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Potential Causes of Higher Mortality Among Elderly Users of Conventional Vs. Atypical Antipsychotics

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Abstract

Objectives. Evidence is growing that conventional antipsychotic medication (APM) use may be associated with greater risks of death than aytpicals. To investigate the potential mechanisms through the conventionals might act, we sought to compare the specific causes of death in elderly patients newly started on conventional vs. atypical APMs.

Design. Cohort study

Setting. Community setting

Participants. All British Columbia residents ≥65 who initiated a conventional or atypical APM (1996 – 2004).

Measurements. Cox proportional hazards models were used to compare risks of developing the specific cause of death within 180 days since APM initiation. We adjusted for potential confounders using traditional multivariable, propensity score, and instrumental variable adjustments.

Results. The study cohort included 12,882 initiators of conventional APMs and 24,359 atypical APMs. Of 3,821 total deaths within the first 180 day of use, cardiovascular (CV) deaths accounted for 49% of deaths. Conventional vs. atypical APM initiators had a significantly higher adjusted hazard of all CV (hazard ratio [HR] 1.23; 95% CI 1.10-1.36), and out-of-hospital CV death (HR 1.36; 95% CI 1.19-1.56). Initiators of conventional APMs also had a higher risk for death due to respiratory diseases, nervous system diseases and other causes.

Conclusions. These data suggest that increased risk of CV deaths might explain about half of the excess mortality in conventional APM initiators. The risk of death due to respiratory causes was also significantly higher in conventional APM use.

Keywords. Antipsychotic medications, conventional, atypical, elderly, short-term mortality, cause of death

Introduction

The US Food and Drug Administration (FDA) issued a Public Health Advisory in 2005 that atypical antipsychotic medications (APMs) significantly increased the risk of death compared with placebo among elderly with dementia.[1] "Black box" warnings were added to labels of all atypical APMs describing these risks and advising that these agents are not approved for use in elderly patients with dementia. The Advisory did not cover conventional APMs due to insufficient data on the mortality associated with them.[1,2]

However, in the absence of warnings for conventional APMs, concern has mounted that clinicians may simply switch elderly patients to these older agents,[3] particularly because their use had until recently been widespread.[4] Extrapolating mainly from studies in younger populations, some have suggested that conventional APMs could pose risks greater than those of the newer drugs in older populations.[5-8] For elderly populations, Nasrallah et al. first reported higher mortality in elderly patients taking haloperidol compared with two atypical drugs (risperidone or olanzapine).[9] We first reported a 37% greater dose-dependent risk of short-term all-cause mortality in elderly patients prescribed conventional agents than those prescribed atypicals in the US population.[10] More recently, we found very similar risk of all-cause mortality in conventional APM initiators in the cohort of Canadian elderly population.[11]

An important next step is to investigate potential mechanisms through which they may act. In the FDA's analysis, heart-related events (heart failure and sudden death) and infections (mostly pneumonia) accounted for many deaths.[1] Furthermore, some conventional agents were more likely than atypical agents to affect blood pressure and heart rate, Q-T prolongation causing conduction delays, as well as sedation and extrapyramidal symptoms causing potential swallowing problems.[5-8,12] For these reasons, cardiac, cerebrovascular, and infection may all contribute to an increased risk of death from conventional vs. atypical agents. Therefore, the aim of the current study is to compare the specific causes of short-term mortality in elderly patients newly started on conventional vs. atypical APMs.

Methods

Overall Design and Rationale

A cohort study was conducted to compare risks of developing cause-specific death among conventional APM vs. atypical APM initiators. The analyses were restricted to new users of APMs to guard against potential selection bias caused by including prevalent users because prevalent users are those who stayed on the drug and more likely to exclude those who discontinued the drug due to drug intolerance, or treatment failure.[13] Furthermore, using prevalent users will restrict the ability of a study to capture adverse events that occur early in the course of the drug use.[13] To adjust for potential differences in characteristics of patients using different APMs, traditional multivariable and propensity score–adjusted models[14] as well as an instrumental variable analysis were used.[15-19]

Data Sources

The data source was a large health care utilization database that contained information on discharge diagnosis, outpatient diagnoses and procedure codes from 1996 through 2004 for all residents in British Columbia, where the provincial insurance system provides comprehensive coverage for health care for all including the elderly and disabled. The data source provided basic demographic information, as well as coded diagnostic, procedural, and pharmacy dispensing information with high accuracy.[20] The discharge abstract provided up to 25 fields for diagnoses and 10 fields for procedures that were relevant during the hospitalization. We further linked vital status information from the BC vital statistics agency.

