. It was categorized into AP classes (conventional and atypical), and into three specific atypical agents (risperidone, olanzapine, quetiapine - these were the only atypical agents prescribed at treatment initiation).

Since regulatory warnings addressed specifically the risk of cerebrovascular event, history of cerebrovascular disease among users of APs was also a study outcome. Cerebrovascular history was assessed through the presence of diagnostic codes recorded in the RAMQ medical services claims database (ICD-9: 431 – 437) during the 12 months prior to the date of AP treatment initiation.

Patterns of AP use consisted of prescribed daily dosage at treatment initiation and actual treatment duration over the first year of treatment. Prescribed daily dosage was derived from the number of units dispensed, dosage per unit, and prescribed duration. Since risperidone in Canada is approved only for short-term management of BPSD, we decided to limit the maximal period for duration of AP prescription to one year following the first prescription of AP. Actual duration of AP use during the first year of treatment was obtained using dates of dispensing and prescribed duration. Duration was expressed as the number of days with active prescription and was assessed using prescribed duration of individual dispensings taking into account product switches and overlaps. When the same AP was prescribed throughout, total treatment duration was the sum of individual prescribed durations. When there was a switch in AP product, total duration was the sum of individual treatment durations minus overlapping periods, when applicable. When two prescriptions of the same AP were dispensed on the same date, the prescription with the longest duration was retained. For this analysis, patients with less than one year of follow-up were excluded.

Independent variable

The main independent variable was the 2005 regulatory warning; all AP treatment initiations that preceded the date of the warning (22nd June 2005) were considered to be unexposed, while those subsequent to this date were considered exposed.

Covariates

Covariates included age group (66-69, 70-74, 75-79, 80-84, and 85 and older) at date of entry in the cohort of ChI users, sex, depression (ICD-9: 296.2, 296.3, 298.0, 300.0, 300.1, 300.3, 300.4, 309.1, or 311.9 in combination with dispensing of antidepressants), and dispensing of anxiolytics, which are known to be associated with AP use and could potentially act as potential confounders in the association between the regulatory warning and patterns of AP use [18].

Other covariates were cardiovascular history and risk factors, which were ascertained through the RAMQ medical services database and the RAMQ drug claims database during the 12 months prior to the date of AP treatment initiation. Cardiovascular history included: myocardial infarction (ICD-9: 410 – 412), chronic heart failure (ICD-9: 398.9, 402.0, 402.1, 402.9, 428.0, 428.1, 428.9, or a dispensing of furosemide, furosemide and digoxin, angiotensin converting enzyme inhibitor, spironolactone, or β-blockers), coronary artery disease (ICD-9: 410 – 414, or dispensing of nitrate), peripheral artery disease (ICD-9: 440 – 447, or dispensing of pentoxifylline), and arrhythmia (ICD-9: 427, or dispensing of antiarrhytmics and anticoagulants). Other risk factors consisted of history of dyslipidemia (ICD-9:272, or dispensing of lipid lowering agents including statins) and diabetes (ICD-9:250, or dispensing of insulin or hypoglycemic agents) which are both primary cardiovascular risk factors [19].

Data analysis

Interrupted time series analysis with autoregressive modeling was used to characterize changes in AP treatment initiation over time. We divided the study period into four sub-periods: i) period before the first warning (January 2001 to September 2002); ii) period between the first and second warning (October 2002 to February 2004), iii) period between the second and third warnings (March 2004 to May 2005), iv) period after the third warning (June 2005 to December 2009). Three dummy variables were created and were equal to 0 before the first, second and third warning respectively, and equal to 1 after the warning. Three other variables were created: equal to 0 before the first, second and third warning respectively and equal to the number of months after the warning thereafter. This led to a linear regression model with intercept and slope terms for the period before the first warning, as well as for each of the three warnings, which allowed us to estimate the effect of each warning separately. Autocorrelation between the data points was tested using the Durbin-Watson statistics. The effect of each warning was measured for a period of 12 months after the issuance of the warning.

