Excess Risk of Myocardial Infarction in Patients Treated with Antidepressant Medications: Association with Use of Tricyclic Agents*

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PURPOSE: Several studies have found that depression and the use of antidepressant medications are associated with an increased risk of cardiovascular disease. We assessed the association between the use of antidepressant drugs and myocardial infarction, and whether that association differs between the tricyclic and selective serotonin reuptake inhibitor (SSRI) classes of medication.

PARTICIPANTS AND METHODS: We compared the experience of a cohort of 2,247 working, union health plan members who received at least one prescription for an antidepressant in an accrual period of 1991–1992 with that of 52,750 members who did not. Patients were followed for up to 4.5 years (minimum 6 months). Three antidepressant medication classes were defined: tricyclics, SSRIs, and others. The primary outcome was hospitalization or death due to myocardial infarction.

RESULTS: Adjusted for age and sex, antidepressant users had a relative risk of myocardial infarction of 2.2 (95% confidence interval [CI] 1.3 to 3.7) compared with nonusers of antidepressants. There were 16 myocardial infarctions among 1,650 users of tricyclic antidepressants, 2 among 655 SSRI users, and none among 279 users of other antidepressants. Adjusting for age, gender, baseline heart disease, diabetes, hypertension, hyperlipidemia, anxiety, and cancer, the relative risk of myocardial infarction was 2.2 (95% CI 1.2 to 3.8) in users of tricyclic agents and 0.8 (95% CI 0.2 to 3.5) in users of SSRIs, as compared with subjects who did not use antidepressants.

CONCLUSION: The association between use of tricyclic antidepressants, but not SSRIs, with an increased risk of myocardial infarction in our patients suggests that an earlier report that there is no difference in risk between the antidepressant classes, based on short-term studies, may not apply to long-term adverse cardiovascular outcomes. **Am J Med. 2000;108:2–8.**

There is substantial evidence that depression is associated with an increased risk of myocardial infarction, cardiovascular disease, and all-cause mortality (1–10). The mechanisms underlying the association have not been determined. It is also not known whether treatments for depression, including antidepressant medications, affect this association, or whether there are differences among types of antidepressant medications with regard to adverse cardiovascular outcomes.

Tricyclic antidepressants affect cardiac conduction and rhythm, and could be cardiotoxic. The *Physicians' Desk Reference* suggests extreme caution or close supervision when these drugs are prescribed for patients with cardiovascular disease (11). Although long-term data are scant, it has been suggested that the newer selective serotonin reuptake inhibitors (SSRIs) might be safer than tricyclic agents, especially for patients with cardiovascular disease (12).

However, the preliminary findings of a recent meta-analysis of antidepressant trials indicated no significant differences in the safety or efficacy of tricyclic agents and SSRIs (13,14). In that analysis, the primary measures of safety were discontinuation of treatment, as well as discontinuation due to adverse effects. More than 90% of the included trials involved follow-up of less than 8 weeks. Thus, the meta-analysis could not address the issue of long-term safety. We found only two published studies with long-term follow-up that examined the experience of a substantial number of antidepressant users (5,8). These studies, however, did not include users of SSRIs.

The aim of this study was to examine whether there was an association between use of antidepressant medications and the risk of myocardial infarction, and to assess whether this association varied by type of antidepressant medication.

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METHODS

Setting and Subjects

The study took place among participants in the 1199 National Benefit Fund, a health insurance plan for members of the 1199 National Health and Human Service Employees Union, which represents hospital, nursing home, and other workers in service, clerical, technical, and professional categories in the New York City metropolitan area. The plan includes comprehensive medical and hospital coverage, and almost all full-time workers were also eligible for prescription benefits. There were 65,703 union members who were eligible for prescription benefits in 1991 and 1992, the first years that prescription data were available. The 3,098 participants who were less than 25 years old and the 3,986 who were at or above the retirement age of 65 years during this period were excluded.