Study Population

All British Columbia residents 65 years or older who filled a first recorded (index) prescription for an oral APM between 1/1/1996 and 12/31/2004 were identified as a study population. To ensure a uniform 1-year eligibility period prior to filling the index APM prescription, all study subjects were required to have utilized >1 medical service and >1 prescription in the two 6-month periods prior to the index date. APM initiators were defined as having used no APM in the 12 months prior to the index use and prevalent users were excluded from the cohort. Because chlorpromazine and haloperidol can be used as antiemetics for cancer chemotherapy patients in Canada, patients who had one or more diagnosis of any cancer during the 12 months prior to their exposure to the first APM agents were excluded.

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

Antipsychotic Medications

Atypical APM agents included aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone. Other APMs were considered conventional APMs, including acetophenazine, chlorpromazine, fluphenazine, mesoridazine, perphenazine, promazine, thioridazine, trifluoperazine, triflupromazine, chlorprothixene, haloperidol, loxapine, molindone, pimozide, and thiothixene. Exposure to atypical vs. conventional is based on the first prescription of either class of APM, regardless of later changes or discontinuations within the 180-day study risk-exposure time. Daily dosages were converted to chlorpromazine-equivalent milligrams using the midpoints of recommended ranges in geriatric prescribing guidelines.[21] The median daily dosage in the population was used as a cut-off to assess the effect of higher and lower dosage.

Outcomes

Causes of Death

Information on vital status and causes of death from the BC vital statistics agency are available, and the causes are coded by ICD-9[22] or ICD-10[23] diagnosis codes. Relatively broad categories of causes of death identified by the death certificate agree with physician-adjudicated causes of death.[24] All deaths in the cohort within 180 days after the index day were identified. Cancer deaths within 180 days were excluded because such cancers were likely to be preexisting and may have been associated with conventional APMs used as antiemetics for cancer chemotherapy. Based on suggested pharmacologic effects of conventional APMs[5-8,12] and the FDA analysis,[1] we were specifically interested in the following causes of deaths; overall cardiovascular, out-of-hospital (OOH) cardiovascular, overall infection, and pneumonia.

Potential Confounders

The patient characteristics were identified during the 6 months prior to each subject's exposure to the first APM agents. Sociodemographic data (age and gender) as well as clinical conditions that might affect short-term mortality were measured. Clinical conditions were defined as having both diagnosis for a condition and treatment indicating the presence of the condition. These comorbidities include arrhythmias, diabetes, cerebrovascular disease (e.g., both cerebral hemorrhagic and ischemic events), heart failure (HF), myocardial infarction, other evidence of ischemic heart disease (e.g., PTCA, CABG, or nitroglycerin use), other cardiovascular conditions (e.g., valvular disease, aneurysms, and peripheral vascular disease), cancers, HIV, dementia, delirium, mood disorders, psychotic disorders, and other psychiatric disorders. Health care utilization including hospitalizations, nursing home stays, use of other psychiatric medications, and total number of medications used (excluding APMs and drugs used to define covariates) were also measured.[25]

Statistical Analysis

Distributions of sociodemographic, clinical, and utilization characteristics among conventional and atypical APM initiators were calculated and then mortality rates during the first 180 days since initiation of either drug class were plotted. A 180-day follow-up period was chosen based upon the duration of trials in the FDA's reanalysis (which ranged from 4-26 weeks, with a modal duration of 10 weeks).[8]

Unadjusted and multivariable (adjusting for calendar year and all covariates listed above) Cox proportional hazards models of cause-specific mortality in 180 days were constructed, as were models of mortality within 1-5, 6-20, 21-39, 40-79, and 80-180 days. Adjusted models were run separately in strata defined by dementia and nursing home status. We also investigated whether a dose-response relationship existed in adjusted models by separating conventional APM initiators into those at the median dosage or less vs. greater than the median daily dosage. In confirmatory analyses, Propensity score adjustments was used to balance measured risk factors

for mortality between drug user groups.[14] Propensity scores were derived from predicted probabilities in logistic regression models of conventional vs. atypical APM use. The final model contained all covariates shown in Table 1 and strongly predicted the type of APM used (c-statistic[26]= 0.78). The propensity score substituted multiple covariates in the Cox model.

