

# Effective Health Care Research Reports

Number 2

## **Comparative Safety of Conventional and Atypical Antipsychotic Medications: Risk of Death in British Columbia Seniors**

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Research from the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network



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## **Contents**

Introduction .....	1
Methods.....	1
Results .....	4
Discussion .....	5
Acknowledgment.....	6
References .....	7
Figures.....	9
Tables .....	12

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## **Abstract**

**Context:** A Health Canada and Food and Drug Administration (FDA) Advisory has warned that atypical antipsychotic medications (APMs) increase mortality in older patients.

**Objective:** To assess the short-term mortality in a population-based cohort of all British Columbia seniors who initiated conventional vs. atypical APMs.

**Design.** Cohort study.

**Setting.** Population-based linked health care utilization data of all British Columbia residents 65 years and older from 1996 through 2004.

**Patients.** Senior BC residents who were initiated on antipsychotic medications and had no recorded cancer diagnosis.

**Intervention.** Conventional APMs vs. atypical APMs.

**Main Outcome Measures:** All cause mortality.

**Results:** 12,882 seniors initiated conventional APM therapy and 24,359 atypical APMs. Within the first 180 days of use, 1,822 patients (14.1%) who initiated treatment with conventional APMs died, compared with 2,337 patients (9.6%) who initiated treatment with atypical APMs (unadjusted mortality ratio = 1.47; 95% confidence interval: 1.39 – 1.56). Multivariable adjustment resulted in a 180-day mortality ratio (MR) of 1.32 (1.23-1.42). The increase in mortality was highest in users of haloperidol (MR = 2.14; 95% CI: 1.86 to 2.45) but lower for loxapine (MR = 1.29; 95% CI: 1.19 to 1.40). The greatest mortality increase occurred with use of higher (> median) conventional APM dosages (MR=1.67; 1.50-1.86) and during the first 40 days after initiation (MR=1.60; 1.42-1.80). Results were confirmed in propensity score analyses and instrumental variables estimation adjusting for unmeasured confounders.

**Conclusions.** Elderly patients using conventional APMs are at no lower risk of mortality than those using atypical APMs. The observed 32% increased mortality risk of conventional APMs is unlikely to be explained by confounding.

## **Introduction**

Antipsychotic medications (APMs) are disproportionately used in the elderly and are prescribed to over a quarter of Medicare beneficiaries in nursing homes.<sup>1,2,3</sup> Reasons for this APM use include dementia, delirium, psychosis, agitation, and affective disorders, with much use outside approved indications.<sup>4</sup> In addition to rising use, there have been rapid shifts from first-generation conventional agents (e.g., chlorpromazine, haloperidol, and loxapine) to more actively marketed second-generation atypical agents (e.g., clozapine, olanzapine, quetiapine, and risperidone).<sup>5</sup>

In a Public Health Advisory on June 15, 2005, Health Canada warned that atypical APMs increase the risk of death vs. placebo by 60% in a pooled analysis of 17 short-term randomized controlled trials among elderly demented patients.<sup>6</sup> Health Canada requested that “all manufacturers of these drugs include a warning and description of this risk in the safety information sheet for each drug.” The Advisory did not extend to conventional APMs, although it was noted that this is an important issue to study in the future.<sup>7,8</sup>

In the absence of data on the risks of death posed by conventional APMs, there is mounting concern that clinicians may switch elderly patients to these older agents,<sup>9</sup> particularly since their replacement by the newer drugs occurred so rapidly and recently.<sup>5</sup> Based mainly on extrapolations from younger populations, some have suggested that conventional APMs could in theory pose risks equal to or greater than those of the newer drugs in older populations.<sup>10,11,12,13</sup> A cohort study of U.S. Medicare patients eligible for state-funded low-income pharmacy assistance programs found a 37% increased 180-day mortality of conventional APMs versus atypicals.<sup>14</sup> However, patients enrolled in state pharmacy assistance programs are not representative to a general elderly population since they on average have lower income and higher morbidity and mortality.

