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Atypical Antipsychotic Drugs and the Risk of Sudden Cardiac Death

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Abstract

Background—Users of typical antipsychotics have increased risk of serious ventricular arrhythmias and sudden cardiac death. However, less is known regarding the cardiac safety of the atypical antipsychotic drugs, which have largely replaced the older agents in clinical practice.

Methods—We calculated the adjusted incidence of sudden cardiac death among current users of antipsychotics in a retrospective cohort of Tennessee Medicaid enrollees. The primary analysis included 44,218 and 46,089 baseline users of single typical and atypical drugs, respectively, and 186,600 matched nonuser controls. To assess residual confounding related to antipsychotic indication, we performed a secondary analysis of antipsychotic users with no baseline diagnosis of schizophrenia or related psychoses, propensity-score matched with nonusers.

Results—Current users of both typical and atypical antipsychotics had greater rates of sudden cardiac death than did nonusers of any antipsychotic, with adjusted incidence-rate ratios (IRRs) of 2.00 (95% CI, 1.69–2.35) and 2.27 (1.89–2.73), respectively. Former antipsychotic users had no significantly increased risk (IRR = 1.13 [0.98–1.30]). For both classes of drugs, the risk for current users increased significantly with dose. For typical antipsychotics the IRRs increased from 1.31 (0.97–1.77) for low doses to 2.42 (1.91–3.06) for high doses (p<.001). For atypical agents the IRRs increased from 1.59 (1.03–2.46) for low doses to 2.86 (2.25–3.65) for high doses (p=.015). The IRR for atypical vs typical antipsychotics was 1.14 (.93–1.39). Similar findings were present in the propensity-score matched cohort.

Conclusion—Current users of both typical and atypical antipsychotics had a similar, dose-related increased risk of sudden cardiac death.

There are extensive data linking the typical antipsychotics with increased risk of sudden cardiac death. These medications block repolarizing potassium currents *in vitro*[1,2] and prolong the QT interval,[1,3,4] one important causal mechanism for the ventricular tachyarrhythmias that often lead to sudden cardiac death.[5] There are numerous case reports of torsade de pointes and sudden death in conjunction with use of the typical antipsychotics.[6,7] Controlled epidemiologic studies have demonstrated a dose-related increased risk of sudden cardiac death for these medications.[8–11] Indeed, thioridazine, once one of the most

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frequently prescribed antipsychotics, now carries a black-box warning for increased risk of cardiac arrhythmias and sudden death.[12]

At present, less is known regarding the cardiac safety of the atypical antipsychotic drugs, which have largely replaced the older agents in clinical practice. Several atypical antipsychotics block repolarizing potassium currents[2] and prolong ventricular repolarization,[1,13] and the electrophysiologic effects of some drugs are comparable to those of the older agents. However, although torsade de pointes has been reported with atypical antipsychotics,[14–16] whether these drugs increase the risk of sudden cardiac death to the same extent as the older medications is unknown. We thus conducted a large retrospective cohort study designed to compare the risk of sudden cardiac death for the two classes of antipsychotic drugs.

Methods

Primary Cohort

Study data were obtained from computerized files of Tennessee Medicaid, which have been used extensively for pharmacoepidemiologic research.[17,18] Each person-day of Medicaid enrollment between 1 January 1990 through 31 December 2005 (study period) was evaluated to determine if it qualified for cohort inclusion. The cohort was restricted to persons 30 to 74 years of age because for younger persons sudden cardiac death is very rare and may have a different etiology,[19] and for older persons we found death certificates to be less reliable for identifying sudden cardiac deaths. Cohort membership required 730 days of prior enrollment (gaps <7 days allowed) with full pharmacy benefits and regular use of medical care (≥ 1 filled prescription and outpatient encounter in each of the two preceding years). The cohort excluded patients at high risk for deaths from non-cardiac causes (Appendix 1).

The cohort included every Medicaid enrollee with at least one qualifying day of antipsychotic use during the study period. The first day of followup, or t_0, was defined as the first qualifying day. The cohort also included two controls matched on age, sex, and t_0, randomly selected from qualifying nonusers of antipsychotics on t_0.

Followup extended from t_0 through the first of: the end of the study, death, loss of Medicaid enrollment, or whenever the cohort eligibility criteria were no longer met. Controls could subsequently become antipsychotic users and patients who left the cohort could reenter. Followup did not include hospitalization and the following 30 days because in-hospital deaths were not considered study endpoints and Medicaid files do not include drugs dispensed in the hospital.

Propensity-Score Matched Cohort

To assess residual confounding by factors associated with antipsychotic indication, we identified a secondary cohort that used propensity scores[20] to create a nonuser control group with a similar psychiatric illness profile. This matched cohort excluded antipsychotic users with a diagnosis of schizophrenia or related psychosis in the 730 days prior to t_0, as antipsychotic treatment is the standard of care for these conditions. Qualifying antipsychotic users thus primarily had mood disorders (a growing reason for antipsychotic use), for which there are alternative medications. For each qualifying user, up to two controls were adaptively matched on propensity score (Appendix 1), within strata defined by t_0, birth year, gender, and a marker of severe psychiatric illness (prior psychiatric hospitalization, bipolar diagnosis, or lithium prescription).

