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Ventricular Arrhythmias and Cerebrovascular Events in the Elderly Using Conventional and Atypical Antipsychotic Medications

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Abstract

Background. Although an FDA Advisory has warned that atypical antipsychotic medications (APMs) increase mortality in older patients, evidence has been growing that conventional APM use may be associated with even greater risks of death.

Objectives. To identify intervening medical conditions that may be responsible for a greater risk of mortality from conventional vs. atypical APMs.

Methods. We conducted a retrospective cohort study of 22,890 patients ≥65 receiving pharmacy benefits in Pennsylvania who began a conventional or atypical APM between 1994-2003. Cox proportional hazards models were used to compare hazards of developing the following health outcomes within 30, 60, and 120 days since APM initiation: acute myocardial infarction, cerebrovascular events, congestive heart failure, pneumonia, other serious infections, and ventricular arrhythmias. We controlled for potential confounders using conventional multivariable models. Secondary confirmatory analyses employed methods based on propensity scores and instrumental variables.

Results. Conventional vs. atypical APM users had a significantly higher adjusted hazard of developing ventricular arrhythmias by 30 days (adjusted HR 1.20; 95% CI 1.03-1.39). Conventional vs. atypical APM users had significantly greater hazards of developing cerebrovascular events at both 60 days (adjusted HR 1.10; 95% CI 1.02-1.19) and 120 days (adjusted HR 1.09; 95% CI 1.02-1.16). The findings were also observed in the alternative analyses employing propensity score adjustments and instrumental variable methods.

Conclusions. These results suggest that the development of conditions such as ventricular arrhythmias and cerebrovascular accidents may explain a greater risk of mortality from conventional vs. atypical APMs in the elderly.

Keywords. Elderly, antipsychotic medications, conventional, atypical, arrhythmias, cerebrovascular accidents.

Introduction

The US Food and Drug Administration (FDA) issued an Advisory in 2005 that atypical antipsychotic medications (APMs) significantly increased the risk of death vs. placebo in 17 short-term randomized controlled trials among elderly with dementia.[1] "Black box" warnings were added to labels of all atypical APMs (i.e., aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone) 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 (e.g., phenothiazines and butyrophenones) 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] In a recent observational study of elderly beginning use of APMs, patients prescribed conventional agents had a 37% greater, dose-dependent risk of short-term mortality than those prescribed atypicals.[9] A recent meta-analysis of randomized trials among elderly with dementia found the conventional agent, haloperidol, increased short-term mortality vs. placebo by 107%, a risk greater than that for atypical agents.[10] Another observational study found higher mortality in those given haloperidol vs. two atypical drugs (risperidone or olanzapine).[11]

An important next step in understanding whether conventional APMs truly pose greater hazards than atypical agents 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, anticholinergic properties affecting blood pressure and heart rate, Q-T prolongation causing conduction delays, as well as sedation and extrapyramidal symptoms causing potential swallowing problems, are all more common with conventional than atypical agents.[5-8,12] For these reasons, cardiac (e.g., myocardial infarction and ventricular arrhythmias), cerebrovascular (e.g., stroke and transient ischemic events), and infection (e.g., aspiration pneumonia) outcomes may all be potential mediators of an increased risk of death from conventional vs. atypical agents.

The aims of the current study were to examine whether elderly newly started on conventional vs. atypical APMs, have greater risks of cardiac, cerebrovascular, and infection outcomes. Reasons for using both drug groups (e.g., dementia, delirium) may themselves be risk factors for these outcomes so we restricted analyses to only patients given an APM. We also restricted analyses to just new users to guard against selection bias among prevalent users from early symptom emergence, drug intolerance, or treatment failure.[13] To control for potential differences in characteristics of those prescribed different APMs, we used traditional multivariable and propensity score adjusted Cox proportional hazards models[14] as well as instrumental variable (IV) estimation.[15-18] Because we observed previously[9] that the relative risk of death from conventional vs. atypical APMs may not be uniform over time, we separately examined the hazards of developing conditions within 30, 60, and 120 days of initiating an APM. Identifying potential mechanisms is critical for answering whether conventional agents truly pose greater hazards than atypicals and should not simply replace the latter drugs stopped in response to recent FDA warnings.[3]

