Cyclic antidepressants and the risk of sudden cardiac death

**Background:** Tricyclic and other related cyclic antidepressants (TCAs), used frequently for the treatment of depression and several other indications, have cardiovascular effects that may increase the risk of sudden cardiac death. We thus sought to quantify the risk of sudden cardiac death among TCA users, according to dose, as well as among users of selective serotonin reuptake inhibitors (SSRIs).

**Methods:** We conducted a retrospective cohort study in Tennessee Medicaid, from Jan 1, 1988, through Dec 31, 1993, which included large numbers of antidepressant users and computer files describing medication use and comorbidity. The cohort included 1,282,091 person-years of follow-up for persons aged 15 to 84 years who were not in a nursing home and were free of life-threatening noncardiac illness. This included 58,956 person-years for current use of TCAs alone, 6291 person-years for SSRIs only, and 96,220 person-years for former use.

**Results:** The cohort included 1487 confirmed sudden cardiac deaths occurring in the community. When compared with nonusers of antidepressants, current users of TCAs had a dose-related increase in the risk of sudden cardiac death. Rate ratios increased from 0.97 (95% confidence interval [CI], 0.72-1.29) for doses lower than 100 mg (amitriptyline or its equivalent) to 2.53 (95% CI, 1.04-6.12) for doses of 300 mg or more (P = .03, test for dose-response). The rate ratio for SSRIs was 0.95 (95% CI, 0.42-2.15). There was no evidence that TCA doses lower than 100 mg increased the risk of sudden cardiac death in subgroups defined by pre-existing cardiovascular disease, female sex, age 65 years or older, or use of amitriptyline.

**Conclusions:** Our data suggest that SSRI antidepressants and TCAs in doses of less than 100 mg (amitriptyline equivalents) did not increase the risk of sudden cardiac death. However, higher doses of TCAs were associated with increased relative risk, which suggests that such doses should be used cautiously, particularly in patients with an elevated baseline risk of sudden death. (Clin Pharmacol Ther 2004;75:234-41.)

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There has been a long-standing concern that tricyclic and other related cyclic antidepressants (TCAs) increase the risk of sudden cardiac death.\(^1,2\) Although TCAs are effective antidepressants, they have several dose-related adverse cardiovascular effects that could increase the risk of sudden cardiac death.\(^1-17\) Two early studies in the United Kingdom examined this question in small numbers of hospitalized patients with cardiovascular disease. The first found an increased risk of sudden unexpected death among amitriptyline users,\(^18\) whereas the second reported no mortality differences between users and nonusers of TCAs.\(^19\) To date, no controlled studies addressing this question have been conducted for the much larger population of outpatient TCA users.

At present, the more recently introduced selective serotonin reuptake inhibitor (SSRI) antidepressants, which have minimal known cardiovascular effects,\(^4,6,7,20\) usually are the initial therapeutic choice in affective disorders. However, TCAs continue to be prescribed frequently for patients in whom SSRIs are ineffectual or are not well tolerated and, in lower doses (typically <100 mg of amitriptyline or its equivalent), to treat a variety of other disorders including sleep problems,\(^21\) migraine,\(^22\) chronic pain,\(^23,24\) and gastrointestinal disorders.\(^25\) Thus we conducted a large retrospective cohort study to examine the association between TCAs and the risk of sudden cardiac death. Given that much of the continuing clinical use of these agents is at doses lower than those normally used to treat depression, a key study question was the safety of TCAs when used at these lower doses. The study used a Medicaid database, which included large numbers of antidepressant users and computerized files from which study data could be obtained.\(^20\)

**METHODS**

**Study cohort.** The study used data from a previous population-based study of sudden cardiac death\(^27\) that included events occurring from Jan 1, 1988, through Dec 31, 1993. The former study required a multiyear, extensive field investigation of medical records for several thousand potentially qualifying deaths. The current study uses that set of verified sudden deaths in a population with information on prescription medication use to assess risks associated with antidepressants.

