ORIGINAL ARTICLE

Antipsychotics and the Risk of Sudden Cardiac Death

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Background: Case reports link antipsychotic drugs with sudden cardiac deaths, which is consistent with dose-related electrophysiologic effects. Because this association has not been confirmed in controlled studies, we conducted a retrospective cohort study in Tennessee Medicaid enrollees, which included many antipsychotic users; there were also computer files describing medication use and comorbidity. The study was conducted before the introduction of risperidone and, thus, did not include the newer atypical agents.

Methods: The cohort included 481744 persons with 1282996 person-years of follow-up. This included 26749 person-years for current moderate-dose antipsychotic use (>100-mg thioridazine equivalents), 31864 person-years for current low-dose antipsychotic use, 37881 person-years for use in the past year only, and 1186501 person-years for no use. The cohort had 1487 confirmed sudden cardiac deaths; from these, we calculated multivariate rate ratios adjusted for potential confounding factors.

Results: When current moderate-dose antipsychotic use was compared with nonuse, the multivariate rate ratio was 2.39 (95% confidence interval, 1.77-3.22; $P<.001$). This was greater than that for current low-dose (rate ratio, 1.30; 95% confidence interval, 0.98-1.72; $P=.003$) and former (rate ratio, 1.20; 95% confidence interval, 0.91-1.58; $P<.001$) use. Among cohort members with severe cardiovascular disease, current moderate-dose users had a 3.53-fold (95% confidence interval, 1.66-7.51) increased rate relative to comparable nonusers ($P<.001$), resulting in 367 additional deaths per 10000 person-years of follow-up.

Conclusions: Patients prescribed moderate doses of antipsychotics had large relative and absolute increases in the risk of sudden cardiac death. Although the study data cannot demonstrate causality, they suggest that the potential adverse cardiac effects of antipsychotics should be considered in clinical practice, particularly for patients with cardiovascular disease.

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ANTIPSYCHOTIC AGENTS, the primary treatment for schizophrenia and other psychoses,[1] long have been suspected to increase the risk of serious ventricular arrhythmias and, thus, sudden cardiac death.[2,3] The literature includes numerous case reports of torsades de pointes and sudden death in patients taking thioridazine,[4-6] haloperidol,[7,8] risperidone,[9,10] and other antipsychotics.[3] Users of antipsychotic medications are overrepresented in registries of sudden deaths.[11] Cohort studies[12-15] of schizophrenic patients have reported a persistent excess of cardiovascular disease–related mortality. Several[3,16] have speculated that this is, at least in part, attributable to antipsychotic use.

An increased risk of sudden cardiac death is consistent with the dose-related effects of antipsychotic medications on cardiac electrophysiologic properties. Haloperidol and sertindole block repolarizing potassium currents in vitro,[17,18] hypothesized to be the mechanism underlying drug-induced torsades de pointes.[2] In an isolated feline heart model, haloperidol, risperidone, sertindole, clozapine, and olanzapine produced dose-dependent prolongation of the QT interval.[16] In isolated spontaneously beating guinea pig Purkinje fibers, chlorpromazine and thioridazine induce early "after depolarizations,"[19] a hypothesized trigger for torsades de pointes.[16] Approximately 25% of patients taking phenothiazines and other antipsychotics have electrocardiographic abnormalities, including prolongation of the QT interval,[3,20] which is thought to increase the risk of serious ventricular arrhythmias.

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Although these data suggest that antipsychotic medications might increase the risk of sudden cardiac death, this question has not been addressed in controlled epidemiologic studies. Thus, we con-

PARTICIPANTS AND METHODS

STUDY DESIGN AND SOURCES OF DATA

The cohort included Tennessee Medicaid enrollees from January 1, 1988, through December 31, 1993. An enrollment file indicated each person's periods of enrollment and demographic characteristics and has been linked with Tennessee death certificates,[22] which identify the date and cause of death. Encounter files record prescriptions filled at the pharmacy, outpatient visits, inpatient admissions, and nursing home stays. These data were used to identify the study cohort, to determine exposure to study drugs, to identify potential cases of sudden cardiac death, and to classify cohort members according to preexisting cardiovascular and other disease.