Prescription Data

During the study, the National Prescription Administrators, Inc. managed the prescription benefits. Their administrative data tapes were used to identify antidepressant and other medication use. There were no copayments or deductibles for prescription medications, so it is likely that eligible participants used the benefit plan to fill all of their prescriptions. Records were kept only for prescriptions filled, not for prescriptions written that were not filled. Medications were recorded by generic name and therapeutic codes of the American Hospital Formulary Service (15). Those with a therapeutic category code of antidepressant (codes 2816040000 through 2816040910) were subdivided into three classes: tricyclic agents, SSRIs, and a composite of monoamine oxidase (MAO) inhibitors or atypical agents. This coding was reviewed by a psychopharmacologist and confirmed by reference to the *Physicians' Desk Reference*. Some patients had prescriptions for more than one class of antidepressant medication. Antianxiolytic agents were not included, since they were also prescribed for patients with anxiety but not depression; these medications were coded separately. American Hospital Formulary Service codes were also used to classify medications that would indicate other illnesses, including hypertension, hyperlipidemia, heart disease, diabetes, and cancer. Heart disease drugs were defined as cardiovascular agents that are not primarily prescribed for hypertension or hyperlipidemia. One or more prescriptions filled during 1991 to 1992 were considered indication of use of a drug category.

Outcome Data and Follow-up

Since the National Benefit Fund provided hospitalization and death benefits, computerized records were available for discharge diagnoses and cause of death, coded according to *International Classification of Diseases, 9th Revision* (ICD-9) criteria (16). Hospitalization with a discharge diagnosis of myocardial infarction, or death due to myocardial infarction, was the primary outcome. Data for all hospitalizations for cardiovascular disease, as well as cardiovascular and all-cause mortality, were also collected. Codes 410.0 through 410.9 were categorized as myocardial infarction. Deaths or hospitalization discharges with codes 390.0 through 459.9 were categorized as being due to cardiovascular disease, including myocardial infarction.

The years 1991 to 1992 were considered as the accrual period. Follow-up began on January 1, 1993, and lasted until June 30, 1997, or the loss of National Benefit Fund eligibility. A minimum of 6 months follow-up time was required. Of the 58,619 patients who met the selection criteria described above, 3,622 had less than a 6-month minimum follow-up time, leaving 54,997 patients for analysis.

Statistical Analysis

Baseline characteristics of the patients were compared by use of antidepressant medications and by drug class. Comparisons with nonusers of antidepressant medications were made with the chi-square test for categorical variables and by analysis of variance for continuous variables. Event rates (per 1,000 person-years) were determined by use of antidepressant medication, adjusted for age and sex with the direct standardization method. Age- and sex-adjusted relative risks (RR) and 95% confidence intervals (CI) were calculated for antidepressant use and for each of the three classes of antidepressant medication, with no antidepressant use as the reference category. Subjects were also stratified by use of medications for heart disease and for hypertension. Proportional hazards models (17) were used to determine the associations of antidepressant use and each drug class with outcomes while adjusting for potential confounders. Unless otherwise noted, a two-tailed alpha <0.05 was used as the criterion for statistical significance. All statistical analyses were performed with SPSS for Windows software (18).

RESULTS

Of the 54,997 patients, 2,247 (4%) filled at least one prescription for an antidepressant medication during the accrual period (1991 to 1992). Compared with nonusers of antidepressants, those who filled at least one prescription for antidepressant medication were somewhat older, more likely to be female, and more likely to have filled a prescription for the treatment of diabetes, hypertension, heart disease, hyperlipidemia, anxiety, or cancer (Table 1). Baseline characteristics did not differ significantly among patients treated with the three antidepressant classes, except for age, sex, and treatment for anxiety.