Antipsychotic and Other Medication Exposure

Antipsychotics and other study medications were identified from Medicaid pharmacy files. These included the date the prescription was dispensed, drug, quantity, dose, and days of supply (edited to resolve infrequent discrepancies with quantity). Computerized pharmacy records are an excellent source of medication data because they are not subject to information bias[17] and have high concordance with patient self-report of medication use.[21–23] The residual misclassification should be limited and is most likely to bias towards the null.[17]

Each person-day of study followup was classified according to probable antipsychotic use. *Current use* was the interval between prescription filling and the end of days of supply (up to 7 day carryover from previous prescriptions), when the person was most likely to be taking the drug. *Indeterminate use* included up to 90 days following last current use and *former use* included all subsequent person-time that was not current or indeterminate use. *Nonuse* consisted of person-days with no prescribed antipsychotic use on that day or at any time in the past. Current use was further classified according to dose expressed as approximate equivalents of 100mg chlorpromazine (Appendix 1)[24,25] and then categorized as low (<100mg), moderate (100mg–299mg), or high dose (≥300mg). Individual drugs analyzed were thioridazine and haloperidol as well as atypical antipsychotics with ≥3000 person-years of current use (≥5 sudden death cases expected under the null): clozapine, quetiapine, olanzapine, and risperidone.

Study Endpoint

The study endpoint was sudden cardiac death occurring in a community setting.[26–28] This was defined as a sudden pulseless condition that was fatal, consistent with a ventricular tachyarrhythmia, and occurred in the absence of a known noncardiac condition as the proximate cause of the death.[27] This excluded deaths of patients admitted to the hospital, that were not sudden, or with evidence for an extrinsic (e.g., cocaine) or noncardiac (e.g., pneumonia) etiology or a different cardiac etiology (e.g., heart failure).

Endpoints were identified from computerized death certificates linked with records of terminal medical care encounters. The case definition was developed from and validated by our previous study[8,29,30] for which medical records were reviewed for deaths occurring between 1986 and 1993. Qualifying deaths occurred outside of the hospital or other institution and, based on our previous investigation, had an underlying cause of death compatible with sudden cardiac death (Appendix 1). These deaths were further restricted to those with no evidence of care in the emergency department on the day of death inconsistent with a sudden cardiac death. Our previous study[8] had reviewed medical records for 616 of such qualifying deaths that occurred in the present cohort. Of these, 530 (86%) were confirmed cases of sudden cardiac death (unpublished data). If nondifferential, the residual misclassification should bias to the null.[31]

Statistical Analysis

The relative risk of sudden cardiac death according to antipsychotic use status (adjusted for dose [Appendix 1]) was estimated with the incidence rate-ratio (IRR), as calculated from Poisson regression models. The models (Appendix 1) included demographic characteristics and variables reflecting comorbidity at baseline and subsequent changes during followup. Baseline comorbidity included both cardiovascular/other somatic disease as well as psychiatric/neurologic illness. The former included prescribed medications and recorded diagnoses as well medical care utilization and a measure of compliance with drugs (Appendix 1) for long-term use.

We calculated a summary cardiovascular risk score from the large number of baseline cardiovascular/somatic variables. The score was defined for the entire cohort as the predicted probability of sudden death, conditional on no antipsychotic exposure (estimated with Poisson regression analysis among antipsychotic nonusers), and then expressed as 20 quantiles. This technique permits more parsimonious models when there are numerous covariates and facilitates description of baseline cardiovascular risk.[32]

We conducted several supplementary analyses to test key assumptions. These included an analysis that permitted only 1 cohort entry/person as well as inclusion of additional baseline and time-dependent variables in the model (Appendix 1). Findings were essentially identical to those reported here.

All analyses were done with SAS version 9.0. All p-values are two-sided.

The Vanderbilt Committee for the Protection of Human Subjects and the Tennessee Bureau of TennCare and Department of Health approved the study. The study was funded by grants from federal agencies, which had no role in study conduct or reporting. The listed authors were entirely responsible for study design, data analysis, manuscript preparation, and publication decisions; no other persons were involved. The first manuscript draft was written by the primary author.

Results

The primary cohort included 93,300 antipsychotic users and 186,600 matched controls. There were 44,218 and 46,089 users of single typical and atypical antipsychotics at cohort entry. The propensity-score-matched cohort included 67,824 antipsychotic users and 116,069 nonusers.

In the primary cohort, users and nonusers of antipsychotics had comparable baseline demographic characteristics (Table 1). The mean age was 46 years, 65% were female, 70% were of white race, and 57% had urban residence. Antipsychotic users were more likely to have Medicaid enrollment related to disability (63%) than were nonusers (37%) but had a slightly lower mean baseline cardiovascular risk score (9.2 versus 9.6). As expected, antipsychotic users had higher prevalence of baseline psychiatric comorbidity; however, there was substantial comorbidity among nonusers as well, particularly for affective disorders. In the propensity-score-matched cohort, antipsychotic users and nonusers had identical propensity scores and comparable baseline psychiatric comorbidity.

When compared with users of typical antipsychotics, atypical users were slightly younger, less likely to have Medicaid enrollment related to disability, and had higher baseline cardiovascular risk (Appendix 2). They also had higher antipsychotic doses, in part due to the preponderance of low-dose use for thioridazine (54% low dose). Atypical users also were less likely to have a diagnosis of schizophrenia (14% vs 27% for typical users), but more likely to have diagnosed mood disorders (bipolar: 23% vs 12% for typical agents; other mood: 60% vs 36% for typical agents), except for users of clozapine (indicated for treatment-resistant psychosis24), for whom 89% had a diagnosis of schizophrenia.

During the 1,042,159 person-years of cohort followup, there were 1870 sudden cardiac deaths, or 17.9 per 10,000 person-years. The unadjusted rate increased from 4.7 per 10,000 for those aged 30–34 at baseline to 47.6 per 10,000 for those 70–74 and was more than twice as high for males (27.1 per 10,000) as for females (12.9 per 10,000).