COHORT AND FOLLOW-UP

Cohort members had 365 days or more of continuous enrollment during the study period (to assure availability of Medicaid encounter data); were aged 15 to 84 years; were not in a long-term care facility (except those in such a facility for mental conditions) in the past 365 days; and had no evidence of a life-threatening noncardiac illness (chronic renal failure, chronic liver disease, metastatic or other cancer with a poor prognosis, severe chronic obstructive pulmonary disease, or the human immunodeficiency virus infection). Study follow-up began on January 1, 1988, or at a later time when the criteria for cohort membership were met. Follow-up ended on the first of the following: December 31, 1993; the date of death; or whenever the criteria for cohort membership no longer were met. Person-time during hospitalization and the 30 days following hospital discharge was not included in the follow-up, primarily because medications dispensed in the hospital are not included in Medicaid files.

The study cohort included 481744 persons with 1282996 person-years of follow-up. Of the study cohort, 54% were aged 15 through 44 years, 21% were aged 45 through 64 years, and 25% were aged 65 years or older. Females made up 70% of the cohort (reflecting Medicaid demographics[21]), and 59% of the cohort was white.

ANTIPSYCHOTIC EXPOSURE

Antipsychotics and other medications were identified from computerized Medicaid pharmacy files, which included drug, dose, and days of supply dispensed. Automated pharmacy records are an excellent source of medication data because these records are not subject to information bias[23-25] and have concordance of better than 90% with patient self-reports of medication use.[25-28] The residual misclassification is conservative and, thus, would bias against detecting a drug effect.[23,29]

The study drugs (with equivalents to 100 mg of thioridazine[1]) were haloperidol (2 mg), fluphenazine hydrochloride (2 mg), thiothixene (5 mg), trifluoperazine hydrochloride (5 mg), perphenazine (10 mg), molindone hydrochloride (10 mg), loxapine (15 mg), triflupromazine (25 mg), mesoridazine (50 mg), chlorprothixene (50 mg), clozapine (75 mg), chlorpromazine (100 mg), and thioridazine (100 mg).

For each member of the cohort, every person-day of follow-up was classified according to antipsychotic use. *Current use* included the time from the filling of the prescription through the end of the days of supply (allowing up to 7 additional days). *Former use* included cohort members who were not current users but who had had some use in the past 365 days. *Nonuse of antipsychotics* was defined as no antipsychotic use in the past 365 days.

Clinical use of antipsychotics encompasses at least a 20-fold dose range.[1] Animal[16,19] and human[3,20] data indicate that the potential proarrhythmic effects are dose related. Thus, all current use was further classified a priori as low or *moderate dose*, with the latter defined as greater than 100 mg of thioridazine or its equivalent, ie, doses at which electrocardiographic abnormalities are most frequent.[3]

Study follow-up thus included 58613 person-years of current antipsychotic use and 37881 person-years for use in the past year only. Current use consisted of 31864 person-years (54%) for doses of 100 mg or less and 26749 person-years (46%) for doses greater than 100 mg. Individual antipsychotics included haloperidol (21%), thioridazine (20%), perphenazine (17%), thiothixene (9%), chlorpromazine (7%), other individual drugs (22%), and multiple drugs (4%) (the percentage of current use is given in parentheses). Clozapine accounted for less than 1% of antipsychotic use.

SUDDEN CARDIAC DEATH

The study outcome was *sudden cardiac death* occurring in a community setting.[30-33] This was defined as a sudden pulseless condition (arrest) that was fatal (within 48 hours) and was consistent with a ventricular tachyarrhythmia occurring in the absence of a known noncardiac condition as the proximate cause of the death.[32] *Probable sudden cardiac deaths* were defined as a witnessed sudden collapse with no pulse and respiration (or agonal), an unwitnessed collapse in a person known to be alive within the previous hour, ventricular fibrillation or tachycardia before the start of cardiopulmonary resuscitation, or autopsy findings consistent with a ventricular tachyarrhythmia. *Possible sudden cardiac deaths* were those in which no arrest was witnessed and the person was found unconscious or dead, but with evidence that the subject had been alive in the preceding 24 hours. Both definitions excluded deaths from arrests that occurred in a hospital or other institutional

ducted a large retrospective cohort study of the risk of sudden cardiac death among antipsychotic users. The study was conducted in a Medicaid population, which included many antipsychotic users; there were also computerized files from which study data could be obtained.[21] The study was conducted before the introduction of risperidone, olanzapine, and quetiapine fumarate and, thus, did not include the newer atypical agents.