We sought to assess the short-term mortality in a population-based cohort of all British Columbia seniors who initiated conventional vs. atypical APMs. We also examined whether the risk of death differed by dosage or duration of drug use as well as dementia status and nursing home residency.

## **Methods**

### **Study Design and Patients**

We conducted a cohort study of all British Columbia residents 65 years or older who filled a first recorded (index) prescription for an oral APM between January 1, 1996 and December 31, 2004. To ensure a uniform 1-year eligibility period prior to filling the index APM prescription, all study subjects were required to have utilized  $\geq 1$  medical service and  $\geq 1$  prescription, in the two 6-month intervals before the index date. APM initiators were defined as having used no APM in the year prior to the index use. We restricted the analysis to just APM initiators to guard against selection bias among prevalent users from early symptom emergence, drug intolerance, or treatment failure.<sup>15</sup> Patients with a diagnosis of cancer at the index date were excluded to

avoid residual confounding introduced by selective prescribing of conventional APMs (chlorpromazine, haloperidol) as antiemetics in the most serious cancer patients who are more likely to die within 180 days.

Patients were identified in linked administrative data from the Ministry of Health containing information on all physician services (Medical Services Plan), hospitalizations with up to 25 diagnostic codes, and all prescription drug dispensings that were recorded independent of payor by the province-wide PharmaNet database. We further linked vital status information from the BC vital statistics agency. Underreporting and misclassification appear minimal because of the electronic data entry of all drug dispensings and hospital diagnoses showed good specificity and completeness.<sup>16</sup> Linkage was performed using a personal health number unique to every BC resident and is considered complete among patients using the provincial health care system.

All traceable personal identifiers were removed to protect patient confidentiality. The Institutional Review Board of the Brigham and Women's Hospital approved this study and data use agreements with the BC Ministry of Health were in place.

## **Antipsychotic Medication Exposure**

Atypical APM agents<sup>17</sup> included in the analyses were clozapine (0.3% of all atypical agents), olanzapine (10.1%), quetiapine (14.9%), risperidone (74.7%). Other APMs were considered conventional APMs,<sup>17</sup> including chlorpromazine (7.4% of all conventional agents), fluphenazine (0.2%), mesoridazine (0.1%), perphenazine (1.5%), promazine (2.4%), thioridazine (3.1%), trifluoperazine (5.0%), thiothixene (<0.1%), haloperidol (11.0%), loxapine (69.4%), and pimozide (2.4%).

Daily dosages were converted to chlorpromazine-equivalent mg using the midpoints of recommended ranges in geriatric prescribing guidelines.<sup>18</sup> We used the median daily dosage in the population as a cut-off to assess the effect of higher and lower dosage.

## **Outcomes**

The study outcome was death of any cause as recorded by BCstats, the provincial vital statistics bureau.

## **Potential Confounders**

A set of potential confounders was measured based on health care utilization data within 6 months before the initiation of index drug use (index date). These included socio-demographic characteristics (age, sex, race, nursing home residence), generic markers of comorbidity that have shown good validity in predicting mortality<sup>19</sup> (hospitalization for any reason, number of physician visits, number of distinct prescription drugs excluding APMs listed above, Charlson comorbidity score<sup>20</sup>), psychiatric morbidity (dementia, delirium, mood disorders, psychotic disorders, and other psychiatric disorders), prior use of anticholinergic drugs, and current co-medication with anticholinergic drugs. We also identified the presence of conditions that are independent predictors of death and were related to APM use in earlier research, including arrhythmias defined by the presence of ventricular and other cardiac arrhythmia diagnoses plus use of a Group I-IV antiarrhythmia medication, diabetes defined by the presence of diagnoses

plus use of anti-diabetic medications, cerebrovascular disease (both cerebral hemorrhagic and ischemic events), congestive heart failure (CHF), acute myocardial infarction (MI) other evidence of ischemic heart disease (angina defined as having a diagnosis and nitroglycerin use, percutaneous coronary interventions, or coronary artery bypass graft surgery), other cardiovascular conditions (valvular disease, aneurysms, peripheral vascular disease).