Current users of typical antipsychotics had an adjusted rate of sudden cardiac death 2.00 (95% CI, 1.69–2.35) times that of nonusers (Table 2). A similar increased risk was present

for current users of atypical antipsychotics, who had a rate of sudden cardiac death more than twice that of nonusers (IRR=2.27[1.89–2.73]) and not significantly different from that for the typical agents (IRR=1.14 [.93–1.39]). The rates of sudden cardiac death for both typical and atypical antipsychotic users were greater than those for former antipsychotic users (p<.0001), who had no significantly increased risk of sudden cardiac death (IRR=1.13[0.98–1.30]). A significantly increased rate of sudden cardiac death was present for each of the six frequently prescribed individual antipsychotics (Table 2).

The risk of sudden cardiac death increased with dose for current users of both typical and atypical antipsychotics (Figure 1). For the typical agents, the IRRs increased from 1.31 (0.97–1.77) for low doses to 2.42 (1.91–3.06) for high doses (p<.001, test for dose-response). For the atypical drugs, the IRRs increased from 1.59 (1.03–2.46) for low doses to 2.86 (2.25–3.65) for high doses (p=.015, test for dose-response). There was a dose-response trend for each of the six frequently prescribed individual drugs (Figure 2), which was statistically significant for thioridazine (p=.005) and of borderline significance for risperidone (p=.051). Current users of thioridazine in high doses (≥300mg) had the greatest increased risk, an IRR of 5.05 (3.09–8.27).

In the propensity-score-matched cohort (Table 3), current users of both typical and atypical antipsychotics had increased risk of sudden cardiac death, with respective IRRs of 1.84 (1.50–2.26) and 1.99 (1.61–2.46) and there was a significant dose-response for each class (p<.001, p=.0457, respectively). The IRR for atypical vs typical antipsychotics was 1.08 (0.82–1.43).

We performed several additional analyses to further test the robustness of study findings. To assess the influence of the adverse metabolic effects of chronic antipsychotic use,[12] analysis was restricted to those with less than 365 days of cumulative duration of use. The respective IRRs for the typical and atypical drugs were 1.73 (1.09–2.72, p=.019) and 1.87 (1.29–2.73, p<.001). To assess possible bias from inclusion of persons with antipsychotic use prior to the beginning of followup, which could preferentially eliminate patients susceptible to pro-arrhythmic effects,[33] we analyzed cohort members with no antipsychotic use in the two years preceding t_0. The respective IRRs for current users of typical and atypical antipsychotics were 1.74 (1.14–2.67, p<.001) and 1.86 (1.35–2.57, p<.001). To assess the effects of secular trends in antipsychotic use and incidence of sudden cardiac death, we restricted analysis to 1998–2005; the respective IRRs for current users of typical and atypical antipsychotics were 1.78 (1.35–2.35, p<.001) and 2.03 (1.65–2.50, p<.001).

Discussion

The frequent occurrence of serious movement disorders limited use of the typical antipsychotics.[24] Because atypical antipsychotics are less likely to cause this adverse effect, they have been considered a safer treatment alternative,[34] and thus have rapidly replaced the older drugs in clinical practice. Overall antipsychotic use has increased, with the number of physician office visits related to an antipsychotic prescription nearly doubling between 1998 and 2002.[34]

Although a link between the typical antipsychotics and torsade de pointes/sudden cardiac death has been established,[5,35] this risk was thought to be lower for the atypical drugs.[36] However, the limited data available on the surrogate markers for torsade de pointes—inhibition of the potassium current I_{Kr} and prolongation of QTc--suggest that commonly used atypical drugs have electrophysiological effects that overlap with those of the typical antipsychotics.[1,13] There now are case reports of torsade de pointes for several atypical antipsychotics.[14–16] Our data show that in a large retrospective cohort of adults, current

users of the atypical antipsychotics had a dose-dependent increase in the risk of sudden cardiac death essentially identical to that for the typical agents.

The primary study limitation is the potential for confounding by factors associated with antipsychotic use. For persons with serious mental illness, these include cardiovascular and other somatic disease, concurrent use of other pro-arrhythmic medications, mood disorders, behavioral risk factors including substance abuse, poor self-care and smoking, and other effects of mental illness.[12] Thus, both the study design and analysis included several provisions to manage confounding.

We controlled for an extensive set of cardiovascular disease variables. In the Medicaid population studied, antipsychotic users had slightly lower baseline prevalence of diagnosed cardiovascular disease than did comparable nonusers, reflecting the fact that many nonusers qualified for Medicaid because of somatic illness. The requirement that cohort members have regular use of medical care in each of the two pre-baseline years should reduce bias from under-diagnosis of cardiovascular disease in patients with mental illness. The analysis also controlled for concurrent use of other pro-arrhythmic medications, as well as diagnosed or treated mood disorders.

With regard to behavioral risk factors, the cohort excluded persons with recorded diagnoses of substance abuse or without regular medical care. Although study information on smoking was limited, the analysis controlled for cardiovascular diseases caused by smoking[37] that mediate much of the increased risk of sudden death. Furthermore, a sensitivity analysis (Appendix 1) suggested that residual confounding by smoking had at most a minor effect on relative risk estimates. Although unmeasured behavioral factors may influence study findings, the absence of a significantly increased risk of sudden death among former users of antipsychotics and the marked dose-response are evidence of a drug effect *per se*.