Bivariate analyses were conducted using $\chi 2$ tests to compare the proportion of AP users with a cerebrovascular history before and after the 2005 warning. The association between the warning and the presence of cerebrovascular history among patients who initiated an AP treatment was assessed through multivariate logistic regression analysis controlling for all of the above-listed covariates. Mean prescribed daily dose and total treatment duration during the two periods were compared through Student's t-test, and multiple linear regression modeling was used to adjust for covariates.

All analyses were conducted with SAS version 9.2 (SAS Institute Inc. NC, USA). Statistical level of significance was set at 0.05.

Results

From 1st January 2000 to 31st December 2009, 37,138 individuals were included in the source population of community-dwelling elderly with dementia. Of them, 10,969 (29.5%) initiated an AP treatment during the study period and were included in the cohort of new AP users. The baseline characteristics and medical history of these incident users are shown in Table 1 for the entire study period, as well as for the periods before and after the 2005 warning. The majority (50.1%) of AP users was aged 80 years or older, and women accounted for 66.0%.

Monthly trends in the rate of AP treatment initiation are presented in Figure 1. Dispensing rates decreased over time for risperidone as well as for the whole class of atypical APs, while that of quetiapine increased over the study period. No time trend in olanzapine use was observed. Wide fluctuations between the data points can be observed in Figure 1 primarily because the number of new users of individual AP products at each month of the study period is low (<100). For this reason, interrupted time series analysis was conducted only for the class of atypical APs. Comparisons in the slopes for the period before and after each warning revealed a significant decrease in the rate of treatment initiation following the first warning on risperidone in 2002 ($p=0.046$) while no significant change was observed after the warning on olanzapine in 2004 ($p=0.20$) and the warning on atypical APs in 2005 ($p=0.37$).

As shown in Table 1, patients treated with APs after the 2005 warning were older ($p<0.001$) than those preceding the warning; no difference in sex distribution was observed between the two time periods ($p=0.93$). The proportion of patients with a history of cerebrovascular event was similar between the two time periods: 6.9% before the 2005 warning and 7.4% after the 2005 regulatory warning ($p=0.28$). No difference was observed between the two time periods for history of myocardial infarction, coronary artery disease, and peripheral artery disease. Compared to the period prior to 2005, a greater proportion of AP users after the warning had a history of chronic heart failure (4.8% compared to 5.7%; $p=0.05$), arrhythmia (8.3% compared to 12.0%, $p<0.001$) dyslipidemia (24.6% compared to 39.8%, $p<0.001$), and diabetes (13.2% compared to 16.3%, $p<0.001$) after the warning. No difference was observed over time for depression while dispensing of anxiolytics was less frequent after the warning (47.8% compared to 43.9%, $p<0.001$). Results from the multivariate logistic regression analysis presented in Table 2 show that the 2005 warning did not have an effect on the proportion of patients with a history of cerebrovascular event after controlling for covariates (OR=1.05; 95% CI: 0.90 – 1.22).

As shown in Table 3, the prescribed daily dosage of risperidone was slightly lower after the 2005 warning than prior to the warning (mean of 0.44 mg compared to 0.49 mg, $p<0.001$), while that of olanzapine was higher (3.78 mg and 3.44 mg, respectively for each time period, $p=0.009$) and remained stable for quetiapine (32.82 mg compared to 31.55 mg, $p=0.40$). Results from the multiple linear regression analysis revealed a statistically significant association between the 2005 warning and a decrease in the mean prescribed daily dose for risperidone ($p<0.001$) while an increase was observed for olanzapine ($p=0.009$). Association between the warning and daily dose of quetiapine did not reach statistical significance ($p=0.06$). There was no period difference in mean number of days with active prescriptions (mean of 224.2 days after the 2005 warning compared to 220.4 days before the 2005 warning, $p=0.19$) and no association was found with the 2005 warning through multiple linear regression analysis ($p=0.20$).