Several patient characteristics were not available within the study database, most importantly limitations in activities of daily living (ADL), cognitive impairment, and physical impairment. In theory, these variables could be differentially related to the use of conventional APMs and atypical APM, and at the same time are predictors of mortality.<sup>21</sup> We therefore analyzed data from the Medicare Current Beneficiary Survey,<sup>22</sup> a nationwide in-home survey conducted among 17,776 community dwelling beneficiaries  $\geq 65$  years in 2001 and 2002 combined, with a 97% response rate. We compared patients' ADL status, cognitive and physical impairment, between patients reporting use of atypical APMs (n=192) and conventional APMs (n=101). In these analyses, ADL limitations as well as cognitive impairment were more likely in atypical APM users (OR=1.31; 95% CI 1.02-1.68; and OR=1.14; 0.92-1.42), while any physical impairment was well balanced between users of either APM (OR=0.99; 0.89-1.09). The imbalance in ADL status and cognitive impairment among these Medicare beneficiaries that are similar to the study population in age and race/ethnicity suggest that any failure to adjust for such covariates will lead to an underestimation of an association between conventional APM use and death.<sup>23,24</sup> Results were similar in the 1999 MCBS survey.

## **Statistical Analysis**

**Multivariable Cox regression:** We computed distributions of sociodemographic, clinical, and utilization characteristics among conventional and atypical APM users and then calculated mortality rates during the first 180 days since initiation of either drug class. A 180-day follow-up period was chosen based upon the duration of trials in the FDA's reanalysis (which varied from 4-26 weeks, with a modal duration of 10 weeks).<sup>6</sup> Unadjusted and multivariable (controlling for calendar year and all covariates listed above) Cox proportional hazards models were constructed to estimated mortality ratios within 180 days after APM initiation without censoring analogous to an intention-to-treat analysis in randomized trials. Models of mortality rates within 0-40 days, 40-79 days, and 80-180 days of APM use were also constructed. Adjusted models were run separately in strata defined by dementia and nursing home status. We also investigated if a dose-response relationship existed in adjusted models by separating conventional APM users into those taking less than and including vs. greater than the median daily dosage.

**Propensity score analysis:** We developed propensity score adjusted Cox regression models<sup>25</sup> for more efficient estimation.<sup>26,27</sup> Propensity scores were derived from predicted probabilities estimated in logistic regression models of conventional vs. atypical APM use. The final non-parsimonious propensity score model contained all covariates listed above and discriminated well between the APM type used (c-statistic = 0.78). Cox regression models of mortality were stratified across tenths of the propensity score.

**Instrumental variable estimation:** We also used instrumental variable (IV) analysis to provide estimates that would remain unbiased even if important confounding variables were unmeasured.<sup>28,29,30</sup> An IV is an observable factor related to treatment choice but unrelated to patient characteristics and outcomes. As in other recent work,<sup>31</sup> we employed the prescribing physician's preference for conventional vs. atypical APMs (as indicated by their most recent new

APM prescription) as the instrument. Using two-stage linear regression for the IV estimation and additional adjustment for measured patient characteristics, we calculated the risk difference of 180-day mortality between conventional vs. atypical APM users. Linear regression to estimate risk difference is valid in large samples like ours.<sup>32</sup> Because patient-level observations were clustered in physicians, standard errors of the regression parameters were computed robustly to account for the within-physician correlation of outcomes.<sup>33</sup>

**Sensitivity analysis:** Important predictors of death like generic frailty may not be fully recorded in health care utilization databases.<sup>34</sup> If frailty among elderly patients would be associated with an increased risk of death and using conventional APM users were more likely to be frail than users of atypical APMs this could result in an overestimation of the relative risk of death among conventional APM users. We used sensitivity analyses to quantify the extent of such residual confounding as a function of these associations.<sup>35</sup>