RESULTS

The characteristics of the cohort varied according to use and dose of antipsychotic (**Table 1**). Current users of doses greater than 100 mg of thioridazine or its equivalent were younger and more likely to be male than other cohort members. After standardization for age and sex,

setting, that were not sudden, or that had documentation suggesting an extrinsic (eg, substance overdose) or noncardiac (eg, pneumonia) cause or a different cardiac cause (eg, heart failure or bradyarrhythmia).

Computerized data were screened for all cohort deaths to identify potential cases. We began with deaths potentially consistent with sudden cardiac death: those associated with hypertensive heart disease (excluding malignant hypertension), ischemic heart disease (not aneurysms), cardiomyopathy, conduction disorders, dysrhythmias, myocarditis, cardiomegaly, heart failure, uncomplicated diabetes, atherosclerotic heart disease, or unspecified heart disease; sudden death; or death from an unknown cause. We then further excluded those deaths the computerized records of terminal medical care indicated were likely to have occurred in the hospital or to be of either noncardiac cause or cardiac cause inconsistent with a ventricular tachyarrhythmia.

For the potential cases, study nurses reviewed the records of all medical care encounters around the time of death, including from the hospital or emergency department (when present), emergency medical services runs, and medical examiner reports. A study physician (S.M.), masked with regard to medication use, then classified each reviewed death; questionable cases were reviewed by a similarly masked cardiac electrophysiologist (K.T.M.).

Cohort members had 4404 deaths during follow-up that met the computerized screening criteria. Of these, 614 (14%) occurred at home with no record of a terminal medical encounter, and we were unable to obtain records for 822 (19%) of the deaths. Of the 2968 deaths for which records were obtained, we excluded 174 that were for arrests that occurred in hospitals or other institutions, 505 that were due to other causes, and 802 for which the records lacked information on the time or circumstances of death or the time the subject was last alive. The remaining 1487 deaths (701 probable and 786 possible) constitute the study cases of sudden cardiac death.

DATA ANALYSIS

Rates standardized to the age and sex distribution of the cohort were calculated by the direct method. Multivariate rate ratios and 95% confidence intervals (CIs) were calculated from Poisson regression models. These models controlled for potential confounders that included calendar year, demographic characteristics (age, sex, and race), *noncardiovascular illness* (defined as a hospital admission, except for mental illness), and cardiovascular disease. The comorbidity measures were calculated for each person-day of follow-up from medical care encounters in the preceding 365 days.

Cardiovascular disease was defined from hospital admissions, emergency department visits, and physician visits with cardiovascular diagnoses and from use of medications to treat cardiovascular disease or predisposing conditions (digitalis glycosides, loop diuretics, thiazide diuretics, antiarrhythmic agents, angiotensin-converting enzyme inhibitors, β-blockers, calcium channel blockers, hypoglycemic agents, lipid-lowering drugs, and nitrates). A summary cardiovascular risk score was created from regression models of the effect of these factors on rates of sudden cardiac death in nonusers of antipsychotics, where the regression coefficients determined the weights given to each factor. As results thus obtained were virtually identical to those from more complex models with detailed terms for cardiovascular disease, the summary score was used to control for cardiovascular disease. Models included a term for the interaction between age and cardiovascular disease, as the effect of such disease on the risk of sudden cardiac death was substantially more pronounced at younger ages.