Variables	N (%) (n=10,969)	Before 2005 warning N (%) (n=4,154)	After 2005 warning N (%) (n=6,815)	p-value
Baseline characteristics				
Age group				
66-69	770 (7.0)	333 (8.0)	437 (6.4)	<0.001
70-74	1,673 (15.3)	681 (16.4)	992 (14.6)	
75-79	3,029 (27.6)	1,116 (26.8)	1,913 (28.1)	
80-84	2,991 (27.3)	1,103 (26.6)	1,888 (27.7)	
85+	2,506 (22.9)	921 (22.2)	1,585 (23.3)	
Sex				
Male	3,729 (34.0)	1,410 (33.9)	2,319 (34.0)	0.93
Female	7,240 (66.0)	2,744 (66.1)	4,496 (66.0)	
Medical History				
Cerebrovascular event	790 (7.2)	285 (6.9)	505 (7.4)	0.28
Myocardial infarction	362 (3.3)	148 (3.6)	214 (3.1)	0.23
Chronic heart failure	585 (5.6)	199 (4.8)	386 (5.7)	0.05
Coronary artery disease	2,544 (23.2)	969 (23.3)	1,575 (23.1)	0.79
Peripheral artery disease	405 (3.7)	160 (3.9)	245 (3.6)	0.49
Arrhythmia	1,164 (10.6)	344 (8.3)	820 (12.0)	<.001
Dyslipidemia	3,732 (34.0)	1,022 (24.6)	2,710 (39.8)	<.001
Diabetes	1,658 (15.1)	547 (13.2)	1,111 (16.3)	<.001
Depression	858 (7.8)	340 (8.2)	518 (7.6)	0.27
Anxiolytic dispensing	4,974 (45.4)	1,984 (47.8)	2,990 (43.9)	<.001

Table 1: Characteristics of elderly patients with dementia who are new users of antipsychotics.

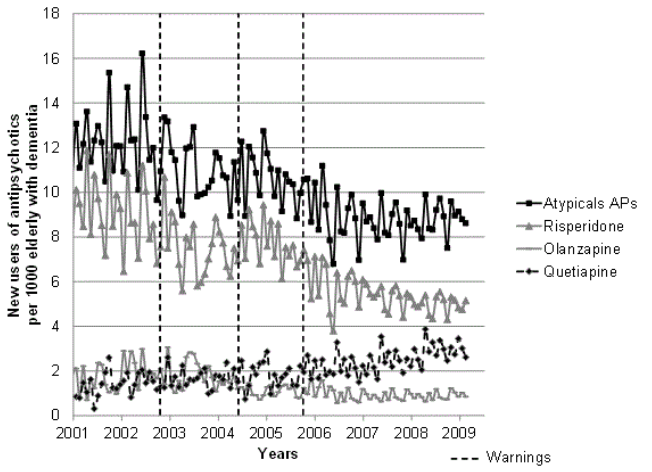

Figure 1: Dispensing rate of new antipsychotic treatments among community-dwelling elderly patients with dementia (2001-2009).