The mean ($\pm$ SD) length of follow-up was 3.3 $\pm$ 1.4 years among patients who had any antidepressant use,

Table 1. Baseline Characteristics of Patients by Use of Antidepressant Medication*

Characteristic*	Any Antidepressant Medication (%) (n = 2,247)	No Antidepressant Medication (%) (n = 52,750)	Antidepressant Class		
			Tricyclic Agent (%) (n = 1,650)	SSRI (%) (n = 655)	MAO-Inhibitor/ Atypical Agent (%) (n = 279)
Age (years), mean ± SD	45.3 ± 9.4	43.3 ± 10.1	45.5 ± 9.3	44.3 ± 9.5	45.7 ± 10.0
Male sex	23	32	22	22	27
Prescription for					
Diabetes	9	5	9	8	8
Hypertension	40	22	41	38	42
Heart disease	10	5	10	9	11
Hyperlipidemia	7	3	7	8	5
Anxiety	43	9	43	53	57
Cancer	5	4	4	5	5

* Antidepressant use as a whole and each class of antidepressant use differed significantly ($P < 0.01$) from no antidepressant use for each characteristic. In addition, there were significant differences in age, gender, and treatment for anxiety by antidepressant class.
SSRI = selective serotonin re-uptake inhibitor; MAO = monoamine oxidase.

compared with 3.6 ± 1.3 years for patients without antidepressant use ($P < 0.05$). Length of follow-up did not differ between the antidepressant class categories.

Antidepressant Use and Subsequent Myocardial Infarction and Other Outcomes

Adjusting for age and sex, subjects using any antidepressant medication had more than twice the risk of a subsequent myocardial infarction than those not using antidepressants (Table 2). They also had greater mortality and were more likely to be hospitalized for cardiovascular disease.

Among patients who did not use medication for heart disease, those who used antidepressant medications were more likely to have an adverse outcome, although for myocardial infarction the difference did not quite reach statistical significance. For patients who were treated with medication for heart disease, use of antidepressant medications was associated with more than a 2.5-fold increase in the risk of a subsequent myocardial infarction (Table 2).

Among patients who did not receive a prescription for an antihypertensive agent, antidepressant use was not associated with subsequent myocardial infarction, but was significantly associated with hospitalization for cardiovascular disease (RR = 1.7, 95% CI 1.3 to 2.2) and with all-cause mortality (RR = 2.1, 95% CI 1.3 to 3.2). Among those receiving antihypertensive medication, the use of antidepressant medication was associated with an increased risk of myocardial infarction (RR = 2.2, 95% CI

Table 2. Age- and Sex-adjusted Event Rates by Use of Antidepressant Medications, Overall and Stratified by Prescription Medicine for Heart Disease

Outcome Event	Any Antidepressant Medication	No Antidepressant Medication	Relative Risk* (95% Confidence Interval)
	Rate per 1000 Person-Years (Number of Events)		
All subjects	n = 2,247	n = 52,750	
Myocardial infarction	2.1 (16)	1.0 (191)	2.2 (1.3–3.7)
Cardiovascular hospitalization	18.8 (148)	11.2 (2134)	1.7 (1.5–2.0)
All-cause mortality	4.7 (34)	2.7 (523)	1.7 (1.2–2.4)
No heart disease drug use	n = 2,025	n = 50,274	
Myocardial infarction	1.4 (10)	0.8 (160)	1.8 (0.9–3.4)
Cardiovascular hospitalization	15.6 (113)	9.3 (1805)	1.6 (1.4–2.0)
All-cause mortality	4.6 (31)	2.4 (462)	1.8 (1.3–2.6)
With heart disease drug use	n = 222	n = 2,476	
Myocardial infarction	9.2 (6)	3.5 (31)	2.6 (1.1–6.2)
Cardiovascular hospitalization	48.9 (35)	37.5 (329)	1.4 (1.0–1.9)
All-cause mortality	4.3 (3)	6.9 (61)	0.7 (0.2–2.1)

* Compared with no antidepressant use as reference.