To describe how diagnosed cardiovascular disease varied with antipsychotic use and to determine if this modified the effect of antipsychotic drugs, we used the summary risk score to define 4 disease categories. The first included the substantial fraction of the cohort that had none and, thus, had the lowest possible value for the risk score. For members of the cohort with diagnosed disease, the risk score defined approximate tertiles (of the cases) of severity, labeled as mild, moderate, or severe cardiovascular disease.

For example, patients receiving only a thiazide diuretic, only digoxin, or digoxin and a loop diuretic were classified as having mild, moderate, and severe cardiovascular disease, respectively. For cohort members with none, mild, moderate, and severe cardiovascular disease, the respective age- and sex-standardized rates of sudden cardiac death were 6.2, 10.0, 22.5, and 147.2 deaths per 10000 person-years.

Other indicators of illness considered, but not included in the models because they did not alter rate ratio estimates for antipsychotic use, were use of anticonvulsants, anticoagulants, oral corticosteroids, bronchodilators, antidepressants, benzodiazepines, and lithium.

We conducted a secondary analysis to assess the magnitude of possible confounding by smoking, which was not available in the study data. We identified a group of patients known to have a high prevalence of smoking: those with chronic respiratory diseases caused by smoking (diagnoses for chronic bronchitis or emphysema).[34-36] We then calculated the relative risk of sudden cardiac death for these patients, which indicated how well the cardiovascular disease risk score controlled for the effect of smoking.

All statistical analyses were performed with SAS statistical software, version 6.12 (SAS Institute Inc, Cary, NC). All *P* values are for 2-sided tests. Statistical significance was defined by an α level of .05.

moderate-dose current users had fewer medications for cardiovascular illness and fewer cardiovascular disease–related hospitalizations or emergency department visits. Thus, they had slightly lower summary cardiovascular disease illness scores: 9.1% had moderate or severe cardiovascular disease compared with 12.7% of nonusers. Current users of moderate-dose antipsychotics also had lower rates of hospitalization for other medical illnesses. In contrast, former users of antipsychotics had a greater baseline prevalence of cardiovascular illness, smoking-related respiratory disease, and other serious disease.

Cohort members had 1487 sudden cardiac deaths, or 11.6 deaths per 10000 person-years of follow-up. The risk of sudden cardiac death increased with age (rates of 1.9, 18.7, and 26.6 per 10000 person-years for persons

Table 1. Characteristics of the Cohort, by Antipsychotic Use Status*

Characteristic	Antipsychotic Use			
			Current Use†	
	Nonuser	Past Year Only	≤100 mg	>100 mg
Person-years of follow-up	1 186 501	37 881	31 864	26 749
Age group, y				
15-44	54.6	53.2	39.0	60.2
45-64	19.8	28.9	36.0	33.2
65-84	25.6	18.0	25.0	6.6
Female sex	70.5	65.5	67.4	52.8
White race	58.2	66.7	71.5	55.3
Cardiovascular medications‡				
Insulin or oral hypoglycemic agents	7.2	9.2	9.6	8.0
Digoxin	4.9	6.3	5.5	3.5
Loop diuretics	7.4	10.1	8.4	5.7
Thiazide diuretics	15.2	18.4	18.0	12.3
Nitrates	5.6	6.9	5.6	3.3
ACE inhibitors	6.5	8.1	7.0	5.0
β-Blockers	6.6	10.7	10.2	6.9
Calcium channel blockers	6.9	8.7	6.9	5.0
Cardiovascular hospitalization or emergency department visit‡	2.6	4.3	2.6	2.1
Summary cardiovascular disease score‡§				
None	65.6	54.5	56.0	65.4
Mild	21.6	29.5	30.5	25.5
Moderate	10.5	13.2	11.6	8.1
Severe	2.2	2.9	1.8	1.0
Other medical hospital admission‡	12.3	21.2	14.4	11.3
Smoking-related respiratory illness‡	1.5	2.5	2.1	1.6