Analysis of the propensity-score-matched cohort provided an additional check as to whether study findings were due to confounding by antipsychotic indication or associated factors. This cohort excluded persons with a baseline diagnosis of schizophrenia or related psychoses, for whom such confounding is of greatest concern, and achieved a comparable distribution of baseline psychiatric comorbidity for antipsychotic users and nonusers. Findings were very similar to those from the primary cohort. However, some relative risk point estimates were slightly, albeit nonsignificantly, lower, which underscores the fact that in this observational study residual confounding cannot be entirely ruled out.

Our study did not assess the mechanisms by which either class of antipsychotics increased risk of sudden cardiac death. Although antipsychotics have chronic adverse cardiovascular effects,[12] the risk of sudden death was elevated in an analysis excluding long-term users, which suggests that acute drug effects are involved. We believe the most plausible explanation is that antipsychotic drugs increase the risk of serious ventricular arrhythmias, probably through blockade of potassium channels and prolongation of cardiac repolarization. However, other mechanisms may be involved, including autonomic effects, inhibition of other ion channels, or other acute cardiotoxicities, such as the myocarditis associated with clozapine use.[38]

In conclusion, current users of both typical and atypical antipsychotics in the study cohort had a similar dose-related increased risk of sudden cardiac death. This suggests that with regard to this adverse effect, the atypical antipsychotics are no safer than the older drugs.

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Appendix 1. Key study variables and additional details for the statistical analysis

1. Key Study Variables

Key study variables are listed in Table A1.1.

Table A1.1

Key Study Variables

A. Variables leading to study exclusion, defined relative to 730 days preceding t_0 unless otherwise specified	
1. Nursing home	Nursing home residence (except <30 days after hospital discharge)
2. Recent hospital stay	Discharge date in 30 days preceding t_0
3. Serious illness	Cancer other than non-melanoma skin cancer, HIV, renal failure, liver disease, respiratory failure, organ transplantation, multiple sclerosis, home oxygen excluding CPAP, or hospice care
4. Drug dependency	Recorded diagnosis of cocaine, opioid, or other recreational drug dependency
B. Dosage equivalents for the study antipsychotics (in parentheses)	
1. Typical	Acetophenazine (60), chlorpromazine (100), chlorprothixene (50), fluphenazine (2), haloperidol (2), loxapine (15), mesoridazine (50), molindone (10), perphenazine (10), pimozide (2), thioridazine (100), thiothixene (5) trifluoperazine (5), triflupromazine (25)
2. Atypical	Aripiprazole (7.5), clozapine (75), olanzapine (5), quetiapine (75), risperidone (2), ziprasidone (60)
C. Death certificate cause of death codes	
1. ICD9	401.9, 402, 410, 411, 412, 413, 414, 425.4, 427.5, 427.1, 427.4, 427.8, 427.9, 429.2, 429.9, 440.9, 798.2, 798.9
2. ICD10	I10, I11.9, I20, I21, I22, I23, I24, I25, I42.8, I42.9, I46, I47, I47.2, I49.0, I49.8, I49.9, I51.6, I51.9, I70.9, R96.1, and R98
D. Baseline cardiovascular/somatic covariates used for calculation of cardiovascular risk score	
1. Medications	Anti-arrhythmics, angiotensin converting-enzyme inhibitors and angiotensin receptor blockers, anticoagulants, antidiabetics, aspirin, non-aspirin anti-platelet agents, β-blockers, calcium-channel blockers, digoxin and other inotropic agents, statins, other lipid-lowering agents, loop diuretics, thiazide and other diuretics, nitrates, other antihypertensives, and pentoxifylline/related drugs
2. Diagnoses	Prior revascularization, myocardial infarction or other coronary heart disease, heart failure, conduction disorder or arrhythmia, valve disorders, cerebrovascular disease, peripheral vascular disease, hypertension, hyperlipidemia, renal failure, obesity, smoking-related illnesses, and chronic obstructive pulmonary disease
3. Medical care use	Frequency prior inpatient admissions, emergency department visits, and outpatient encounters
4. Compliance index	Medications of interest were statins, beta-blockers, low-dose aspirin, diuretics, calcium-channel blockers, angiotensin-converting enzyme inhibitors, antiotensin 2 receptor blockers, and oral hypglycemics. For persons who neither started or stopped in the 730 days prior to baseline, we counted the number of these medications for which filled days of supply was less than 80% of the interval between the first and last day of supply.
E. Baseline variables in regression model, defined as of t_0 and the preceding 730 days	
1. Demographics	Age, gender, race, urban residence
2. Medicaid enrollment	Disabled indicates those receiving benefits because of disability qualifying for SSI payments; uninsured indicates those ordinarily would not qualify for Medicaid due to elevated income or lack of other qualifying criteria (such as dependent children or disability). In our experience, these enrollees are healthier than others.
2. Cohort entry year	Calendar year
3. Cardiovascular risk score	See D above. After controlling for age and sex, there was more than a 6-fold difference in the rate of sudden cardiac death between the highest and lowest quantiles of the risk score.
4. Psychiatric comorbidity	Schizophrenia and other psychoses, mood disorders (bipolar disorders, major depression, other mood disorders), organic mental illness, dementia, alcohol or prescription drug dependence, history of convulsions or seizure disorder, and psychiatric health care utilization.
F. Time-dependent covariates in regression model, defined for each day from t_0 through the end of followup	

1. Time since t_0	Interval between t_0 and the day of followup classified
2. Antipsychotic use	Nonuser, former user, current user multiple drugs, current user single typical, current user single atypical. Each person-day of followup was placed into one of these mutually exclusive categories. A single person could contribute person-time to each of these categories.
3. Hospital, psych	None prior 365 days, prior 91–365 days, prior 1–90 days
4. Hospital, any	None prior 365 days, prior 91–365 days, prior 1–90 days
5. ED visit, any	None, prior 91–365 days, prior 31–90 days, prior 1–30 days

2. Calculation of propensity score

The propensity score, defined as the predicted probability of being an antipsychotic user, was calculated from a logistic regression model in the primary cohort that included demographic characteristics, cardiovascular risk score, and prior psychiatric diagnoses/ medications.