## Results

Utilization of antipsychotic medications (APMs) has increased during the study period from 1.5 per 100 seniors to 2.5 per 100 British Columbia seniors (**Figure 1**). The use of atypical APMs increased particularly rapid and exceeded the use of conventional APMs in January 2000. Patients who initiated conventional APM agents (n = 12,882) were slightly younger and more likely to be male than those who began use of atypical APMs (n = 24,359, **Table 1**). The initiators of the conventional agents were slightly more likely than new users of the atypical agents to have cerebrovascular disease, diabetes, AMI, other cardiovascular diseases, CHF, and non-MI ischemic heart disease but less likely to have dementia, delirium, psychoses, mood disorders, and other psychiatric disorders at baseline. Conventional APM users had lower rates of using antidepressants, but higher rates of using other psychotropic medications, total number of drugs, hospitalizations, and nursing home stays.

Within the first 180 days of use, 1,822 patients (14.1%) who initiated treatment with conventional APMs died, compared with 2,337 patients (9.6%) who initiated treatment with atypical APMs (**Table 2**) resulting in an unadjusted mortality ratio of 1.47 (95% confidence interval: 1.39 – 1.56) and an unadjusted mortality difference of 4.5 per 100 (95% CI: 3.8 – 5.3).

Adjusted mortality ratios (MR) comparing the risk of death for initiators of conventional vs. atypical APMs are shown in **Table 3**. Mortality was meaningfully increased in conventional than atypical APM users in multivariable adjusted models of 180-day mortality that controlled for a large number of potential confounders (MR = 1.32). Comparing the most frequently prescribed APMs individually with risperidone showed increased mortality rates for haloperidol (MR = 2.14; 95% CI: 1.86 to 2.45) and loxapine (MR = 1.29; 95% CI: 1.19 to 1.40) but no difference for olanzapine (MR = 0.94; 95% CI: 0.80 to 1.09). Yearly adjusted mortality ratio estimates varied little and in a non-systematic way from 1997 to 2004 (**Figure 2**). The greatest increase in adjusted mortality risk for conventional vs. atypical APMs occurred with use of higher (> median) conventional APM dosages (MR = 1.67) and during the first 40 days after initiation (MR = 1.60). In analyses restricted by dementia status or nursing home residency, patients who began use of conventional vs. atypical APM starters had consistently greater 180-day mortality. A multivariable analysis of the mortality difference estimated an increase of 3.5 per 100 (95% CI: 2.7 – 4.3) in conventional APM users.

Confirmatory analyses using propensity score adjustments yielded no substantive changes relative to traditional multivariable Cox regression analyses. For example, the mortality ratio for conventional vs. atypical APMs within 180 days after propensity score adjustment was 1.39 (95% CI: 1.30-1.49).

In instrumental variable analyses, conventional APMs continued to be associated with greater risks of 180-day mortality relative to atypical APMs. The IV adjusted risk difference of 4.2 per 100 (95% CI: 1.2-7.3) means that for every 100 patients treated with a conventional APM instead of an atypical APM, there were about 4 additional deaths. The IV adjusted results were not different from the conventional multivariable estimates ( $p = 0.62$ ). Our instrument had a strong correlation with the actual treatment choice (OR = 6.1; 5.8-6.4).

Sensitivity analyses revealed that very large relative risks of 5 or greater would be needed linking a hypothetical confounder to both conventional APM use as well as mortality in order to fully explain the observed increased mortality from conventional APMs if no such increase existed (**Figure 3**).

## Discussion

In this study of 37,241 BC residents 65 years and older initiating treatment with antipsychotic medications, patients prescribed conventional agents had a 35% greater, dose-dependent risk of short-term mortality than those prescribed atypical agents. To place this magnitude of risk in perspective, all measured health conditions except heart failure and HIV infection, conferred smaller adjusted mortality rate ratios in our analyses.