Table 3. Age- and Sex-adjusted Event Rates by Class of Antidepressant Use

	Tricyclic Agent		SSRI		MAO-Inhibitor/Atypical Agent	
	Rate per 1000 Person-years (Number of Events)	Relative Risk (95% Confidence Interval)	Rate per 1000 Person-Years (Number of Events)	Relative Risk (95% Confidence Interval)	Rate per 1000 Person-Years (Numbers of Events)	Relative Risk (95% Confidence Interval)
All Subjects	n = 1,650		n = 655		n = 279	
Myocardial infarction	2.6 (14)	2.8 (1.6–4.7)	1 (2)	1.1 (0.3–4.3)	0 (0)	
Cardiovascular hospitalization	19.6 (113)	1.8 (1.5–2.2)	17.2 (36)	1.5 (1.1–2.1)	21.6 (21)	1.9 (1.2–2.9)
All-cause mortality	4.1 (21)	1.4 (0.9–2.2)	4 (8)	1.4 (0.7–2.9)	5 (5)	1.8 (0.7–4.3)
No heart disease drug	n = 1,486		n = 598		n = 249	
Myocardial infarction	2 (9)	2.3 (1.2–4.5)	0.4 (1)	0.7 (0.1–5.0)	0.0 (0)	
Cardiovascular hospitalization	16.8 (86)	1.7 (1.4–2.1)	14.9 (27)	1.4 (1.0–2.1)	21.3 (18)	2.1 (1.3–3.3)
All-cause mortality	3.8 (18)	1.4 (0.9–2.3)	4.6 (8)	1.7 (0.8–3.5)	6.1 (5)	2.2 (0.9–5.4)
With heart disease drug	n = 164		n = 57		n = 30	
Myocardial infarction	7.8 (5)	2.9 (1.1–7.4)	2 (1)	1.6 (0.2–11.6)	0 (0)	
Cardiovascular hospitalization	39.4 (27)	1.4 (1.0–2.1)	27.75 (9)	1.4 (0.7–2.7)	15.7 (3)	0.7 (0.2–2.2)
All-cause mortality	3 (3)	0.9 (0.3–2.8)	0 (0)		0 (0)	

SSRI = selective serotonin reuptake inhibitor; MAO = monoamine oxidase.

1.2 to 3.9) and cardiovascular hospitalization (RR = 1.4, 95% CI 1.1 to 1.7), but not with all-cause mortality (RR = 1.2, 95% CI 0.7 to 2.0).

Risk of Adverse Events by Antidepressant Class

Compared with patients who did not use any antidepressant medications, those treated with tricyclic agents were substantially more likely to be hospitalized for myocardial infarction (Table 3), whereas use of SSRIs was not associated with the risk of myocardial infarction. Each of the antidepressant classes was associated with cardiovascular hospitalizations.

The association between use of tricyclic agents and the risk of myocardial infarction remained significant in analyses that were stratified by use of medications for heart disease (Table 3), while the association with cardiovascular hospitalizations was significant only among those who were not treated with medication for heart disease.

Multivariate Analysis

Adjusting for sex, age, and treatment for hypertension, hyperlipidemia, diabetes, heart disease, anxiety, and cancer, antidepressant use was significantly associated with the rate of myocardial infarction (hazard ratio = 1.8, 95% CI 1.1 to 3.1). For cardiovascular hospitalizations, the

Table 4. Multivariate-adjusted Association between Selected Risk Factors and Myocardial Infarction, by Class of Antidepressant Use