3. Adjustment for antipsychotic dose

The doses were systematically different for the two classes of antipsychotics as well as for individual antipsychotics. For example, 54% of thioridazine current use was for low dose (<100mg chlorpromazine equivalents), whereas only 16% of olanzapine current use was for low dose. Thus, a direct comparison of the two drugs would confound dose (which is very important) with individual drug. For this reason, we performed a dose adjustment for calculation of class- and individual drug-specific IRRs. We first tabulated the overall distribution of current use by dose for all antipsychotic use. Approximately 20% was for low dose, 40% for moderate dose, and 40% for high dose. Then, for each individual drug we calculated the dose-specific IRRs (seen in Figure 2). The log of the dose-adjusted IRR was then calculated from the following contrast: $.2*\beta1 + .4*\beta2 + .4*\beta3 - \beta4$, where $\beta1$, $\beta2$, $\beta3$ are the estimated log IRRs for low, moderate, and high dose respectively and $\beta4$ is that for the nonuser person-time.

4. Supplemental analyses

In addition to the primary and propensity score analyses reported in the paper, we performed several supplemental analyses to test the sensitivity of our findings to certain key assumptions. These are listed in Table A1.2. None of these had findings that differed materially from the primary analysis and thus suggest our findings are not sensitive to these assumptions.

Table A1.2

Supplemental Analyses

Assumption	**Supplemental Analysis**
1. Independence for persons in cohort multiple times	Restricted cohort to allow only one entry per person.
2. Confounding by additional baseline variables	Ran models that included history of suicide attempts and baseline use of medications for psychiatric or neurological disorders (antidepressants, benzodiazepines, mood stabilizers, other psychotropic medications, anticonvulsants, and narcotic analgesics.
3. Confounding by time-dependent use of proarrythmic drugs	Ran models with time-dependent covariates for cyclic antidepressants,[1] erythromycin,[2] methadone,3 cisapride,4 terfenadine,5 astemizole,[6] anti-

Assumption	Supplemental Analysis
	arrhythmic medications that can cause torsade de pointes (disopyramide, procainamide, amiodarone, sotalol, quinidine),[7,8] other medications thought to cause torsade de pointes,[9] or prolong QT.[10,11]
4. Confounded by other changes in comorbidity during followup	Included variables important in cardiovascular risk score as time dependent covariates. These included recent psychiatric/neurologic diagnoses (schizophrenia, substance abuse, organic disorder, seizure disorder, dementia, psychiatric ED visit as well as recent evidence of worsening cardiovascular disease (new prescription for ACE inhibitor, digoxin, insulin, or loop diuretic, new diagnosis of coronary heart disease or heart failure, coronary artery revasularization).
5. No bias caused by using controls for typicals in atypical analysis and vice-versa	Performed separate analyses for each antipsychotic drug class, limiting controls to those matched for that class.
6. Cardiovascular risk score can be estimated in nonusers	Performed analysis with risk score estimated using the entire cohort.
7. Dependence not induced by matching on t_0	Ran analysis that estimated variance assuming a possible correlation between members of a matched set.

5. Sensitivity Analysis of Effect of Confounding by Smoking

The information provided by study files on smoking is incomplete, as it relies upon a recorded diagnosis. Given that smoking increases the risk of sudden cardiac death and persons with mental illness have increased prevalence of smoking, there is thus the potential for uncontrolled confounding. The following sensitivity analysis estimates the magnitude of such potential confounding. It does so using the *confounding risk ratio* (see Breslow and Day12) which quantifies the degree of confounding due to an unmeasured variable. The confounding risk ratio is calculated as:

$$\omega=\frac{RR_cQ_1+(1-Q_1)}{RR_cQ_0+(1-Q_0)} \quad Breslow\&Day, \qquad \text{Eq 3.1}$$

RR_c = Risk ratio (or rate ratio) for confounder

Q_1 = confounder prevalence in user group

Q_0 = confounder prevalence in nonuser group

Each of these quantities can be estimated for the study cohort, as described below.

a. Increased risk conferred by smoking: RR_c

RRc is the relative risk conferred by smoking. Several studies suggest that current smokers have a two-fold increased risk of sudden cardiac death.[13–23]

b. Prevalence of smoking in Tennessee Medicaid: Q_0

The estimated prevalence of current smoking among all persons in Tennessee was 27% in 1997 (*Prevalence of Tobacco Use in Tennessee, 1997–2007*. Tennessee Department of Health, 2008). The prevalence of smoking in adult Medicaid enrollees is 50% higher than that of the general population (MMWR 2001; 50(44):979–982). Thus, the estimated prevalence of current smoking among antipsychotic nonusers in the cohort is 40%.

c. Prevalence of smoking in persons with serious mental illness: Q_1

The National Comorbidity Survey reported the prevalence of current smoking in 1990–1991 to be 45% in adults with schizophrenia or major depression and 61% in adults with bipolar disorders.[24] A study of newly diagnosed schizophrenics admitted to a psychiatric hospital between 1989 and 1995[25] reported a 52% prevalence of current smoking at the time of admission. The highest figure, that of 61%, is used for the sensitivity analysis.

d. Calculations

Given these assumptions, the estimate of the confounding risk ratio is 1.15. That is, the observed relative risk estimate is 15% greater than the relative risk completely adjusted for the effect of current smoking. This is likely to be an overestimate for two reasons. First, smokers with a recorded diagnosis are identified in the study files, which would reduce misclassification. Second, some of the effects of smoking are mediated by factors that are measured in our study. For example, smokers have greater prevalence of prior (eg, history of AMI) and current (eg, angina) cardiovascular disease, which would be adjusted for in our analysis.