Methods

Data Sources

Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE) program

Information from PACE, the largest US state prescription benefits program for the elderly, was available from 1/1/94-12/31/03.[19] PACE has no deductibles or maximum annual benefit and charges a modest copayment of $6 for each prescription. The income ceiling for eligibility is $14,000 if single and $17,200 for a couple, resulting in a recipient population of both indigent and near-poor elderly. These generous benefits and requirements for financial need result in essentially no out-of-pocket (i.e., out-of-system) medication use.

Pennsylvania Medicare

Medicare data included both Part A (hospitalizations and nursing home stays) and Part B (outpatient services and procedures) on all PACE enrollees during 1/1/94-12/31/03. Medicare data on mortality were drawn from the Death Master File, which undergoes extensive verification and weekly updates by the Social Security Administration.[20]

We assembled data on all filled prescriptions, procedures, physician encounters, hospitalizations, and long-term care into a relational database. All traceable person-specific identifiers were transformed into anonymous, coded study numbers to protect subjects' privacy. This study was approved by the Brigham and Women's Hospital IRB.

Study Population

All individuals were >65 and filled a first recorded (index) prescription for an oral APM from 1/1/94-12/31/03. To ensure a uniform 6-month eligibility period prior to filling the index APM prescription, all study subjects were required to have utilized >1 medical service and >1 prescription, both within the 6 months prior to the index date as well as in the >6 months before the index date.

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.[21]

Outcomes Potentially Mediating the Increased Hazards of Conventional vs. Atypical APMs

The following outcomes were assessed in the 180 days *after* the index day:

Acute myocardial infarction (AMI). Hospitalization with ICD-9 diagnoses[22] (in the principal or secondary position) or DRG[23] codes for acute myocardial infarction.[24]

Ventricular arrhythmia. Ventricular arrhythmia diagnosis[25] plus use of a Group I-IV antiarrhythmia medication.

Cerebrovascular events. Diagnoses of cerebrovascular events (e.g., both cerebral hemorrhagic and ischemic events).[26]

Congestive heart failure. Hospitalization with a diagnostic code for congestive heart failure.[27]

Pneumonia. Diagnostic codes for pneumonia plus prescription for an antibiotic medication.[28]

Other serious bacterial infections. Hospitalization with a diagnostic code for bacteremia/septicemia, cellulitis, encephalitis/meningitis, endocarditis/myocarditis, pyelonephritis, septic arthritis, osteomyelitis, or opportunistic infection.[28]

Other Covariates

We defined the following patient characteristics in the 6 months prior to each subject's index date:

Sociodemographic data. Age, gender, and race.

Comorbidities. We employed ICD-9 diagnostic codes, CPT procedure codes[29], DRG hospitalization codes, and medication use to define the presence of clinical conditions prior to initiation of antipsychotic medication. Acute myocardial infarction, cardiac arrhythmia, cerebrovascular events, congestive heart failure, pneumonia, and other serious bacterial infections were defined as above. Diabetes was defined by the presence of diagnoses plus use of anti-diabetic medications. Additional conditions included other evidence of ischemic heart disease (e.g., angina, PTCA, CABG, or nitroglycerin use), other cardiovascular conditions (e.g., valvular disease, aneurysms, peripheral vascular disease), cancers, HIV, dementia, delirium, mood disorders, psychotic disorders, and other psychiatric disorders.