	Model with Tricyclic Agents	Model with SSRIs*	Model with MAO-Inhibitors/Atypical Agents
Variable (units)	Hazard Ratio (95% Confidence Interval)		
Antidepressant use*	2.2 (1.2–3.8)	0.8 (0.2–3.5)	Not computable
Age (10 years)	1.6 (1.4–1.8)	1.6 (1.4–1.8)	1.6 (1.4–1.8)
Male gender	3.5 (2.7–4.7)	3.4 (2.5–4.5)	3.4 (2.6–4.6)
Prescription for			
Diabetes	2.9 (2.1–4.1)	3.0 (2.1–4.3)	3.1 (2.2–4.4)
Hypertension	1.7 (1.3–2.4)	1.7 (1.2–2.3)	1.7 (1.2–2.3)
Heart disease	2.1 (1.4–3.1)	2.2 (1.4–3.3)	2.1 (1.4–3.2)
Hyperlipidemia	1.2 (0.7–1.9)	1.1 (0.7–1.9)	1.1 (0.7–1.9)
Anxiety	0.9 (0.6–1.5)	0.9 (0.6–1.5)	1.0 (0.6–1.6)
Cancer	2.1 (0.5–8.3)	2.4 (0.6–9.8)	2.5 (0.6–10.1)

* No antidepressant use as reference category.

SSRI = selective serotonin reuptake inhibitor; MAO = monoamine oxidase.

Table 5. Multivariate-adjusted Association between Cardiovascular Hospitalization and All-Cause Mortality, by Class of Antidepressant Use

Antidepressant class*	Hazard Ratio (95% Confidence Interval)	
	Cardiovascular Hospitalization	All-Cause Mortality
Tricyclic agents	1.4 (1.2–1.7)	1.1 (0.7–1.6)
SSRIs	1.2 (0.9–1.7)	1.0 (0.5–2.0)
MAO-inhibitors/ atypical agents	1.4 (0.9–2.1)	1.2 (0.5–3.0)

* As indicator variables in separate models with no antidepressant use as reference. Other covariates were age, gender, and use of medication for hypertension, heart disease, hyperlipidemia, diabetes or hyperglycemia, anxiety and cancer.
SSRI = selective serotonin reuptake inhibitor; MAO = monoamine oxidase.

hazard ratio was 1.4 (95% CI 1.2 to 1.6). Antidepressant use was not significantly associated with all-cause mortality (hazard ratio 1.3, 95% CI 0.9 to 1.8). Use of tricyclic agents was significantly associated with myocardial infarction (Table 4), whereas use of SSRIs was not. Use of tricyclic agents was also associated with cardiovascular hospitalization, but not with all-cause mortality (Table 5).

DISCUSSION

We found that the association between use of tricyclic agents and subsequent myocardial infarction was substantially greater than that observed for use of SSRIs, and persisted after multivariate adjustment for potential confounders. In addition, use of any antidepressant medication was significantly associated with myocardial infarction, cardiovascular hospitalization, and all-cause mortality. To the extent that antidepressant use serves as a surrogate marker for underlying depression, this finding is consistent with the reported association of depression with myocardial infarction and other cardiovascular disease (1–10). Since we could not identify depressed patients who were not using antidepressant medications, it was not possible to examine the effect of pharmacologic treatment on the association of depression with cardiovascular disease. Nonetheless, our findings suggest that pharmacologic treatment for depression does not eliminate the increased risk of myocardial infarction associated with depression, and are thus consistent with studies that have found an increased risk in patients who were taking antidepressant medications (5,8) or had a history of treatment for depression (9).

A randomized trial will be required to determine whether antidepressant use in general, and the different classes of agents in particular, affect the association between depression and cardiovascular disease. However, the estimates of the relative risks of myocardial infarction and cardiovascular events in this study for any antidepressant use, and for use of tricyclic agents, were similar to those of the studies in which depression was measured by interview or survey scale instruments, and in which antidepressant use was either unknown or uncommon (2–4,6,7).

There are several potential mechanisms that may explain the association of depression with myocardial infarction and cardiovascular disease (19–22). Hopelessness, a dimension of depression, has been associated with the progression of atherosclerosis (23), which might explain the association between depression and cardiac events that occur many years later (3,10). In our study, the maximum length of follow-up was 4.5 years, and it is possible that a substantial number of patients who took antidepressant medications during the accrual years might have had an onset of depression considerably earlier.