6. Supplemental Analysis: Atypical vs Typical Antipsychotics in Persons with Schizophrenia or Related Psychosis

To quantify the extent to which the risk of sudden cardiac death varied between the two classes of antipsychotics in patients with schizophrenia-related psychoses, we performed an analysis that restricted the primary cohort to persons with a baseline diagnosis of schizophrenia or related psychoses. The analysis compared current use of atypical versus typical antipsychotics. Nonusers were not the reference category because treatment of these serious psychoses with antipsychotics is the standard of practice. The resultant IRR was 1.24 (0.87–1.77).

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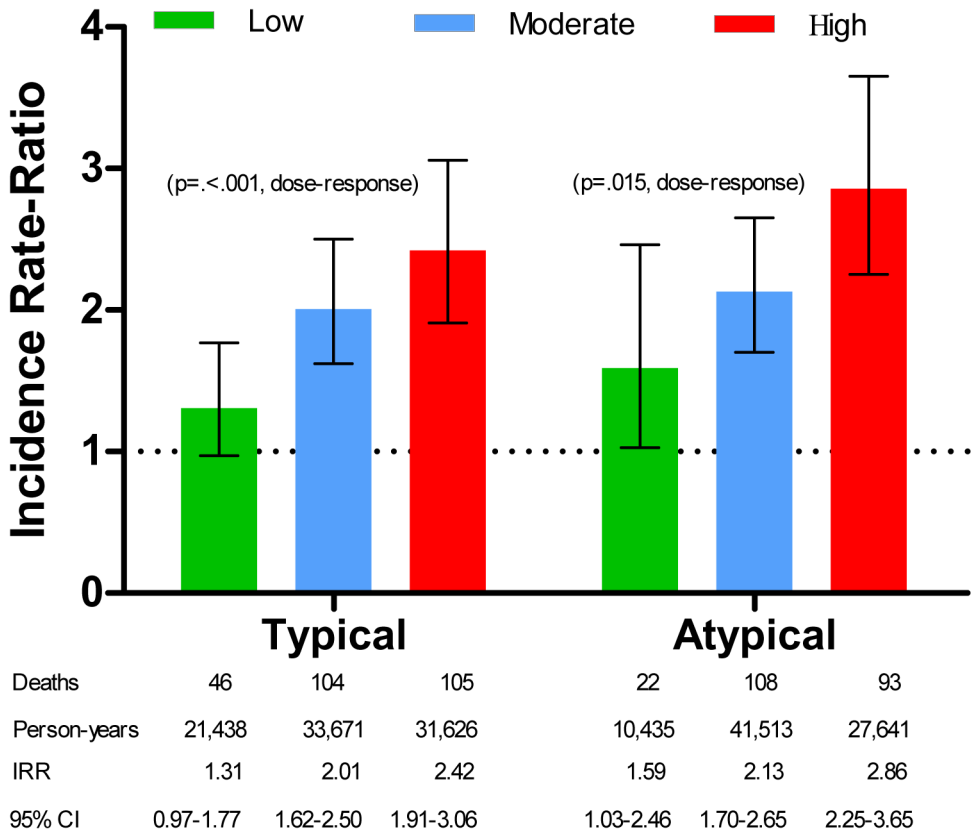

Figure 1.
Adjusted incidence rate-ratio for sudden cardiac death among current users of antipsychotics, according to antipsychotic type and dose (chlorpromazine equivalents: low, <100mg; moderate, 100mg–299mg; high, ≥300mg). The reference category is that of nonusers of any antipsychotic drug. Vertical bars denote 95% confidence intervals.

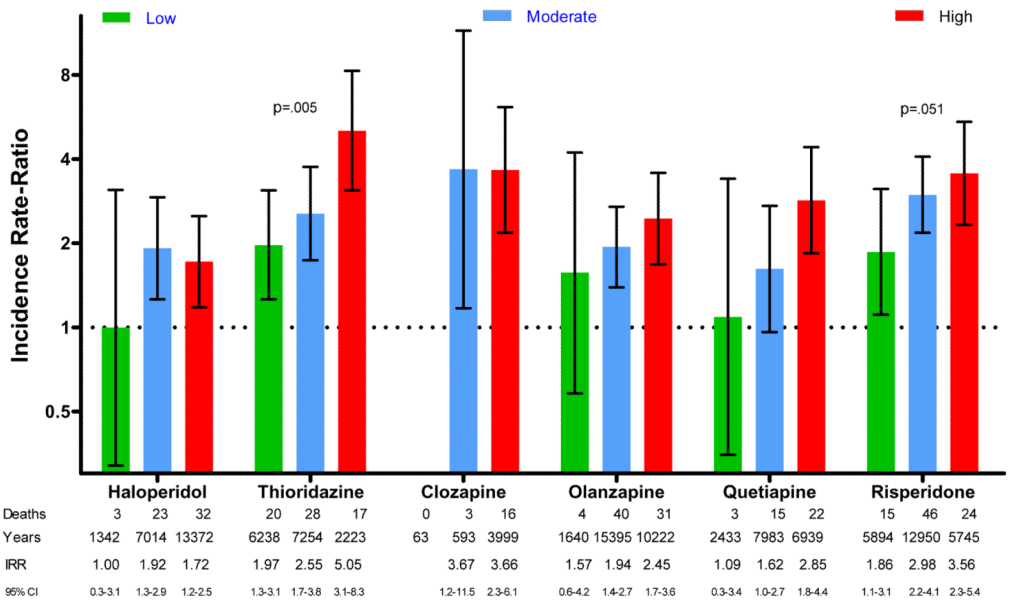

Figure 2.