Our results are remarkably close to the increased 180-day mortality of conventional APMs observed in US Medicare patients eligible for state-funded low-income pharmacy assistance programs (RR = 1.37; 95% CI: 1.27-1.49).<sup>14</sup> This was confirmed shortly afterwards in a meta-analysis of randomized trials,<sup>36</sup> one conventional agent, haloperidol, increased the risk of short-term mortality vs. placebo by 107% —an estimate higher than for atypicals and remarkably close to the 60-70% increased risk of atypicals vs. placebo<sup>36</sup> plus the 35% risk increase of conventionals observed in our study.

Nonrandomized studies using health care utilization data are particularly scrutinized for their limited control of confounding and their potential for misclassifying diagnoses.<sup>37</sup> Confounding would occur if conventional APMs were more likely to be given to patients who were frailer and at greater risk of dying compared with atypical APMs. We therefore controlled for calendar time, sociodemographic, clinical, and health care utilization factors likely to be independent predictors of mortality using traditional multivariable, propensity score, as well as instrumental variable techniques.

Our ability to fully adjust for those factors was limited by their measurement in our database. Random misclassification of confounders leads to incomplete adjustment of confounding bias.<sup>38</sup> Model prediction of mortality based on measured covariates in users of atypical and conventional APMs (Harrell's  $c^{39} = 0.69$  and 0.68) indicated non-differential assessment of patient characteristics. This is evidence that our analyses did not differentially adjust important confounding variables with regard to exposure status.

We restricted our population to new initiators of APMs to control for indications and to make sure the chronology of use is aligned in both groups and that patient characteristics are measured

before APM use, uninfluenced by any treatment effects.<sup>15</sup> We further analyzed data as intention-to-treat because of the known potential for drug intolerance or treatment failure that may lead to informative censoring. Such intention-to-treat analyses will make sure that any bias will be towards the null.<sup>13</sup> During the study period i.e. before the FDA health advisory<sup>7</sup> was posted in 2005 recommendations were published to avoid conventional APMs in frail elderly authorities<sup>4,10,11,12,13,40</sup> and any residual confounding may have therefore led to underestimation of mortality from conventional agents.

Finally, we employed instrumental variable estimation, which by design controls for unmeasured patient characteristics and could confirmed our results. Like other statistical approaches, the validity of IV estimation relies on assumptions. First, the instrument must be related to the actual exposure, which we could demonstrate in our study. Second, an instrument must not be correlated with patient risk factors conditional on measured and adjusted covariates. We found that large imbalances of risk factors among the actual treatment groups (**Table 1**), were substantially reduced in the IV analysis (data not shown). While we have shown earlier how IV methods perform when using health care utilization databases to study the safety of prescription drug use,<sup>41</sup> this does not rule out that some residual confounding persisted.

Non-differential exposure misclassification (e.g., not consuming filled prescriptions or switching APM classes) and any rare misclassification of British Columbia mortality information would bias results towards the null; differential misclassification (e.g., worse adherence with conventional APMs, as has been found<sup>42</sup>) again may have led to an underestimation of mortality from conventional agents. An alternative interpretation untestable in our data is that health care providers managed the indication using harsher co-interventions (e.g., physical restraint, sedatives, etc.) when conventional therapy failed.

Potential mechanisms through which conventional APMs might increase short-term mortality are speculative. In the FDA analysis on which its Public Health Advisory was based, heart-related events (heart failure, sudden death) and infections (mostly pneumonia) accounted for most deaths.<sup>6</sup> Anticholinergic properties (affecting blood pressure and heart rate), Q-T prolongation (causing conduction delays), and extrapyramidal symptoms (causing swallowing problems) are at least and probably more common with conventional than atypical agents and should be investigated as potential underlying causes.<sup>4,10,11,12,13</sup>

Together with earlier findings, these results strongly suggest conventional APMs be included Health Canada and FDA's Public Health Advisory, which currently warns only of increased risk of death from atypical APMs in elderly with dementia.

