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 1 282996 person-years of follow-up. This included 26 749 person-years for current moderate-dose antipsychotic use (>100-mg thioridazine equivalents), 31 864 person-years for current low-dose antipsychotic use, 37 881 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 10 000 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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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, 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 481,744 persons with 1,282,996 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), 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 and have concordance of better than 90% with patient self-reports of medication use. The residual misclassification is conservative and, thus, would bias against detecting a drug effect.

The study drugs (with equivalents to 100 mg of thioridazine) 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. Animal and human 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. Study follow-up thus included 58,613 person-years of current antipsychotic use and 37,881 person-years for use in the past year only. Current use consisted of 31,864 person-years (54%) for doses of 100 mg or less and 26,749 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. 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. 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 setting.

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 non-cardiac (eg, pneumonia) cause or a different cardiac cause (eg, heart failure or bradycardia/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 cardiologist 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.

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

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<tr>
<th>Characteristic</th>
<th>Nonuser</th>
<th>Past Year Only</th>
<th>≤100 mg</th>
<th>&gt;100 mg</th>
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<tbody>
<tr>
<td>Person-years of follow-up</td>
<td>1186501</td>
<td>37881</td>
<td>31864</td>
<td>26749</td>
</tr>
<tr>
<td>Age group, y</td>
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<tr>
<td>15-44</td>
<td>54.6</td>
<td>53.2</td>
<td>39.0</td>
<td>60.2</td>
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<td>45-64</td>
<td>19.8</td>
<td>28.9</td>
<td>36.0</td>
<td>33.2</td>
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<td>65-84</td>
<td>25.6</td>
<td>18.0</td>
<td>25.0</td>
<td>6.6</td>
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<tr>
<td>Female sex</td>
<td>70.5</td>
<td>65.5</td>
<td>67.4</td>
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<td>White race</td>
<td>58.2</td>
<td>66.7</td>
<td>71.5</td>
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<tr>
<td>Cardiovascular medications‡</td>
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<td></td>
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<tr>
<td>Insulin or oral hypoglycemic agents</td>
<td>7.2</td>
<td>9.2</td>
<td>9.6</td>
<td>8.0</td>
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<td>Digoxin</td>
<td>4.9</td>
<td>6.3</td>
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<td>Loop diuretics</td>
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<td>5.7</td>
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<td>Nitrates</td>
<td>5.6</td>
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<td>ACE inhibitors</td>
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<td>8.1</td>
<td>7.0</td>
<td>5.0</td>
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<td>β-Blockers</td>
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<td>10.7</td>
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<tr>
<td>Calcium channel blockers</td>
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<td>6.9</td>
<td>5.0</td>
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<tr>
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<td>2.6</td>
<td>4.3</td>
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<td>2.1</td>
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<tr>
<td>Summary cardiovascular disease score§</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>65.6</td>
<td>54.5</td>
<td>56.0</td>
<td>65.4</td>
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<tr>
<td>Mild</td>
<td>21.6</td>
<td>29.5</td>
<td>30.5</td>
<td>25.5</td>
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<tr>
<td>Moderate</td>
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<td>13.2</td>
<td>11.6</td>
<td>8.1</td>
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<td>Severe</td>
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<td>2.9</td>
<td>1.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Other medical hospital admission‡</td>
<td>12.3</td>
<td>21.2</td>
<td>14.4</td>
<td>11.3</td>
</tr>
<tr>
<td>Smoking-related respiratory illness‡</td>
<td>1.5</td>
<td>2.5</td>
<td>2.1</td>
<td>1.6</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Antipsychotic Use</th>
<th>Nonuser</th>
<th>Past Year Only</th>
<th>≤100 mg</th>
<th>&gt;100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-years of follow-up</td>
<td>1186501</td>
<td>37881</td>
<td>31864</td>
<td>26749</td>
</tr>
<tr>
<td>Sudden cardiac deaths</td>
<td>1337</td>
<td>53</td>
<td>51</td>
<td>46</td>
</tr>
<tr>
<td>Rate per 10 000 person-years†</td>
<td>11.3</td>
<td>15.7</td>
<td>14.4</td>
<td>26.9</td>
</tr>
<tr>
<td>Multivariate rate ratio</td>
<td>1</td>
<td>1.20</td>
<td>1.30</td>
<td>2.39</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>Referent</td>
<td>0.91-1.58</td>
<td>0.98-1.72</td>
<td>1.77-3.22</td>
</tr>
</tbody>
</table>

*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.

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, 1.95-5.16), 2.12 (95% CI, 1.08-4.14), and 3.53 (95% CI, 1.66-7.51). Thus, for every 10 000 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 10 000 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).

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 10 000 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 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 alone38 and, thus, to have 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 morbidity, 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 death36 and more common among persons with mental illness, particularly heavy smoking. However, even if the distribution 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 Studies23,40-49 of sudden cardiac death and smoking have reported that current smokers have an approximate 2-fold increased risk, with estimates ranging from 0.84 to 3.5.39 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...
with antipsychotics. \(^1, 5, 11\) We sought to minimize inclusion
sured factors influenced study findings.

Lipidemias, hypertension, and diabetes. Nevertheless, it
largely mediated by intervening variables such as hyper-
– unmeasured lifestyle factors, such as obesity (weight gain
statistically significant. Similar reasoning suggests that
of infections) by requiring documentary evidence consis-
tence of deaths caused by poor self-care (eg, delay for treatment
of deaths in schizophrenia: a ten-year follow-up based on

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