Variables	Crude OR* (95%CI)	Adjusted OR (95%CI)
Exposure to 2005 regulatory warning	1.09 (0.94 – 1.26)	1.05 (0.90 – 1.22)
Age group		
66-69	Reference	Reference
70-74	1.11 (0.77 – 1.61)	1.05 (0.72 – 1.53)
75-79	1.24 (0.88 – 1.75)	1.14 (0.80 – 1.61)
80-84	1.54 (1.10 – 2.16)	1.34 (0.95 – 1.88)
85+	1.50 (1.07 – 2.12)	1.30 (0.92 – 1.84)
Sex		
Females	Reference	Reference
Males	1.54 (1.33 – 1.78)	1.50 (1.29 – 1.74)
Medical History		
Myocardial infarction	2.52 (1.88 – 3.38)	1.41 (1.02 – 1.93)
Chronic heart failure	1.90 (1.64 – 2.22)	1.47 (1.25 – 1.73)
Coronary artery disease	2.06 (1.77 – 2.40)	1.43 (1.20 – 1.70)
Peripheral artery disease	2.86 (2.18 – 3.74)	2.17 (1.64 – 2.86)
Arrhythmia	2.18 (1.81 – 2.63)	1.61 (1.32 – 1.97)
Dyslipidemia†	1.39 (1.20 – 1.61)	
Diabetes†	1.21 (1.00 – 1.46)	
Depression†	1.14 (0.88 – 1.47)	
Anxiolytic dispensing	1.36 (1.17 – 1.57)	1.30 (1.12 – 1.51)

*OR=odds ratio; 95%CI=95% confidence interval

†p-value >0.20 in bivariate analysis, variable not retained for multivariate analysis

Table 2: Effect of the 2005 regulatory warning on the proportion of new users of antipsychotics, with a history of cerebrovascular event.

Variables	Total (n=10,969)	Before 2005 warning (n=4,154)	After 2005 warning (n=6,815)†	p-value
Mean prescribed daily dose in mg (SEM*)				
Risperidone (n=7,076)	0.46 (0.004)	0.49 (0.007)	0.44 (0.005)	<0.001
Olanzapine (n=1,288)	3.63 (0.073)	3.44 (0.097)	3.78 (0.107)	0.009
Quetiapine (n=2,362)	32.51 (0.545)	31.55 (0.947)	32.82 (0.654)	0.40
Mean number of days of active prescription (SEM*)	222.4 (1.4)	220.3 (2.1)	224.2 (2.0)	0.19

*SEM: standard error of the mean

†except for the calculation of the mean number of days of active prescription, n=5,047 after the 2005 warning (exclusion of year 2009)

Table 3: Patterns of use of antipsychotics for the period before and after the 2005 regulatory warning.

Discussion

In this community-dwelling population of elderly with dementia, there was a decrease over time in the rate of AP treatment initiation with atypical APs subsequent to issuance of the Health Canada safety warnings. However, this decrease was only statistically significant after the 2002 warning. Our findings revealed that APs continue to remain widely prescribed to these patients. There was a reduction in the proportion of new treatments initiated with risperidone and an increase in those initiated with quetiapine. These results suggest the presence of a switch in product preference by physicians at treatment initiation, which resulted in an increase in off-label use. It is nevertheless interesting to note that quetiapine is the only atypical AP which was not addressed in a specific safety warning. Furthermore, quetiapine is also prescribed for the management of sleep disturbances, which may explain an increase in its use [20]. This hypothesis could not be investigated in the current study owing to absence of data on indication in the RAMQ drug claims database.

Results showed that age and comorbidity of patients who initiated treatment after the 2005 warning increased compared to those initiated prior to the warning. In fact, patients appeared to have more cardiovascular history such as chronic heart failure, arrhythmia, dyslipidemia, and diabetes. However, prevalence of dyslipidemia should be considered with caution. The definition used allowed us to address the under-representation of certain diagnostic codes in the database and it constitutes a proxy that can overestimate this comorbidity due to the inclusion of lipid lowering agents that are widely used in the elderly. The observed increase in comorbidity may be attributable to residual confounding by age or other external factors. Multivariate analysis took into consideration age groups (in 5-year intervals) but not exact age. One may therefore conclude that the regulatory warning did not reverse the observed trend of increasing cerebrovascular history and cardiovascular comorbidity, likely due to external factors that were unmeasured. Adjusting for unmeasured external factors would have required the use of a parallel reference population unexposed to the warnings during the study period, which was not possible due to the fact that regulatory warnings were implemented nationally.