Health Care Utilization. Health care utilization potentially predictive of developing the outcomes of interest was also assessed, including hospitalizations, nursing home stays, use of other psychiatric medications, and total number of medications used (excluding APMs and drugs used to define covariates).[30]

Analyses

Distributions of sociodemographic, clinical, and utilization characteristics among conventional and atypical APM users were calculated. Unadjusted and multivariable (controlling for calendar year and all covariates listed above) Cox proportional hazards models were constructed of developing individual outcomes of interest. Models of developing outcomes within 30, 60, and 120 days of APM initiation were constructed based upon our earlier finding of roughly proportional hazards of death between conventional and atypical APM users within these time intervals.[9]

In confirmatory analyses, we repeated Cox models using propensity score adjustments to balance independent risk factors for outcomes between drug user groups.[14] Propensity scores were derived from predicted probabilities in logistic regression models of conventional vs. atypical APM use. Final non-parsimonious models contained all covariates shown in Table 1 and strongly predicted the type of APM used (c-statistic = 0.845). We then stratified Cox models of individual outcomes across deciles of the propensity score. We also used instrumental variable (IV) analysis to provide estimates that would remain unbiased even if important confounding variables were unmeasured.[15-17] An IV is an observable factor related to treatment choice but unrelated to patient characteristics and outcomes. As in other recent work[18], 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 developing 180-day outcomes between conventional vs. atypical APM users. All confirmatory analyses were limited to outcomes found to be significant in the primary analysis.

Results

Patients who began use of conventional APM agents (N=9,142) were slightly younger and more likely to be male and non-white than those who began use of atypical APMs (N=13,748)(Table 1). New users of the conventional agents were less likely than new users of the atypical agents to have cerebrovascular disease, dementia, delirium, psychoses, and other psychiatric disorders, but more likely to have CHF, non-MI ischemic heart disease, and cancer. Conventional APM users had lower rates of using antidepressants, other psychotropic medications, total number of drugs, hospitalizations, and nursing home stays. In the first 180 days of use, 17.9% of patients who began conventional APMs died, compared to 14.6% of those who began atypical APMs. Counts of events by cohort and follow-up period are given in Table 2.

Unadjusted hazard ratios comparing the risk of developing conditions for new users of conventional vs. atypical APMs are shown in Table 3. Adjusted hazard ratios comparing the risk of developing conditions for new users of conventional vs. atypical APMs are shown in Table 4. By 30 days, adjusted hazards were significantly higher for conventional than atypical APM use only in models of developing ventricular arrhythmias (adjusted HR 1.20; 95% CI 1.03-1.39). By 60 days, conventional vs. atypical APM use was only associated with a significantly increased hazard of developing cerebrovascular events (adjusted HR 1.10; 95% CI 1.02-1.19). Similarly, only the hazards of developing cerebrovascular events were significantly greater for conventional than atypical APM use at 120 days (adjusted HR 1.09; 95% CI 1.02-1.16).

Confirmatory analyses using propensity score adjustments[14] yielded nearly identical results to the traditional multivariable Cox analyses. Results from the IV analysis agreed with the direction and statistical significance of the traditional multivariable Cox analyses for all outcomes examined.

Discussion

In this study of over 20,000 elderly patients initiating APM treatments, use of conventional agents was associated with significantly increased hazards of developing

ventricular arrhythmias and cerebrovascular events relative to use of atypical agents. The increased hazards for these two conditions may explain at least in part the greater risk of mortality that has been observed from conventional vs. atypical APMs in elderly patients.[9]

On one hand, our finding of a potential hazard of ventricular arrhythmias from conventional APM use is not new and provides some reassurance concerning our analyses' ability to identify known effects. Soon after their introduction, conventional APMs were associated with the development of arrhythmias, cardiac arrest, and sudden death.[31-35] Prolongation of cardiac repolarization and QTc intervals is thought to be responsible and generally more common with conventional than atypical agents, an exception being ziprasidone.[36] Most[36,37] but not all[32] earlier epidemiological data comparing APM agents have found higher risks of ventricular arrhythmia and cardiac arrest with conventional vs. atypical use. Possible explanations for any discrepancy include adequacy of study power and control for "channeling" of patients at highest risk for arrhythmias away from conventional agents due to earlier warnings.