Adjusted incidence rate-ratio for sudden cardiac death among current users of six frequently prescribed individual antipsychotic drugs, according to dose(chlorpromazine equivalents: low, <100mg; moderate, 100mg–299mg; high, ≥300mg). The reference category is that of nonusers of any antipsychotic drug. Vertical bars denote 95% confidence intervals.

Table 1

Baseline characteristics* of cohort members according to antipsychotic use status at cohort entry.

	Primary Cohort		Propensity-Score-Matched Cohort Ex-cluding Schizophrenia/Related Psychoses	
Antipsychotic Use Status:	**Not User**	**Current User**	**Not User**	**Current User**
Cohort members, N	186,600	93,300	116,069	67,824
Demographic characteristics and somatic comorbidity				
Year of cohort entry, mean (std)	1998.4 (5.0)	1998.4 (5.0)	1998.5 (4.7)	1999.0 (4.8)
Study followup, years, median (iqr)	2.2 (4.0)	2.9 (4.9)	2.4 (4.1)	2.6 (4.1)
Age in years, mean (std)	45.7 (11.8)	45.7 (11.8)	46.4 (12.0)	46.3 (11.8)
Male, %	34.8%	34.8%	32.1%	30.3%
Race non-white, %	30.0%	28.5%	25.8%	24.2%
Urban residence, %	56.6%	57.5%	53.3%	54.2%
Medicaid enrollment due to disability, %	37.4%	62.9%	60.7%	57.6%
Cardiovascular risk score, mean (std)	9.6 (5.8)	9.2 (5.8)	9.5 (5.8)	9.4 (5.7)
Propensity score, mean	n/a	n/a	0.51	0.51
*Psychiatric characteristics***				
Antipsychotic dose moderate or high****, %	n/a	69.0%	n/a	62.0%
Schizophrenia, %	1.4%	21.3%	0.0%	0.0%
Other psychosis, %	1.0%	9.7%	0.0%	0.0%
Bipolar disorder, %	2.6%	18.2%	14.2%	17.1%
Major depression or other mood disorder, %	17.2%	48.4%	51.3%	52.6%
Dementia, %	0.6%	3.1%	2.9%	2.9%
Alcohol or prescription drug dependency, %	4.9%	8.3%	9.6%	7.9%
History of suicide attempt, %	1.2%	3.5%	3.5%	3.5%
Prior psychiatric hospital stay, %	3.8%	21.7%	15.0%	14.7%
Lithium, %	1.2%	9.3%	6.1%	7.6%
Mood stabilizer, %	8.3%	24.0%	22.2%	24.4%
Antidepressant, %	41.5%	73.0%	76.3%	79.4%
Benzodiazepine, %	34.1%	56.0%	58.8%	61.6%

*Factors defined from medical care encounters reflect any encounter within the 730 days preceding t_0, except for cardiovascular risk score and antipsychotic dose, which are those at the start of cohort followup. ‘std’ = standard deviation, ‘iqr’ = interquartile range.

*** A cohort member may have multiple diagnoses present.

**** Doses equivalent to ≥100mg chlorpromazine: cutpoints for thioridazine, 100mg; haloperidol, 2mg; clozapine, 75mg; olanzapine, 5mg; quetiapine, 75mg; risperidone, 2 mg. See Appendix 1 for other drugs.

Table 2

Adjusted incidence rate-ratios for sudden cardiac death according to antipsychotic current use status* and frequently prescribed individual drugs.

	Person-years	Sudden Deaths	IRR	95% CI	*p*-value
Nonuser	624,591	895	1	*Reference*	
Former user	189,981	311	1.13	0.98–1.30	.0822
Current, typical**	86,735	255	2.00	1.69–2.35	<.0001
Haloperidol	21,728	58	1.61	1.16–2.24	0.0049
Thioridazine	15,715	65	3.19	2.41–4.21	<.0001
Current, atypical**	79,589	223	2.27	1.89–2.73	<.0001
Clozapine	4,654	19	3.67	1.94–6.94	<.0001
Olanzapine	27,257	75	2.04	1.52–2.74	<.0001
Quetiapine	17,355	40	1.88	1.30–2.71	0.0008
Risperidone	24,589	85	2.91	2.26–3.76	<.0001

*Excludes 45,381 person-years and134 deaths for indeterminate users of antipsychotics as well as15,883 person-years and 52 deaths for concurrent users of multiple antipsychotics.

**Adjusted for dose, see Appendix 1.

Table 3

Propensity-score matched cohort that excludes persons with baseline diagnosis of schizophrenia or related psychoses. Adjusted incidence rate-ratios for sudden cardiac death according to antipsychotic current use status*, dose** and frequently prescribed individual drugs.