An instrumental variable analysis was also used to provide estimates that would remain unbiased even if important confounding variables were unmeasured.[17-19] In the recent work,[15,16] the instrument employed was the prescribing physician's preference for conventional vs. atypical APMs (as indicated by their most recent new APM prescription). Using two-stage linear regression for the instrumental variable estimation and additional adjustment for measured patient characteristics, the risk difference of 180-day mortality between conventional vs. atypical APM initiators was calculated.

Results

In the study, 12,882 initiators of conventional APMs, and 24,359 initiators of atypical APMs were identified. The most frequently used conventional APM was loxapine (69%) followed by haloperidol (11%), and chlorpromazine (7%). Risperidone (75%) was the most frequently used conventionals followed by quetiapine fumarate (15%), and olanzapine (10%). The median daily dosage at the time of initiation for conventional APM was 10mg for loxapine, 2mg for haloperidol, 71mg for chlorpromazine, 3mg for trifluoperazine, 25mg for thioridazine, 2mg for pimozide, 4mg for perphenazine, 20mg for thiothixene, 2.5mg for fluphenazine and 75mg for mesoridazine. The median dosage for atypical APM was 0.5mg for risperidone, 25mg for quetiapine fumarate, 5mg for olanzapine, and 150mg for clozapine. The initiators of the conventional agents were less likely than initiators of the atypical agents to be male, and have cerebrovascular disease, AMI, other cardiovascular diseases, dementia, delirium, psychoses, mood disorders, and other psychiatric disorders, but more likely to have HF and non-MI ischemic heart disease at baseline. (**Table 1**) Conventional APM initiators had lower rates of using antidepressants, other psychotropic medications, total number of drugs, hospitalizations, and nursing home stays.

The number of events and event rate (%) within 180 days after the initiation of APM agents are shown in **Table 2**. In the first 180 days of use, 12.7 % of conventional APMs initiators died due to non-cancer causes, compared to 9.0 % of atypical APM initiators. All specific causes of deaths except for arrhythmic death and death due to mental disorders were increased in conventional vs. atypical APM initiators. For disease outcomes, conventional vs. atypical APM initiators had higher incidence of all infection outcomes and some cardiac events including heart failure and arrhythmias.

Prevalence of various causes of deaths and adjusted hazard ratios for new users of conventional vs. atypical APMs are shown in **Table 2**. Among 3,821 non-cancer deaths, 1,866 (49%) were cardiovascular, and greater than 60% of the cardiovascular deaths were OOH; 379 (10%) were infectious, and 88% of the infectious deaths were pneumonia-related. Other frequent causes included cancer, respiratory diseases, nervous system and mental disorders, each of which accounted for 7-9% of all deaths. Of 286 deaths due to nervous system disorders, 188 were from Alzheimer's disease and 40 were from Parkinson's disease.

Among those taking conventional APMs, we found a significantly greater risk of death due to non-cancer deaths or specific causes of deaths such as cardiovascular diseases, respiratory diseases, nervous system and other causes (**Table 3**). The risk of deaths due to infections tended to be higher among conventional APM initiators but did not reach statistical significance. We further estimated multivariate adjusted risk differences for each cause of death and total death due to non-cancer causes. The excess risk in conventional APM initiators was 11.2 per 1,000 patient-years (95% CI : 6.1 - 16.3) for all cardiovascular deaths, 9.8 (95% CI : 5.8 – 13.9) for OOH cardiovascular deaths, 5.2 (95% CI : 2.9 – 7.5) for deaths due to respiratory, and 2.1 (95% CI : -0.4 – 4.5) for infection-related deaths. The excess risk for non-cancer mortality was 25.7 per 1,000 patient-years (95% CI : 17.4 – 37.0). The excess risk for cardiovascular deaths accounted for 44% of the total excess risk, and respiratory and infection-related deaths accounted for another 28%.