The cohort consisted of Tennessee Medicaid enrollees.\(^26\) An enrollment file indicated each person’s periods of enrollment and demographic characteristics and has been linked with Tennessee death certificates,\(^28\) which identify date and cause of death. Encounter files recorded filled prescriptions, 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 pre-existing cardiovascular and other disease.

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

**Antidepressant use.** Antidepressants 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\(^29,30\) and have concordance of better than 90% with patient self-reports of medication use.\(^30,31\) Study drugs included antidepressants that were TCAs or SSRIs. Trazodone, because it is often used in low doses for sedation in patients who are not depressed,\(^21,34\) was considered separately as a potential confounder. Other antidepressants were not considered, because there was very little use of the monoamine oxidase inhibitors or bupropion (INN, amfebutamone) and the study was conducted before the introduction of other novel antidepressants (such as venlafaxine or nefazodone) into clinical practice.

For each member of the cohort, every person-day of follow-up was classified according to antidepressant use. Current use included the time from the filling of the prescription through the end of the days of supply (up to 7 additional days was allowed). Nonuse of antidepressants was defined as no antidepressant use in the past 365 days. Former use included cohort members who were not current users but who had some use in the past 365 days. This group should be similar to current users with regard to difficult-to-measure factors associated with receiving an antidepressant. In some analyses follow-up was classified by dose of tricyclic antidepressants, by use of equivalent doses.\(^35,36\) These
were 100 mg for amitriptyline, desipramine, doxepin, imipramine, and clomipramine; 62.5 mg for nortriptyline; 27.5 mg for protriptyline; 112.5 mg for trimipramine; 125 mg for amoxapine; and 75 mg for maprotiline.

**Sudden cardiac death.** The study outcome was sudden cardiac death occurring in a community setting.\(^{37-40}\) This was defined as a sudden pulseless condition (cardiac 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.\(^{39}\) Probable sudden cardiac deaths included the following: a witnessed sudden collapse in a person with no pulse or respiration (or agonal signs), an unwitnessed collapse in a person known to be alive within the previous hour, ventricular fibrillation or tachycardia before cardiopulmonary resuscitation was started, or autopsy findings excluding causes other than a ventricular tachyarrhythmia. Possible sudden cardiac deaths were those in which no cardiac arrest was witnessed and the person was found moribund or dead but with evidence that he or she had been alive in the preceding 24 hours. Both definitions excluded deaths from cardiac arrests that occurred in a hospital or other institutional setting, that were not sudden, or that had documentation suggesting an underlying noncardiac cause (eg, substance overdose or pneumonia) or a different cardiac etiology (eg, heart failure or bradyarrhythmia).

For all deaths during cohort follow-up, we screened computerized death certificates (previously linked with Medicaid\(^{28}\)) and other medical encounter records to identify potential cases. We began with deaths having a coded cause potentially consistent with sudden cardiac death, as follows: hypertensive heart disease (excluding malignant hypertension), ischemic heart disease (not aneurysms), cardiomyopathy, conduction disorders, dysrhythmias, myocarditis, cardiomegaly, heart failure, uncomplicated diabetes, atherosclerotic heart disease, unspecified heart disease, sudden death, or death from unknown cause. We then further excluded those deaths that the computerized records of terminal medical care indicated had occurred in the hospital or were either of noncardiac etiology or of cardiac etiology 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 those from the hospital or emergency department (when present), emergency medical service runs, and medical examiner reports. A study physician (S.M.), masked to medication use, then classified each death; questionable cases were reviewed by a similarly masked cardiac electrophysiologist (K.T.M.).

**Data analysis.** Multivariate rate ratios and 95% confidence intervals (95% CIs) were estimated from Poisson regression models. These models controlled for potential confounders that were evaluated for each person-day of follow-up. These included calendar year, demographic characteristics (age, sex, race), and measures of medical care utilization and comorbidity, identified from medical care encounters in the preceding 365 days. The latter included frequency of outpatient encounters (number of physician visits and filling of one or more prescriptions), antipsychotic use,\(^{27}\) mental illness (inpatient or outpatient encounters with *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnoses codes of 290 through 319), serious noncardiovascular somatic illness (inpatient admission), and cardiovascular disease as defined here.