*Data are given as the percentage of the cohort unless otherwise indicated. ACE indicates angiotensin-converting enzyme.
†The dose is in thioridazine equivalents (see the "Antipsychotic Exposure" subsection of the "Participants and Methods" section).
‡Standardized by the direct method to the age and sex distribution of the entire cohort.
§Defined from diagnosed or treated cardiovascular disease, including medications (digitalis glycosides, loop diuretics, thiazide diuretics, antiarrhythmic agents, ACE inhibitors, β-blockers, calcium channel blockers, hypoglycemic agents, lipid-lowering drugs, and nitrates), outpatient encounters, or hospitalizations, using regression models of the effect of these factors on rates of sudden cardiac death in nonusers of antipsychotics. The *none* category includes the substantial fraction of the cohort with no such disease; *mild*, *moderate*, or *severe* cardiovascular disease define approximate tertiles for the remaining cases. For example, patients receiving only a thiazide diuretic, only digoxin, or digoxin and a loop diuretic were classified as having mild, moderate, and severe cardiovascular disease, respectively. For cohort members with none, mild, moderate, and severe cardiovascular disease, the respective age- and sex-standardized rates of sudden cardiac death were 6.2, 10.0, 22.5, and 147.2 deaths per 10 000 person-years.

Table 2. Rates of Sudden Cardiac Death, by Antipsychotic Dose

Characteristic	Antipsychotic Use			
			Current Use*	
	Nonuser	Past Year Only	≤100 mg	>100 mg
Person-years of follow-up	1 186 501	37 881	31 864	26 749
Sudden cardiac deaths	1337	53	51	46
Rate per 10 000 person-years†	11.3	15.7	14.4	26.9
Multivariate rate ratio	1	1.20	1.30	2.39
95% Confidence interval	Referent	0.91-1.58	0.98-1.72	1.77-3.22

*The dose is in thioridazine equivalents (see the "Antipsychotic Exposure" subsection of the "Participants and Methods" section).
†Standardized by the direct method to the age and sex distribution of the entire cohort.

aged 15-44, 45-64, and 65-84 years, respectively) and was greater in males (19.1 per 10 000 person-years) than in females (8.4 per 10 000 person-years).

When current antipsychotic users of doses greater than 100 mg of thioridazine or its equivalent were compared with nonusers, the multivariate rate ratio was 2.39 (95% CI, 1.77-3.22; $P<.001$) (**Table 2**). The rate ratio for current users of 100 mg or less of thioridazine or its equivalent was 1.30 (95% CI, 0.98-1.72), significantly less than that for moderate-dose current users ($P=.003$). The rate among former users of antipsychotics was not significantly ($P>.20$) different from that of nonusers (rate ratio, 1.20; 95% CI, 0.91-1.58) and was significantly lower than that for current moderate-dose users ($P<.001$). When the analysis was restricted to probable sudden cardiac deaths, the rate ratio for current users of greater than 100 mg of thioridazine or its equivalent was 2.45 (95% CI, 1.59-3.77), and those for current users of 100 mg or less and former users were 1.38 (95% CI, 0.93-2.05) and 1.25 (95% CI, 0.85-1.84), respectively.

The increased risk of sudden cardiac death among moderate-dose current users of antipsychotics was present for subgroups defined by demographic characteristics and use of specific antipsychotics. The multivariate rate ratio for females (2.97; 95% CI, 1.96-4.50) was greater than that for males (1.91; 95% CI, 1.24-2.95). The rate ratios for persons younger than 65 years and for those aged 65 years or older were 2.25 (95% CI, 1.59-3.18) and

2.82 (95% CI, 1.55-5.13), respectively. For specific drugs, the rate ratios were 1.90 (95% CI, 1.10-3.30) for haloperidol, 3.19 (95% CI, 1.32-7.68) for thioridazine, 3.64 (95% CI, 1.36-9.74) for chlorpromazine, and 4.23 (95% CI, 2.00-8.91) for thiothixene. Perphenazine was not included in this analysis because nearly all use was in a low-dose fixed combination product with amitriptyline hydrochloride.