Hazard ratios comparing the rate of cardiovascular death for new users of conventional vs. atypical APMs are shown in **Table 4**. Hazards were significantly higher for conventional than atypical APM use in adjusted models of 180-day mortality that adjusted for a large number of potential confounders. The greatest increase in adjusted mortality risk for conventional vs. atypical APMs occurred with use of higher (> median) conventional APM dosages and during the first 5 days. In analyses restricted by dementia status or nursing home residency, with the exception of patients with dementia, those who initiated conventional vs. atypical APMs had significantly greater risk of 180-day mortality (**Table 4**). When comparing loxapine, the most frequently prescribed conventional APM with the most frequently prescribed atypical APMs, risperidone or quetiapine fumarate, we found mortality ratios for CV deaths were 1.20 (95% CI 1.07–1.34) for loxapine vs. risperidone and 1.48 (95% CI 1.14–1.91) for loxapine vs. quetiapine. When the risk of OOH cardiovascular death was specifically assessed (**Table 4**)**,** a similar but greater risk in conventional APM initiators compared to atypical APM initiators was observed.

The confirmatory analyses using propensity score adjustments yielded no substantive changes relative to the traditional multivariable Cox regression analyses, adding further support to the findings from the conventional analysis. The hazard ratio comparing the risk of OOH cardiovascular death within 180 days between the conventional and atypical antipsychotic drug groups after propensity score adjustment was 1.39 (95% CI 1.30–1.49). In the instrumental variable analyses, use of conventional antipsychotic medications continued to be associated with an increased risk of all CV and OOH CV death within 180 days compared with use of atypical APMs. The adjusted risk difference for all CV death was 1.1 per 100 (95% CI 0.6–1.6). The adjusted estimates in the instrumental variable analyses did not differ from the traditional multivariable estimates ($p = 0.56$). Our instrument was strongly associated with the actual treatment choice (odds ratio 6.1, 95% CI 5.8–6.4).

Discussion

In this study of over 30,000 elderly patients initiating APM treatments, use of conventional agents was associated with a significantly increased risk of dying due to cardiovascular, especially OOH cardiovascular events relative to use of atypical agents, which accounted for half of excess mortality. The risk of death due to respiratory causes was also significantly higher in conventional drug use.

Increased risk of OOH cardiovascular death can be partly explained by increased risk of arrhythmias, cardiac arrest, and sudden death from conventional APM use, which has been shown in previous studies.[27-31] Prolongation of cardiac repolarization and QTc intervals is thought to be responsible and generally more prevalent with conventional than atypical agent with the notable exception of ziprasidone.[32] Most[32,33] earlier epidemiological data comparing APM agents have found higher risks of ventricular arrhythmia and cardiac arrest with conventional vs. atypical agents. Although clozapine has been associated with myocarditis and cardiomyopathy,[34-37] it was used in less than 1% of APM initiators in our population.

OOH cardiovascular death as indicated on the death certificate includes many more causes aside from sudden arrhythmic death.[38] Hence, our results suggest that conventional APM initiators might also have an increased risk of sudden non-arrhythmic cardiovascular death, such as fatal acute myocardial infarction, pulmonary embolism, and massive stroke. Postural hypotension, one of commonly reported side effects of low potency conventional may cause sudden death, which could be classified as in-hospital and OOH cardiovascular deaths. We did not note a greater risk of cardiovascular events leading to hospitalization in conventional vs. atypical APM initiators. (data not shown) This also supports the contention that conventional APM may be associated with cardiovascular events that lead to sudden deaths.

There have been no reports of increased risk of death in conventional vs. atypical APM initiators due to respiratory disease.[21] Hypothetically, anticholinergic side effects of these agents in elderly patients with severe chronic respiratory diseases might cause worsening of symptoms and choking through drying up secretions and difficulty in clearing mucus. Respiratory dyskinesia related to conventional APM use has been reported as a common but under-recognized side effect,[39] which might also contribute to worsening of the underlying respiratory disorders. Conventional initiators had increased risk of death due to respiratory, nervous system, and other miscellaneous causes. Although the hazard ratios for these causes were somewhat higher than that for cardiovascular deaths, the prevalence of these causes was much lower than cardiovascular deaths; and therefore these contributed less to the excess risk of death in conventional APM initiators.

Our results indicating no increased risk of CV or OOH CV deaths by conventional APM vs. atypical APM use in patients with dementia (**Table 4**) do not conflict with the observation by Gill et al. that conventional APM use may increase the risk of all-cause death in patients with dementia.[40] We did observe significant increased risk of all-cause mortality in our population as reported in the previously published study (HR=1.26; 95% CI 1.01–1.56 in patients with dementia)[11] and the effect size was similar to what was observed in Gill's study (HR=1.23; 95% CI 1.00–1.50 in community patients with dementia and HR=1.27; 95% CI 1.09–1.48 in long-

term care patients with dementia).[40] However, our results suggest the causes of deaths responsible in patients with dementia may differ from those in patients with no dementia.