	Person-years	Sudden Deaths	IRR	95% CI	*p*-value
Nonuser	390,072	705		*Reference*	
Former user	159,415	243	0.93	0.80–1.07	.3031
Current, typical***	42,231	125	1.84	1.50–2.26	<.0001
Haloperidol	7,189	21	1.39	0.89–2.19	.1501
Thioridazine	9,547	41	3.05	2.15–4.33	<.0001
Current, atypical***	45,853	116	1.99	1.61–2.46	<.0001
Clozapine	418	4	8.06	2.58–25.23	.0003
Olanzapine	15,076	42	1.99	1.41–2.79	<.0001
Quetiapine	13,730	26	1.49	0.98–2.27	.0618
Risperidone	13,047	41	2.49	1.72–3.62	<.0001
Current typical according to dose					
Low Dose	16,293	36	1.13	0.81–1.59	.4641
Moderate Dose	18,203	55	1.59	1.20–2.11	.0011
High Dose	7,735	34	2.70	1.90–3.84	<.0001
Current atypical according to dose					
Low Dose	8,237	18	1.52	0.94–2.44	.0847
Moderate Dose	25,694	58	1.68	1.28–2.22	.0002
High Dose	11,921	40	2.69	1.93–3.73	<.0001

* Excludes 27,775 person-years and 75 deaths for indeterminate users of antipsychotics as well as 5,119 person-years and 13 deaths for concurrent users of multiple antipsychotics.

** Dose calculated as chlorpromazine equivalents: low, <100mg; moderate, 100mg–299mg; high, ≥300mg. See Appendix 1 for equivalents for study drugs.

*** Adjusted for dose, see Appendix 1.

Appendix 2

Baseline characteristics* according to antipsychotic type and use of frequently prescribed individual drugs.

	All Typical**	Haloperidol	Thioridazine	All Atypical**	Clozapine	Olanzapine	Quetiapine	Risperidone
Cohort members, N	44,218	9,287	7,711	46,089	681	16,687	13,366	12,144
Demographic characteristics and somatic comorbidity								
Year of cohort entry, mean (std)	1994.4 (3.9)	1994.6 (4.0)	1993.9 (3.6)	2002.1 (2.2)	1997.5 (3.5)	2001.8 (1.9)	2003.0 (1.6)	2001.4 (2.5)
Study followup, years, median (iqr)	5.5 (7.3)	5.0 (7.4)	5.8 (7.3)	1.9 (2.5)	5.2 (6.2)	2.2 (2.6)	1.5 (2.0)	2.3 (3.1)
Age in years, mean (std)	47.1 (12.6)	47.8 (13.5)	47.6 (12.9)	44.5 (10.8)	39.5 (10.0)	45.0 (11.0)	44.5 (10.4)	44.7 (11.1)
Male, %	35.2%	43.6%	35.9%	33.5%	62.0%	35.9%	28.7%	34.7%
Race non-white, %	33.2%	43.2%	26.2%	23.6%	23.9%	22.0%	20.2%	28.7%
Urban residence, %	57.6%	62.9%	55.7%	57.2%	74.0%	54.3%	55.2%	60.4%
Medicaid enrollment due to disability, %	73.3%	78.1%	76.4%	52.4%	77.8%	49.1%	50.5%	56.6%
Cardiovascular risk score, mean (std)	9.1 (5.7)	9.4 (5.6)	8.7 (5.7)	9.4 (5.9)	6.6 (5.6)	9.4 (5.8)	9.7 (5.9)	9.4 (5.8)
*Psychiatric characteristics***								
Antipsychotic dose moderate or high****, %	61.8%	88.6%	46.1%	73.9%	97.7%	84.4%	76.7%	51.4%
Schizophrenia, %	27.1%	41.3%	19.2%	13.5%	89.1%	12.9%	5.9%	17.8%
Other psychosis, %	9.8%	16.9%	8.3%	8.8%	18.4%	8.3%	5.2%	12.7%
Bipolar disorder, %	12.1%	13.5%	11.3%	23.3%	20.9%	21.5%	23.0%	23.4%
Major depression or other mood disorder, %	36.3%	29.5%	37.7%	60.2%	31.6%	53.1%	67.8%	62.0%
Dementia, %	2.9%	6.0%	3.1%	3.3%	2.6%	3.0%	3.0%	4.3%
Alcohol or prescription drug dependency, %	7.3%	8.0%	7.3%	9.2%	7.3%	8.8%	10.4%	8.8%
History of suicide attempt, %	1.9%	1.8%	1.9%	5.0%	3.5%	4.3%	6.1%	4.4%
Prior psychiatric hospital stay, %	19.2%	25.0%	16.9%	22.6%	44.6%	19.8%	19.9%	27.6%
Lithium, %	10.5%	11.5%	9.8%	7.9%	18.5%	7.7%	6.4%	9.0%
Mood stabilizer, %	11.7%	12.7%	11.8%	35.0%	30.5%	30.3%	39.7%	33.2%
Antidepressant, %	60.5%	46.3%	55.7%	85.2%	51.2%	83.6%	90.9%	82.4%
Benzodiazepine, %	45.6%	37.0%	46.8%	66.1%	44.3%	65.2%	74.0%	60.1%

* Factors defined from medical care encounters reflect any encounter within the 730 days preceding t_0, except for cardiovascular risk score and antipsychotic dose, which are those at the start of cohort followup. 'std' = standard deviation, 'iqr' = interquartile range.

** Excludes 2993 baseline users of multiple antipsychotics.

*** A cohort member may have multiple diagnoses present.

**** Doses equivalent to ≥100mg chlorpromazine: cutpoints for thioridazine, 100mg; haloperidol, 2mg; clozapine, 75mg; olanzapine, 5mg; quetiapine, 75mg; risperidone, 2 mg. See Appendix 1 for other drugs.