We examined the effect of the presence of diagnosed cardiovascular disease on the association between moderate-dose antipsychotic use and increased risk of sudden cardiac death (**Figure**). In cohort members with none, mild, moderate, or severe disease, the incidence of sudden cardiac death among current moderate-dose antipsychotic users was always at least 60% greater than that for comparable nonusers, with respective multivariate rate ratios of 1.60 (95% CI, 0.89-2.87), 3.18 (95% CI, 1.95-5.16), 2.12 (95% CI, 1.08-4.14), and 3.53 (95% CI, 1.66-7.51). Thus, for every 10000 person-years of follow-up, moderate-dose current antipsychotic users had 4, 21, 23, and 367 additional sudden cardiac deaths among cohort members with no, mild, moderate, or severe cardiovascular disease, respectively.

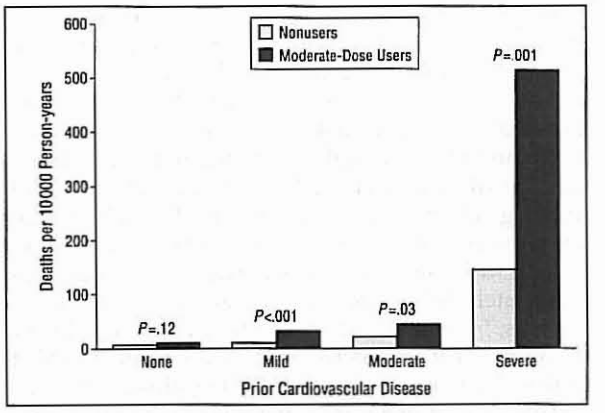
We conducted analyses that excluded several groups considered to have an increased risk of sudden cardiac death and to possibly be overrepresented among antipsychotic users and, thus, to potentially introduce bias. These included those with affective disorders (any diagnosis or use of an antidepressant or lithium), severe mental illness (a hospitalization in the past year), substance abuse (a diagnosis), use of antidepressants, and use of antiarrhythmic agents. After excluding these groups from the cohort, the respective multivariate rate ratios for moderate-dose current antipsychotic use were 2.53 (95% CI, 1.76-3.64), 2.67 (95% CI, 1.98-3.62), 2.62 (95% CI, 1.91-3.58), 2.38 (95% CI, 1.69-3.35), and 2.45 (95% CI, 1.79-3.34).

We conducted a secondary analysis to assess the potential for confounding by smoking. Cohort members with chronic respiratory illnesses caused by smoking had an age- and sex-standardized rate of 19.6 sudden cardiac deaths per 10000 person-years, 71% greater than that of the 11.5 among other cohort members. However, after adjusting for cardiovascular and other illness, the multivariate rate ratio (members with chronic respiratory disease vs other cohort members) was 1.26 (95% CI, 0.94-1.69), not significantly different from 1 ($P>.10$).

COMMENT

In this large epidemiologic study, patients using antipsychotics in doses of more than 100 mg of thioridazine or its equivalent had a 2.4-fold increase in the rate of sudden cardiac death. The relative and absolute rates were increased among moderate-dose antipsychotic users who also had severe cardiovascular disease; consequently, these patients had an additional 367 sudden cardiac deaths per 10000 person-years of follow-up.

The study case definition for sudden cardiac death required documentation from medical records consistent with the occurrence of a cardiac arrest. Consequently, many potentially qualifying deaths were excluded because they occurred at home with no terminal



Rates of sudden cardiac death in current users of moderate-dose antipsychotics (thioridazine, >100 mg/d, or its equivalent) and nonusers, by severity of cardiovascular disease. Rates of deaths in nonusers are standardized to the age and sex distribution of the cohort by direct method. Rates in moderate-dose current users were calculated by multiplying the standardized rate in nonusers by the multivariate rate ratio for moderate-dose current users. *P* values, from Poisson regression, test the difference between moderate-dose current users and nonusers.

medical care encounters or because the medical records were insufficiently detailed to apply our case definition. Deaths that otherwise qualified (coronary cause listed on the death certificate) but that lacked documentation (patient found dead at home, last seen alive 1 week previously) probably included many patients dying of causes unrelated to ventricular tachyarrhythmias (such as stroke, heart failure, or pneumonia). Because patients with mental illness are more likely to live alone[37] and, thus, to have had unwitnessed deaths, this policy should be conservative for estimating the magnitude of the association between antipsychotic drug use and sudden cardiac death.