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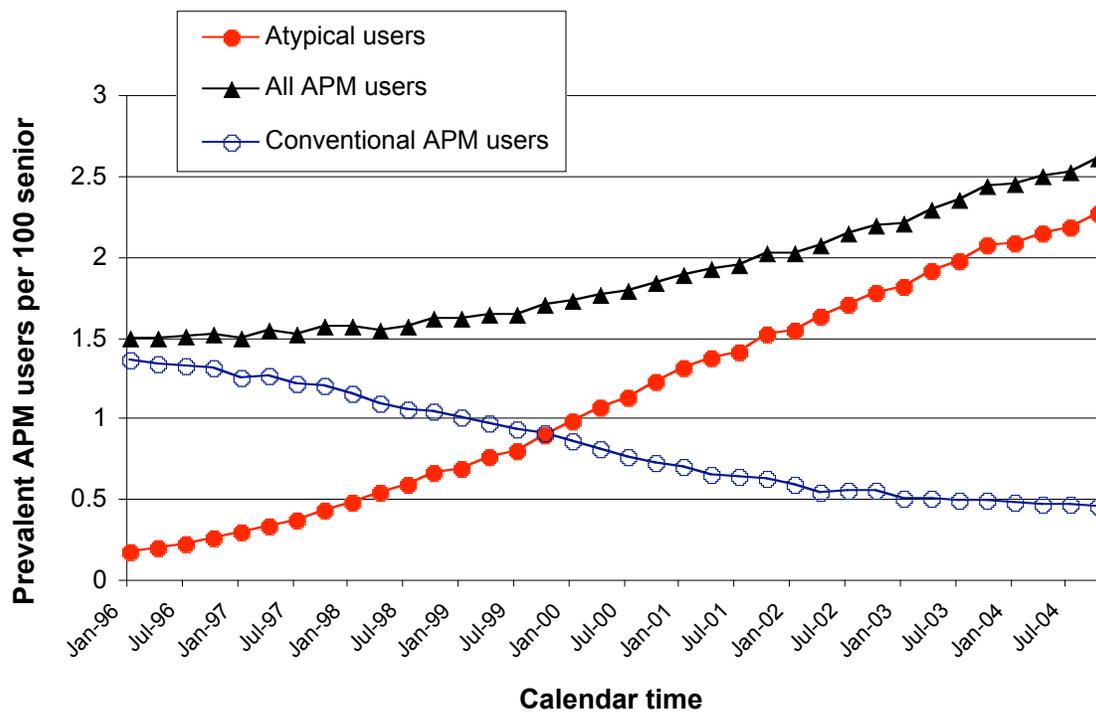
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## Figures

Figure 1. Utilization trends of Conventional and Atypical Antipsychotic Medications among British Columbia Seniors from January 1996 to December 2005.



**Figure 2. Yearly adjusted mortality ratios and 95% confidence intervals comparing conventional versus atypical antipsychotic medications from 1997 to 2004.**