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, antiarrhythmics, angiotensin-converting enzyme inhibitors, \(\beta\)-blockers, calcium channel blockers, hypoglycemics, 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 which the regression coefficients determined the weights given to each factor. These coefficients were obtained from performing the regression for nonusers of antidepressants. The resulting score was then calculated for each cohort member and classified into 10 values; the lowest represented no diagnosed or treated cardiovascular disease, and the remaining 9 were approximate quantiles for the cases. There was a more than 25-fold variation in rates of sudden cardiac death between the highest and lowest values of the score. Because 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.

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

The reference category for antidepressant use rate ratios was that of nonusers. Tests for dose-response used an orthogonal polynomial contrast for linear trend across the categories of current antidepressant use. All statistical analyses were performed with SAS 8.0 (SAS Institute, Cary, NC). All \(P\) values were for 2-sided tests. Statistical significance was defined by \(\alpha = .05\). The
RESULTS

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. Female patients composed 70% of the cohort (reflecting Medicaid demographics26), and 59% were white. There were 66,152 person-years of current antidepressant use, including 58,956 person-years for TCAs alone, which consisted of 29,612 person-years for amitriptyline (50.2% of TCA use), 11,903 for doxepin (20.1%), 5701 for nortriptyline (9.7%), 5226 for imipramine (8.9%), and 6514 for other or multiple drugs (11.0%). There were 6291 person-years for SSRIs only (74.1% fluoxetine, 17.8% sertraline, 7.8% paroxetine, and 0.3% multiple) and 905 person-years for joint use of both classes of antidepressants. This latter person-time (which did not include any study events) was excluded from subsequent analyses, with a total of 1,282,091 person-years of study follow-up remaining. This included 96,220 person-years for former use, of which 91,100 was for persons who had been current users of TCAs.

Both the demographic characteristics of the cohort and their utilization of health care in the past year varied according to use and type of antidepressant (Table I). Antidepressant users were more likely than nonusers to be female. Current users of TCAs had a greater mean age than other study subjects, and SSRI users were less likely to be aged 65 years or older. After standardization for age and sex, the nonusers were less likely to be white, to have Medicaid enrollment related to disability, and to have received either outpatient services or prescribed medications in the past year. They also had less treated cardiovascular or related disease, a lower prevalence of noncardiovascular medical hospital admissions, and less psychotropic drug use than did current or former users of TCAs. After standardization for age and sex, there was a slight excess of treated cardiovascular disease in the SSRI group. TCA users were more likely to have antipsychotic drug use

<table>
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<tr>
<th>Table I. Characteristics of cohort by study antidepressant use status*</th>
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<td><strong>Antidepressant use</strong></td>
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<td>Person-years of follow-up</td>
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<td>Age (y) (mean)</td>
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<td>Mental diagnosis other than depression (%)</td>
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TCA, Tricyclic and other related cyclic antidepressants, SSRI, selective serotonin reuptake inhibitor.

*All factors were standardized by the direct method to the age and sex distribution of the entire cohort (except for age and sex).
than were SSRI users, whereas the latter were more likely to use benzodiazepines and trazodone.

Cohort members had 4404 deaths during follow-up that met the computerized screening criteria. Of these, 614 deaths (14%) occurred at home with no record of a terminal medical encounter, and we were unable to obtain records for 822 deaths (19%). Of the 2968 deaths for which records were obtained, we excluded 174 that were for cardiac arrests that occurred in hospitals or other institutions, 505 of other etiology, 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.

The rate of sudden cardiac death among cohort members was 11.6 deaths per 10,000 person-years of follow-up. The risk of sudden cardiac death increased with age (rates of 2.6, 21.5, and 26.6 per 10,000 person-years for persons aged 15-44 years, 45-64 years, and 65-84 years, respectively) and was greater in male patients (19.1 per 10,000 person-years) than in female patients (8.4 per 10,000 person-years).