The continued usage of APs despite the safety warnings may be due to absence of treatment alternatives for BPSD, especially for patients with cerebrovascular risk factors and vascular dementia. Although non-pharmacological therapy is the first-line treatment suggested in the literature to manage BPSD, there is no evidence of effective alternative pharmacotherapy. However, following the warnings, usage could have been modified towards lower dosage or treatment duration as an attempt to mitigate risks. Our results indicate that the 2005 warning was associated with a small reduction in the mean prescribed daily dose of risperidone over the study period but the clinical relevance of this change is likely negligible. Antipsychotics are considered an off-label treatment in the management of BPSD, except for risperidone in Canada. Consequently, there is no recommendation regarding the initial dosage and dose adjustment for olanzapine and quetiapine [21,22]. Conversely, the Canadian product monograph for risperidone does mention an initial recommended dose of 0.25 mg twice daily, which corresponds to the mean daily dosage that was observed in our study [23]. Despite the fact that olanzapine and quetiapine are considered off-label in elderly with dementia, studies in the literature report that the initial dose of olanzapine should be 5 mg daily and for frail patients, the initial dose should start at 2.5 mg daily and increase progressively if necessary [24]. For quetiapine, an initial dose of 25 mg daily with a gradual increase to the targeted dose of 100 to 150 mg daily is recommended [25]. In our study, we observed a mean daily dose of 3.6 mg daily for olanzapine and 32.5 mg daily for quetiapine, which is below the optimal dosage. Consequently, further lowering of the dose for BPSD may not be an option for physicians to mitigate the risk as it may compromise treatment effectiveness. Decrease in treatment duration was not influenced either by the warnings.

Other studies have addressed the effect of regulatory warnings on AP use using prescription rate as an evaluation criterion. Such studies included all AP dispensings in a specific time interval without consideration of previous use. Our study was restricted to incident users only, which constitutes a strength of our study; prescription profiles being considerably different for new users compared to long-term users. The study of incident use allowed us to investigate the effect of the warnings on the benefit-risk assessment at the physician level at the time of AP treatment initiation.

Our study also had some limitations. Results are only generalizable to community-dwelling patients with dementia. Inpatients and nursing home patients, who account for a large portion of the elderly population with dementia, were not included. It is probable that elderly patients with dementia who are institutionalized have more severe dementia and increased rates of AP prescriptions. Even if ChIs represent a good proxy to identify subjects with dementia, not all patients with dementia are treated with ChIs. This could limit the generalizability of our findings if patients with dementia without ChI use have distinct characteristics compared to those treated. In fact, in Quebec, ChI is reimbursed for the treatment of moderate to severe dementia and treatment may be maintained only in patients who show evidence of effectiveness. Based on these considerations, it is likely that our study yielded conservative findings since AP use among patients who do not qualify for ChI reimbursement is probably greater than

those who respond to ChI treatment. Hence, the severity of BPSD in such patients is expected to be greater than in milder forms of dementia. Another limitation is that no information on the type of dementia was available. There is some evidence in the literature showing that cardiovascular risks factors are associated with the development of vascular dementia [26]. Stratification of the results by type of dementia, Alzheimer's disease and vascular dementia, would have allowed us to examine differences in patterns of AP usage in relation to cardiovascular and cerebrovascular risk factors.

In conclusion, despite the three safety warnings on AP use in the elderly population with dementia, APs, in particular those that are atypical, continue to be used in this frail population. Warnings did not appear to be associated with prescription channelling of APs towards patients with lower cerebrovascular risk profiles nor with decreases in daily dosage or treatment duration.

Use of APs in this population remains a major public health issue owing to the high rate of use (29.5% of patients in our study) and important safety concerns. Any effect of regulatory interventions, even if small, would have therefore been consequential with respect to the number of cerebrovascular events avoided. Further communication or interventions targeted to physicians may be warranted to highlight the fact that only risperidone is approved for use in Canada and assessment of cerebrovascular risk factors should be conducted prior to initiating treatment.

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