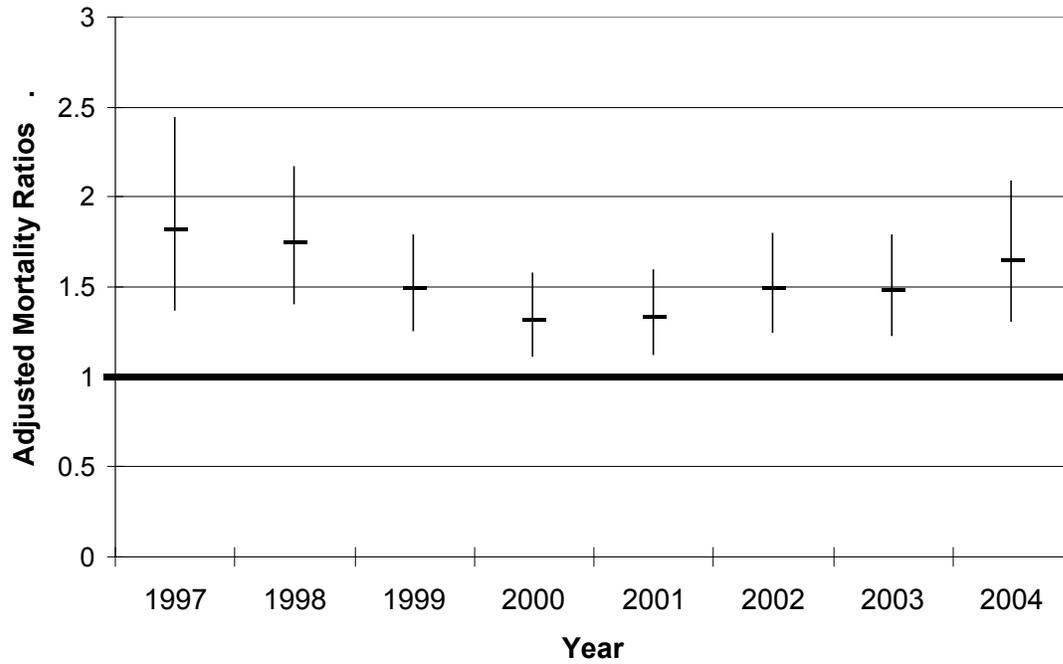
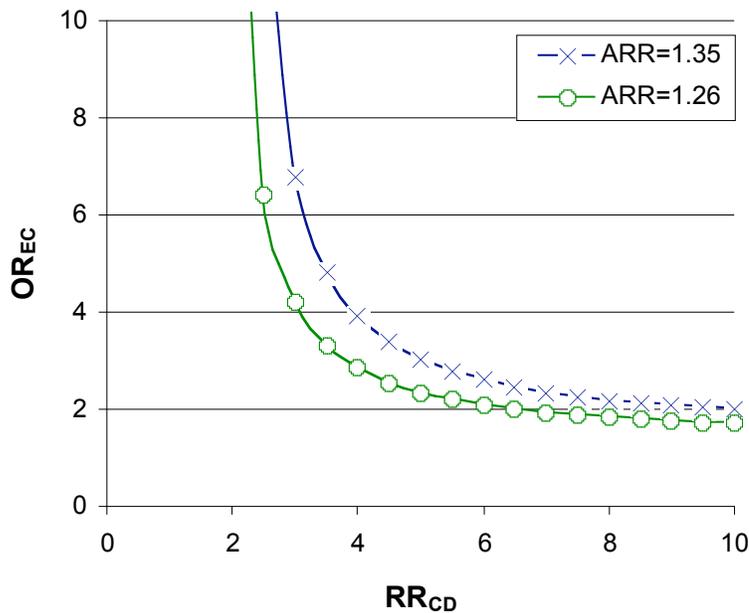


Figure 3. Sensitivity analysis of the observed association between conventional APM use and death.

Plotted is the strength of the associations between an unmeasured confounder and treatment choice (conventional vs. atypical APM,  $OR_{EC}$ ) and the association between an unmeasured confounder and death ( $RR_{CD}$ ) that are required to fully explain the observed association ( $ARR = 1.35$ ) or its lower 95% confidence limit ( $ARR = 1.26$ ). We further assumed a 30% prevalence of exposure equivalent to our study population and a 10% prevalence of the unmeasured confounder.\*



\* Any factor (a single factor or combination of multiple factors) that has a combination of  $RR_{CD}$  and  $OR_{EC}$  values resulting in points higher than and to the right of the plotted lines will be able to fully explain our observed results.