Our results should be interpreted with the following potential limitations. First, several patient characteristics were not recorded in the study database, most importantly limitations in activities of daily living, 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. However, we adjusted for sociodemographic, clinical, and health care utilization factors, which may be independent predictors of developing these conditions through traditional multivariable and propensity score as well as instrumental variable techniques.[14,17-19] Second, because there have been long-standing warnings concerning conventional APMs and ventricular arrhythmias,[32] any residual confounding may have led to underestimation of hazards from conventional agents on this outcome. We also limited our examination to data from essentially before the first warnings regarding atypical agents and stroke, to avoid overestimating cerebrovascular risks from conventional APMs.[41-43] Furthermore, the exposure status was based on the initial dispensing and did not consider discontinuation or change in status within 180-day study period. However, non-differential exposure misclassification (e.g., not taking filled prescriptions or switching APM classes) would bias results towards the null; differential misclassification (e.g., worse adherence with conventional APMs, as has been found)[44] again may have led to underestimation of hazards from conventional agents. Although we attempted to use or adapt established outcome definitions,[45-49] misclassification is still possible and would presumably bias our findings towards the null. In addition, we adjusted for calendar time to account for any improvements in the prevention of cardiac or cerebrovascular events, which could otherwise lead to reduced risks in later years, when atypical use was more common.

These findings give insight into the greater risk of mortality in conventional APM initiators in this cohort of Canadian elderly population.[11] Our study adds to growing evidence that conventional APMs may not be safer than atypical APMs for the elderly and should not simply replace the latter drugs stopped in response to recent FDA warnings.[9,10,50] However, further studies with more detailed data are needed to understand the comparative effect of less frequently used individual APMs and identify potentially vulnerable subpopulations among whom conventional agents should be especially avoided.

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Tables

Table 1. Characteristics of 37,241 British Columbia seniors who initiated conventional or atypical antipsychotic medications

Characteristic	Atypical (n=24,359)		Conventional (n=12,882)		p-value
Age (mean)	80.3		79.88		<.0001
Male patients	8565	35.20%	5120	39.70%	<.0001
History of					
Cardiac Arrhythmia	22	0.10%	6	0.00%	0.143
Cerebrovascular disease	2430	10.00%	1391	10.80%	0.129
Congestive heart failure	1455	6.00%	1084	8.40%	<.0001
Diabetes	3362	13.80%	1939	15.10%	0.001
Myocardial infarction	551	2.30%	354	2.70%	0.0038
Other ischemic heart disease	665	2.70%	493	3.80%	<.0001
Other cardiovascular disorders	4075	16.70%	2609	20.30%	<.0001
HIV infection	4	0.00%	0	0.00%	0.1458
Dementia	3087	12.70%	1247	9.70%	<.0001
Delirium	2060	8.50%	967	7.50%	0.0014
Mood disorders	6198	25.40%	2013	15.60%	<.0001
Psychotic disorders	4103	16.80%	1446	11.20%	<.0001
Other psychiatric disorders	1110	4.60%	403	3.10%	<.0001
Use of other drugs					
Antidepressants	10154	41.70%	3645	28.30%	<.0001
Other psychotropic medications	920	3.80%	542	4.20%	0.0418
Total number of drugs used (mean)	7.34		7.37		<.0001
Hospitalization in previous 180 days	3204	13.20%	1923	14.90%	<.0001
Nursing home residence in previous 180 days	6471	26.60%	3980	30.90%	<.0001

Table 2. Causes of death and cardiovascular and infection hospitalization within 180 days after APM initiation in British Columbia (N=37,241)