On the other hand, our finding of a greater hazard of cerebrovascular accidents from conventional vs. atypical APMs has not been established. Because of the paucity of trials involving conventional agents, the FDA has warned only of increased risks for strokes and transient ischemic events from the atypical agents risperidone, olanzapine, and aripiprazole.[38-40] One potential mechanism through which conventional agents might increase risks of cerebrovascular events beyond those seen with atypical agents, is suggested by their known anticholinergic effects on heart rate and blood pressure. Hypoperfusion has been shown to lead to microinfarcts in dementia patients and investigators have proposed that conventional APMs, in particular, may accentuate this process.[41] Two epidemiologic studies comparing conventional vs. atypical agents have not found statistically significant differences.[42,43] One possible explanation for the discrepancy with our results is raised by our finding that the greater hazards from conventionals did not emerge immediately and may require separately examining intermediate or longer periods of follow-up.

These results should be interpreted with the following potential limitations kept in mind. Conventional agents may have been more likely than atypical APMs to be given to patients at risk of developing arrhythmias and cerebrovascular accidents. For this reason, we controlled for sociodemographic, clinical, and health care utilization factors which may be independent predictors of developing these conditions through traditional multivariable, propensity score, and instrumental variable techniques.[14-18] We also restricted analyses to only APM users as well as to just new users, to control for underlying reasons for APM use and any selection bias among prevalent users from early symptom emergence, drug intolerance, or treatment failure.[13] Because there have been long-standing warnings concerning conventional APMs and ventricular arrhythmias,[36] any residual confounding may have led to underestimation of hazards from conventional agents on this outcome. For the same reason, we limited our examination to data from essentially before the first warnings regarding atypical agents and stroke, to avoid overestimating cerebrovascular risks from conventional APMs.[38-40] Non-differential exposure misclassification (e.g., not consuming 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,[24-28] misclassification is still possible and would presumably bias our findings towards the null. Finally, we controlled for calendar time to adjust 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. However, in spite of these safeguards and convergence of results from confirmatory and sensitivity analyses, it is important to keep in mind that our study is based upon non-experimental administrative claims data, in which the completeness and accuracy of clinical information is uncertain. There still may be other aspects of patients newly prescribed conventional APMs that we were unable to control for, leaving open the possibility of residual confounding. For this reason, circumspect interpretation of these findings is required.

Other potential limitations include the possibility that patients who did not fill antipsychotic medications in the prior six months may not have been new initiators, but instead former users beginning a new episode of care. Our study may also have had both inadequate statistical power to observe true associations as well as the potential to detect spurious associations due to having made multiple comparisons. Finally, the generalizability of these findings to other elderly populations may be uncertain.

If confirmed, these results add 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.[9,10,45] They suggest that conventional APMs may raise the risks of mortality through the development of ventricular arrhythmias and cerebrovascular accidents. However beyond suggesting caution regarding conventional APM use in older populations, our results leave many important questions unanswered. First, any greater risk for ventricular arrhythmias or cerebrovascular accidents from conventional agents may only partially mediate the greater mortality observed among conventional vs. atypical APM users. More research is needed to identify other possible intervening conditions and hence potentially vulnerable subpopulations in which conventional agents should be especially avoided. Furthermore, our study sheds no light on other pharmacologic or non-pharmacologic interventions that could preferentially be used to manage the many conditions and symptoms in older populations for which APMs are currently used.[12] Well-designed studies shedding light on optimal care for the elderly are sorely needed.

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Table 1. Characteristics of elderly new users of conventional and atypical antipsychotic medications (n=22,890)

		% of Conventional APM Users	% of Atypical APM Users
Age (mean):		83.2	83.5
Gender:	Female	77.6	83.0
	Male	22.4	17.0
Race:	White	92.8	94.7
	Non-white	7.2	5.3
Diagnoses:	Cardiac arrhythmia	1.4	1.4
	Cerebrovascular disease	29.1	30.9
	CHF	32.6	31.1
	Diabetes	25.8	26.8
	Hypertension	58.1	65.1
	Myocardial infarction	3.5	3.5
	Other ischemic heart disease	29.3	24.4
	Other cardiovascular disorders	12.7	12.3
	Cancer	15.6	14.0
	HIV	<0.1	<0.1
	Dementia	40.8	52.5
	Delirium	12.2	16.1
	Mood disorders	22.2	36.3
	Psychotic disorders	21.3	24.7
	Other psychiatric disorders	5.9	8.3
Other drug use:	Antidepressants	28.0	43.5
	Other psychotropic medications	11.5	13.5
	Number of different drugs (mean)	6.8	7.9
Hospitalization in prior 180 days		51.2	53.5
Nursing home residence in prior 180 days		15.9	21.4