Depression may inhibit parasympathetic activity or stimulate sympathetic activity with subsequent changes in serum levels of catecholamines (24). Such effects could increase heart rate, decrease heart rate variability, or contribute to electrical instability (19,25–27). The association of depression with cardiovascular disease outcomes may also be related to increased platelet activation, which has been observed in depressed patients (28,29). Platelet activation, mediated by serotonin, can contribute to vasoconstriction, atherosclerosis, and thrombosis (30).

Our findings are consistent with the hypothesis that tricyclic antidepressants aggravate the cardiovascular effects of depression. Tricyclic agents are class I antiarrhythmic drugs, a group of medications that have been associated with an increased risk of sudden death (31,32). They have also been shown to increase heart rate and reduce heart rate variability (33). Cardiac complications of tricyclic antidepressant therapy were observed decades ago (34). The *Physicians' Desk Reference* contained warnings about the cardiac effects of tricyclic agents before the beginning of this study (35), and since 1981 several investigators have warned about the use of tricyclic agents, particularly among those with cardiovascular disease (36–40).

The results of this study are also consistent with the possibility that treatment with SSRIs might ameliorate the adverse effect of depression on cardiovascular disease. For example, SSRIs may inhibit platelet aggregation (41). However, in the absence of a control group of patients who had untreated depression, we cannot distinguish among potentially deleterious effects of tricyclic agents, protective effects of SSRIs, or a combination of both.

Our findings stand in contrast with those of a recent meta-analysis (13), which reported that, contrary to what had been suspected, SSRIs were not significantly safer than tricyclic agents. However, more than 90% of the clinical trials that were included in the meta-analysis were

less than 8 weeks in duration. Thus, that analysis could not detect long-term adverse effects. Only two previous studies examined the long-term outcome of substantial numbers of patients treated with antidepressant mediations, primarily tricyclic agents. In one study (5), 132 antidepressant users had 8 ischemic heart disease events, compared with 181 events among 5,568 nonusers, for an adjusted odds ratio of 2.0 (95% CI 1.1 to 4.0). The other study (8), with 456 patients in the exposed group and 912 randomly chosen controls, reported only all-cause mortality. The age- and sex-adjusted hazard ratio for all-cause mortality associated with antidepressants was 1.7 (95% CI 1.3 to 2.1). The consistency of our findings with these two earlier studies lends validity to our results.

However, our study has several limitations. Outcomes were identified from administrative records, although the ICD-9 codes that we used to identify hospitalizations for myocardial infarction and cardiovascular disease, while imperfect, are reasonably reliable (42,43). Information about several cardiovascular risk factors, such as smoking, body mass index, and exercise, were not available. Other factors, such as serum lipid levels, diabetes, and blood pressure, had to be estimated by using data about prescriptions for hyperlipidemia, diabetes, and hypertension during the accrual period, and prior history of myocardial infarction and cardiovascular disease was also estimated with the use of drugs for heart disease. However, about 80% of antidepressant medications are prescribed by physicians other than psychiatrists (44). If these patients also had blood pressure, and perhaps serum lipid values, measured, that may have led to overreporting of these risk factors among the users of antidepressant medications. Similarly, if the patients treated with antidepressant medications were more likely to be treated for cardiovascular diseases than those who never saw a physician, this would also bias our results toward the null, thereby reducing the strength of any observed association. Notably, despite the warnings in the *Physicians' Desk Reference* about the use of tricyclic agents for patients with cardiovascular disease, users of tricyclic agents were as likely as users of SSRIs to have concomitant use of medications for heart disease and hypertension.

In summary, these results add to the accumulating evidence that depression is associated with subsequent myocardial infarction and cardiovascular disease. The adverse effects of treatment with antidepressant medications were limited to tricyclic agents, suggesting that there may be important differences in the effects of different classes of drugs.

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