	Conventional APM (N=12,882)		Atypical APM (N=24,359)	
	# death	incidence rate*	# death	incidence rate*
Total Death	1632	28.1	2189	19.3
Cardiovascular	801	13.8	1068	9.4
Ischemic heart diseases	325	5.6	434	3.8
Heart failure	123	2.1	138	1.2
Arrhythmia	28	0.5	49	0.4
Ventricular arrhythmia	11	0.2	13	0.1
Cerebrovascular diseases	212	3.6	301	2.7
Stroke	170	2.9	251	2.2
In-hospital cardiovascular	345	5.9	400	3.5
Out-of-hospital cardiovascular	456	7.8	665	5.9
Overall infection (including pneumonia)	161	2.8	218	1.9
Pneumonia	140	2.4	193	1.7
Other infection	21	0.4	25	0.2
Respiratory (except pneumonia)	167	2.9	181	1.6
COPD	107	1.8	117	1.3
Nervous system	120	2.1	166	1.5
Mental	82	1.4	141	1.2
Other	301	5.2	415	3.7
Disease Outcomes				
Overall cardiac events	1426	27.3	2197	21.0
Acute myocardial infarction	90	1.7	161	1.5
Heart failure	376	6.9	561	5.2
Arrhythmia	205	3.8	318	2.9
Ventricular arrhythmia	21	0.4	25	0.2
Any cerebrovascular diseases	326	6.0	422	3.9
Cerebrovascular events	116	2.1	248	2.3
Infarction	58	1.1	97	0.9
Cerebral hemorrhage	30	0.6	52	0.5
Overall infection	548	10.1	727	6.7
All serious infection†	472	8.7	614	5.7
Pneumonia	415	7.7	532	4.9

* Incidence rate is per 100 person-years

† All serious infections include pneumonia, bacteremia/septicemia, cellulitis, encephalitis/meningitis, endocarditis/myocarditis, pyelonephritis, septic arthritis, osteomyelitis, or opportunistic infection

Table 3. Adjusted hazard ratios for all and specific causes of death within 180 days after initiating therapy with conventional vs. atypical antipsychotic medications*

Causes of Deaths	Adjusted Hazard Ratios (95%CI)	Prevalence of Causes
All non-cancer deaths	1.27 (1.18 - 1.37)	100% (3821)
Cardiovascular	1.23 (1.10 - 1.36)	49% (1866)
Out of hospital cardiovascular	1.36 (1.19 - 1.56)	29%(1121)
Infection (including pneumonia)	1.21 (0.95 - 1.53)	10% (379)
Respiratory (excluding pneumonia)	1.71 (1.35 - 2.17)	9% (348)
Nervous System	1.42 (1.01 - 1.86)	7% (286)
Mental disorders	1.02 (0.74 - 1.39)	6% (223)
Other	1.27 (1.07 - 1.51)	19% (735)

*APM denotes antipsychotic medication, and CI confidence interval.

Note: 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, total number of medications used, hospitalization and nursing home stays.

Table 4. Hazard ratios of overall and out-of-hospital (OOH) cardiovascular death within 180 days after initiating therapy with conventional vs. atypical antipsychotic medications*

Model	CV Death Hazard Ratio (95% CI)	OOH CV Death Hazard Ratio (95% CI)
Unadjusted analysis	1.24 (1.02-1.24)	1.13 (1.00-1.29)
Age, gender, and calendar year adjusted analysis	1.07 (0.97-1.18)	1.09 (0.96-1.24)
Adjusted analysis of death within 180 days†		
Use of any conventional APM	1.23 (1.10-1.36)	1.36 (1.19-1.56)
Use of high-dose conventional APM	1.49 (1.26-1.77)	1.85 (1.50-2.29)
Use of low-dose conventional APM	1.17 (1.04-1.31)	1.25 (1.08-1.45)
Adjusted analysis of death by duration of use†		
1-5 days after beginning therapy	1.79 (1.19-2.69)	2.27 (1.45 - 3.57)
6-20 days after beginning therapy	1.45 (1.12-1.88)	1.73 (1.26-2.37)
21-39 days after beginning therapy	1.17 (0.89-1.54)	1.52 (1.06-2.18)
40-79 days after beginning therapy	1.11 (0.89-1.38)	1.06 (0.79-1.41)
80-180 days after beginning therapy	1.20 (1.03-1.41)	1.25 (1.02-1.54)
Adjusted analyses in patient subgroups†		
With dementia	1.12 (0.80-1.56)	1.00 (0.65-1.54)
Without dementia	1.21 (1.08-1.36)	1.38 (1.19-1.60)
In a nursing home	1.24 (1.05-1.45)	1.25 (1.03-1.50)
Not in a nursing home	1.22 (1.06-1.41)	1.49 (1.22-1.82)

*APM denotes antipsychotic medication, and CI confidence interval.

†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, total number of medications used, hospitalization and nursing home stays.