Current users of TCAs had a dose-related increase in the risk of sudden cardiac death (Table II). The rate ratios increased from 0.97 (95% CI, 0.72-1.29) for doses lower than 100 mg (amitriptyline or its equivalent) to 2.53 (95% CI, 1.04-6.12) for doses of 300 mg or more (P = .03, test for dose-response). The rate ratio for SSRIs was 0.95 (95% CI, 0.42-2.15), and rates did not increase with dose (P > .2; data not shown). The rate ratio for former, noncurrent users of antidepressants (0.86 [95% CI, 0.68-1.05]) was not significantly different from 1 (P = .15).

We conducted several subgroup analyses to assess the safety of TCAs among patients thought to be at high risk for the adverse cardiovascular effects of these agents (Table III). These included women, reported to have a greater likelihood of drug-induced long QT syndrome and torsades de pointes41; patients with medical care indicating cardiovascular disease, which increases the risk of sudden cardiac death42 and may increase susceptibility to the proarrhythmic effects of TCAs3,4,15,43; and persons aged 65 years or older, who have a greater incidence of cardiovascular disease. Amitriptyline, which constituted 50% of current TCA use...
and for which there are several case reports of sudden death, also was analyzed separately. This analysis was stratified by TCA dose by use of a cutpoint of 100 mg of amitriptyline or its equivalent. There was no evidence of an increased risk of sudden cardiac death for cohort TCA users below this dose. These subgroup analyses were not conducted for SSRIs because of limited sample size.

In the entire cohort, users of TCAs in doses of 100 mg or greater of amitriptyline or its equivalent had a 41% increased rate of sudden cardiac death (rate ratio, 1.41 [95% CI, 1.02-1.95]; \( P = .038 \)) (Table III). Each of the subgroups had increased rate ratios for this dose; these were statistically significant for patients with treated cardiovascular disease (rate ratio, 1.50 [95% CI, 1.06-2.12]; \( P = .020 \)) or who used amitriptyline (rate ratio, 1.80 [95% CI, 1.16-2.79]; \( P = .008 \)).

In contrast, there was no evidence that TCAs in doses of less than 100 mg of amitriptyline or its equivalent increased the risk of sudden cardiac death in any of the subgroups (Table III). As expected, nonusers of antidepressants with cardiovascular disease or aged 65 years or older had increased rates of sudden cardiac death. However, these were not further increased by use of low doses of TCAs.

Because nonusers of antidepressants might differ from users with regard to unmeasured factors, we conducted an alternative analysis with former users of antidepressants as the reference group. Findings were similar to those in the primary analysis. The rate ratio for users of less than 100 mg (amitriptyline equivalents) was 1.13 (95% CI, 0.80-1.45), which was not significantly different from 1 (\( P = .48 \)). In contrast, the rate ratio for 300 mg or greater (amitriptyline equivalents) was 2.96 (95% CI, 1.20-7.32; \( P = .018 \)).

**DISCUSSION**

Data from this study are reassuring with regard to the risk of sudden cardiac death conferred by low-dose TCAs and SSRIs antidepressants. For patients receiving either less than 100 mg (amitriptyline or its equivalent) or SSRIs, the rate of sudden cardiac death did not differ from that among nonusers of antidepressants. However, there was a significant dose-response trend for the TCAs. The rate for current users of TCA doses of 100 mg or greater was increased 41% relative to nonusers and that for users of 300 mg or greater was increased 2.5-fold. This dose-response may explain some of the discrepancy between earlier studies of sudden unexpected death in inpatients, the study reporting no increased risk assessed a population receiving amitriptyline at a mean dose of less than 100 mg.