Table 2. Counts of events by cohort and follow-up time

Condition	Counts of Events within 30 days Count (%)		Counts of Events within 60 days Count (%)		Counts of Events within 120 days Count (%)	
	Conventional	Atypical	Conventional	Atypical	Conventional	Atypical
Acute myocardial infarction	60 (0.66)	96 (0.70)	99 (1.08)	151 (1.10)	164 (1.79)	249 (1.81)
Cerebrovascular event	1319 (14.43)	1746 (12.70)	1759 (19.24)	2375 (17.28)	2314 (25.31)	3169 (23.05)
Congestive heart failure	1517 (16.59)	2170 (15.78)	2065 (22.59)	2990 (21.75)	2677 (29.28)	3891 (28.30)
Pneumonia	75 (0.82)	96 (0.70)	121 (1.32)	162 (1.18)	183 (2.00)	279 (2.03)
Other serious infection	258 (2.82)	313 (2.28)	395 (4.32)	537 (3.91)	616 (6.74)	882 (6.42)
Ventricular arrhythmia	472 (5.16)	615 (4.47)	721 (7.89)	999 (7.27)	1065 (11.65)	1518 (11.04)

Table 3. Unadjusted relative hazards of developing conditions among elderly new users of conventional vs. atypical antipsychotic medications

Condition	HR (95%CI) in 30 days	HR (95%CI) in 60 days	HR (95%CI) in 120 days
Acute myocardial Infarction	0.93 (0.66, 1.32)	1.00 (0.76, 1.30)	1.03 (0.85, 1.27)
Cerebrovascular event	1.19 (1.10, 1.27)	1.18 (1.11, 1.26)	1.17 (1.11, 1.24)
Congestive heart failure	1.09 (1.02, 1.17)	1.09 (1.02, 1.15)	1.09 (1.03, 1.14)
Pneumonia	1.30 (0.96, 1.78)	1.24 (0.98, 1.58)	0.84 (0.66, 1.05)
Other serious infection	1.33 (1.12, 1.57)	1.03 (0.87, 1.21)	1.12 (1.01, 1.25)
Ventricular arrhythmia	1.21 (1.07, 1.37)	1.15 (1.04, 1.27)	1.12 (1.04, 1.21)

Table 4. Adjusted Relative Hazards of Developing Conditions Among Elderly New Users of Conventional vs. Atypical Antipsychotic Medications

Condition	Adjusted HR* (95%CI) in 30 days	Adjusted HR* (95%CI) in 60 days	Adjusted HR* (95%CI) in 120 days
Acute myocardial infarction	0.89 (0.59, 1.33)	1.02 (0.75, 1.40)	1.16 (0.91, 1.48)
Cerebrovascular event	1.08 (0.99, 1.18)	1.10 (1.02, 1.19)	1.09 (1.02, 1.16)
Congestive heart failure	1.04 (0.95, 1.11)	1.00 (0.93, 1.07)	1.01 (0.95, 1.07)
Pneumonia	1.11 (0.76, 1.63)	1.03 (0.76, 1.38)	0.84 (0.66, 1.05)
Other serious infection	1.20 (0.98, 1.48)	1.03 (0.87, 1.21)	1.00 (0.88, 1.14)
Ventricular arrhythmia	1.20 (1.03, 1.39)	1.10 (0.98, 1.24)	1.06 (0.96, 1.17)

*Controlled for calendar year, age, gender, race, prior arrhythmias, cerebrovascular disease, CHF, diabetes, MI, hypertension, other evidence of ischemic heart disease, other cardiovascular conditions, cancers, HIV, pneumonia, other serious infection, dementia, delirium, mood disorders, psychotic disorders, other psychiatric disorders, use of other psychiatric medications, total number of medications, hospitalizations, and nursing home stays.