More frequent cardiovascular disease among moderate-dose antipsychotic users potentially could have confounded the study findings. However, after adjusting for age and sex, moderate-dose antipsychotic users actually had a slightly lower prevalence of diagnosed cardiovascular disease than did comparable nonusers. This, together with the fact that our analysis controlled for diagnosed cardiovascular illness, suggests that study findings were not explained by confounding by cardiovascular comorbidity, although some part of the excess risk among moderate-dose antipsychotic users may be due to systematic underdiagnosis or undertreatment of cardiovascular illness in patients with serious mental illness.

The study data did not include information on smoking, associated with an increased risk of sudden cardiac death[38] and more common among persons with mental illness, particularly heavy smoking. However, even if the maldistribution of smoking were as extreme as a prevalence of 80% among moderate-dose antipsychotic users and 30% among nonusers, smoking would need to increase the risk of sudden cardiac death by 20-fold for confounding by smoking to explain the study findings.[39] Studies[32,40-49] of sudden cardiac death and smoking have reported that current smokers have an approximate 2-fold increased risk, with estimates ranging from 0.8[45] to 3.5,[46] clearly insufficient to explain the study findings. Interestingly, among patients with cardiovascular disease, the additional risk conferred by smoking is reduced, with adjusted relative risks

ranging from 1.2 to 1.7.[44,47,49] This is the opposite of our finding that, for moderate-dose antipsychotic users, relative risk increased with cardiovascular disease.

Our analysis did control for many of the adverse cardiovascular effects of smoking,[50] such as recent myocardial infarctions, heart failure, angina, and other cardiovascular disease, that are likely to mediate much of smoking's effect on risk of sudden death. Evidence that this reduces confounding is provided by our analysis of patients with chronic obstructive respiratory illness. Approximately 90% of these patients are current or former smokers,[34,36] and 50% admit to current smoking.[35] In our study, these patients had a 71% increased risk of sudden cardiac death, consistent with the magnitude of the association in the literature. After controlling for cardiovascular comorbidity, this decreased to 26% and was not statistically significant. Similar reasoning suggests that our findings would not be materially affected by other unmeasured lifestyle factors, such as obesity (weight gain is a frequent adverse effect of antipsychotics[1]), whose effects on cardiovascular disease–related mortality are largely mediated by intervening variables such as hyperlipidemias, hypertension, and diabetes. Nevertheless, it remains possible that confounding by these unmeasured factors influenced study findings.

We considered the biases potentially caused by the direct or indirect effects of the major mental illnesses treated with antipsychotics.[1,51] We sought to minimize inclusion of deaths caused by poor self-care (eg, delay for treatment of infections) by requiring documentary evidence consistent with a collapse. Similarly, we excluded deaths with evidence of substance abuse. Another potential source of bias is differences in the medical care received by mentally ill patients. The Cooperative Cardiovascular Care Project[52] recently reported that schizophrenic patients hospitalized for an acute myocardial infarction had relative underuse of revascularization procedures but that this was not associated with increased mortality. The absence of a significantly increased rate of sudden death among former and low-dose users of antipsychotics is additional evidence of a drug effect per se, although these groups may have had less severe mental illness.

Our study included only antipsychotics in use before 1994 and, thus, did not include the more recently introduced atypical antipsychotics risperidone, olanzapine, and quetiapine. Although some data[16] suggest that these drugs have proarrhythmic potential similar to that of typical antipsychotics, further study would be useful to clarify the association of the use of these agents with increased risk of sudden cardiac death.

The findings of this study must be interpreted in the context of the proved benefits of antipsychotics[1,51] in the management of the potentially devastating effects of psychotic symptoms on patients and their families. Nevertheless, the large magnitude of the relative and absolute increase in the risk of sudden cardiac death suggests it would be prudent to take precautions to minimize adverse cardiovascular effects among patients prescribed moderate-dose antipsychotics. In particular, greater attention to pretreatment cardiac assessment and care to titrate dose to the lowest effective level seem warranted.

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