As part of our assessment of the safety of low-dose TCAs, we conducted analyses in subgroups with an elevated baseline risk for sudden cardiac death or thought to be particularly vulnerable to adverse drug effects. These included persons with pre-existing cardiovascular disease, persons aged 65 years or older, and women. None of these analyses provided evidence that TCAs in doses of less than 100 mg (amitriptyline or its equivalent) increased the risk of sudden cardiac death. Similarly, for amitriptyline, the TCA most frequently recommended for indications other than depression, there was no increased risk at doses of less than 100 mg, although there was an increase of 80% in risk for higher doses.

There were several limitations of the current study. Although the cohort included large numbers of both TCA users and sudden cardiac deaths, there were more limited numbers of persons taking the doses of 100 mg or greater (amitriptyline equivalents) associated with increased risk. Although there was a statistically significant dose-response trend, the CIs of the point estimates for individual doses were wide. Similarly, the precision of the SSRI point estimate was limited by the smaller numbers of SSRI users.

Previous studies suggest that 85% of deaths that meet our criteria are related to an arrhythmia. However, we excluded many potentially qualifying deaths because they occurred at home with no terminal medical care encounters or the medical records were insufficiently detailed for our case definition to be applied. We did this because deaths that otherwise qualified (coronary heart disease listed on 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, pneumonia, or pulmonary embolus). Because patients with mental illness are more likely to live alone and thus to have had unobserved deaths, our procedures should be conservative with regard to estimating the magnitude of the association between antidepressant drug use and sudden cardiac death.

The study data did not include information on a variety of behavioral risk factors associated with cardiovascular disease, including smoking, body mass index, diet, and physical activity. We addressed this potential confounding in several ways. First, much of the adverse effect of these risk factors is likely to be mediated through a higher prevalence of intervening variables, such as hyperlipidemias, hypertension, and diabetes, and pre-existing cardiovascular disease, such as heart failure, angina, and myocardial infarctions. If
these intervening variables were diagnosed or treated, they were controlled for in the statistical analysis. Second, former users of antidepressants and users of low-dose TCAs and of SSRI antidepressants had no increased risk. Because these groups were likely to have a prevalence of behavioral risk factors similar to that of current TCA users, this finding provides evidence that the effect of residual confounding in our data was not large.

The study also lacked data on the mental disorders for which the antidepressants were prescribed. Because depression may be a risk factor for adverse cardiovascular events, it is theoretically possible that this disorder may account for some of the excess risk among users of higher-dose TCAs. However, the absence of increased risk among former users and users of SSRIs suggests that this potential bias did not materially affect study findings.

The study provided no data as to the mechanism by which high-dose TCAs increased the risk of sudden cardiac death. TCAs have several dose-related adverse cardiovascular effects, including orthostatic hypotension, increased heart rate, decreased heart rate variability, slowed cardiac conduction, and QT prolongation. The absence of greater risk in women, present in a similar study of antipsychotics in this population, provides epidemiologic evidence that factors other than increased risk of torsades de pointes are involved.

The generalizability of the study findings may be limited by the use of a Medicaid population. Medicaid enrollees (in 2002, 51 million [16% of the US population]) have a greater prevalence of behavioral risk factors and chronic disease, which may increase vulnerability to drug effects on the risk of sudden cardiac death. Thus the study findings may be most applicable to these types of high-risk patients; further study in other populations would be useful.

In conclusion, our data suggest that the risk of sudden cardiac death is not increased among persons who use SSRI antidepressants or doses of TCAs of less than 100 mg of amitriptyline or its equivalent. For low-dose TCAs, there is no evidence of increased risk even among older patients or those with pre-existing cardiovascular disease. However, the increased risk among patients receiving higher doses of TCAs suggests that such doses should be used cautiously, particularly in patients aged 65 years or older or with pre-existing cardiovascular disease.

The study would not have been possible without the hard work and dedication of the team of research nurses, Pat Gideon, Diane Levine, Cynthia McMillan, and Jan de Priest, and the administrative support of Teresa Mitchel and Cindy Naron.

Dr Ray has served as a consultant to Pfizer, which is the manufacturer of one of the study antidepressants. Drs Meredith, Thapa, and Murray and Ms Hall have no potential conflicts of interest to disclose.

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