## Tables

**Table 1. Characteristics of 37,241 Initiators of Conventional and Atypical Antipsychotic Medications in BC Seniors**

Characteristic	Atypical (n=24,359)		Conventional (n=12,882)		Odds ratio	p-value
Age in years (mean, standard deviation)	80.3	8.4	79.9	8.8	-	<.0001
Male patients	8565	35.2%	5120	39.7%	1.2	<.0001
History of						
Cardiac Arrhythmia	22	0.1%	6	0.0%	0.5	0.14
Cerebrovascular disease	2430	10.0%	1391	10.8%	1.1	0.01
Congestive heart failure	1455	6.0%	1084	8.4%	1.5	<.0001
Diabetes	3362	13.8%	1939	15.1%	1.1	0.001
Myocardial infarction	551	2.3%	354	2.7%	1.2	0.05
Other ischemic heart disease	665	2.7%	493	3.8%	1.4	<.0001
Other cardiovascular disorders	4075	16.7%	2609	20.3%	1.3	<.0001
Cancer	0	0.0%	0	0.0%	-	-
HIV infection*	4	0.0%	0	0.0%	0.0	0.15
Dementia	3087	12.7%	1247	9.7%	0.7	<.0001
Delirium	2060	8.5%	967	7.5%	0.9	0.0014
Mood disorders	6198	25.4%	2013	15.6%	0.5	<.0001
Psychotic disorders	4103	16.8%	1446	11.2%	0.6	<.0001
Other psychiatric disorders	1110	4.6%	403	3.1%	0.7	<.0001
Use of other drugs						
Antidepressants	10154	41.7%	3645	28.3%	0.6	<.0001
Other psychotropic medications	920	3.8%	542	4.2%	1.1	0.04
Prior anticholinergic drug use	1709	7.0%	1140	8.9%	1.3	<.0001
Current anticholinergic drug use	2591	10.6%	1868	14.5%	1.4	<.0001
Tot. number of drugs used (mean, s.d.)	7.3	5.0	7.37	5.1	-	0.60
Hospitalization in previous 180 days	3204	13.2%	1923	14.9%	1.2	<.0001
Nursing home residence in previous 180 days	6471	26.6%	3980	30.9%	1.2	<.0001

\* Human immunodeficiency virus

**Table 2. Mortality within 180 days after Initiation of Therapy, including unadjusted Risk and Rate estimates**

	Persons	Person-years	Number of events	Risk (in 180 days, per 100 persons)	Rate (per 100 person years)
Conventional APMs	12,882	5,816.4	1,822	14.1	31.3
Atypical APMs	24,359	11,354.3	2,337	9.6	20.6
			Ratio:	1.47 (1.39-1.56)*	1.52 (1.43 – 1.62)
			Difference:	4.55 (3.84 – 5.26)	10.7 (9.07 – 12.4)

\* 95% confidence interval

**Table 3. Mortality Ratios within 180 days after Initiation of Therapy with Conventional vs. Atypical Antipsychotic Medications (APMs).**

Model	Mortality ratios (95% CI)
Unadjusted analysis of death within 180 days	1.47 (1.39-1.56)
Age-gender-calendar year adjusted analysis of death within 180 days	1.11 (1.04-1.19)
Multivariable adjusted analyses of death within 180 days □	
Use of any conventional APM	1.32 (1.23-1.42)
Use of high dose conventional APM	1.67 (1.50-1.86)
Use of low dose conventional APM	1.23 (1.14-1.33)
Multivariable adjusted analysis of death by duration of use □	
<40 Days after beginning therapy	1.60 (1.42-1.80)
40-79 Days after beginning therapy	1.31 (1.14-1.51)
80-180 Days after beginning therapy	1.18 (1.06-1.31)
Multivariable adjusted analysis of death within 180 days by patient subgroups □	
With dementia	1.26 (1.01-1.56)
Without dementia	1.30 (1.21-1.40)
In a nursing home	1.25 (1.12-1.40)
Not in a nursing home	1.35 (1.23-1.49)

□ Hazard ratios were adjusted for calendar year, age, sex, race, the presence or absence of cardiac arrhythmias, cerebrovascular disease, congestive heart failure, diabetes, myocardial infarction, other ischemic heart disease, other cardiovascular disorders, cancer, HIV infection, dementia, delirium, mood disorders, psychotic disorders, other psychiatric disorders, and the use or nonuse of other psychiatric medications, prior use of anticholinergic drugs, current use of anticholinergic drugs, total number of medications used, hospitalization and nursing home stays.