Comparison of Paroxetine and Nortriptyline in Depressed Patients With Ischemic Heart Disease

Steven P. Roose, MD; Fouzia Laghrissi-Thode, MD; John S. Kennedy, MD; J. Craig Nelson, MD; J. Thomas Bigger, Jr, MD; Bruce G. Pollock, MD, PhD; Andrew Gaffney, MD; Meena Narayan, MD; Mitchell S. Finkel, MD; James McCafferty; Ivan Gergel, MD

Context.—Depression and ischemic heart disease often are comorbid conditions and, in patients who have had a myocardial infarction, the presence of depression is associated with increased mortality. Patients with heart disease need a safe and effective treatment for depression.

Objective.—To compare the efficacy, cardiovascular effects, and safety of a specific serotonin reuptake inhibitor, paroxetine, with a tricyclic antidepressant, nortriptyline hydrochloride, in depressed patients with ischemic heart disease.

Design.—Two-week placebo lead-in followed by a double-blind randomized 6-week medication trial.

Setting.—Research clinics in 4 university centers.

Patients.—Eighty-one outpatients meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for major depressive disorder and with documented ischemic heart disease.

Interventions.—Treatment with either paroxetine, 20 to 30 mg/d, or nortriptyline targeted to a therapeutic plasma level, 190 to 570 nmol/L (50-150 ng/mL), for 6 weeks.

Main Outcome Measures.—For effectiveness of treatment, a decline in the score of the Hamilton Rating Scale for Depression by 50% and final score of 8 or less; for cardiovascular safety, heart rate and rhythm, supine and standing systolic and diastolic blood pressures, electrocardiogram conduction intervals, indexes of heart rate variability, and rate of adverse events.

Results.—By intent-to-treat analysis, 25 (61%) of 41 patients improved during treatment with paroxetine and 22 (55%) of 40 improved with nortriptyline. Neither drug significantly affected blood pressure or conduction intervals. Paroxetine had no sustained effects on heart rate or rhythm or indexes of heart rate variability, whereas patients treated with nortriptyline had a sustained 11% increase in heart rate from a mean of 75 to 83 beats per minute ($P<.001$) and a reduction in heart rate variability, as measured by the SD of all normal R-R intervals over a 24-hour period, from 112 to 96 ($P<.01$). Adverse cardiac events occurred in 1 (2%) of 41 patients treated with paroxetine and 7 (18%) of 40 patients treated with nortriptyline ($P<.03$).

Conclusions.—Paroxetine and nortriptyline are effective treatments for depressed patients with ischemic heart disease. Nortriptyline treatment was associated with a significantly higher rate of serious adverse cardiac events compared with paroxetine.

JAMA. 1998;279:287-291

From the Departments of Psychiatry (Dr Roose), Medicine (Dr Bigger), and Pharmacology (Dr Bigger), College of Physicians and Surgeons, Columbia University, New York, NY; Department of Psychiatry (Drs Laghrissi-Thode and Pollock), University of Pittsburgh School of Medicine, Pittsburgh, Pa; Departments of Psychiatry (Dr Kennedy), Medicine (Dr Gaffney), and Clinical Cardiology (Dr Gaffney), Vanderbilt University School of Medicine, Nashville, Tenn; Department of Psychiatry (Drs Nelson and Narayan), Yale University School of Medicine, New Haven, Conn; Department of Medicine, Section of Cardiology, West Virginia University School of Medicine, Morgantown (Dr Finkel); and Department of Clinical Research and Development, SmithKline Beecham Pharmaceuticals, Philadelphia, Pa (Mr McCafferty and Dr Gergel). Drs Roose and Kennedy have received research support and honoraria from Eli Lilly and Company and from SmithKline Beecham Pharmaceuticals. Drs Nelson and Pollock have received research support and honoraria from SmithKline Beecham.

Reprints: Steven P. Roose, MD, Department of Psychiatry, College of Physicians and Surgeons, Columbia University, 722 W 168th St, Unit 98, New York, NY 10032 (e-mail: spr2@columbia.edu).

THE NEED to find a safe and effective treatment for depressed patients with cardiac disease has intensified because of 2 relatively recent findings, one that emphasizes the potential importance of treatment and the other that emphasizes the potential risks. Frasure-Smith et al[1] reported compelling new evidence that patients who develop depression following a myocardial infarction (MI) are at significantly greater risk for death than medically comparable post-MI patients who are not depressed.[1] In their study, 222 patients were evaluated approximately 1 week after MI and 16% of the sample met criteria for major depression. Over the next 6 months, the depressed patients had a 3.5 times greater risk of cardiac death than patients not diagnosed as depressed. Subsequently, this finding was extended to establish that depression was a significant predictor of post-MI cardiac mortality at 18 months. Intriguingly, the risk associated with depression is greatest in patients who have 10 or more ventricular premature depolarizations (VPDs) per hour.[2] This observation is compatible with other findings that suggest that the association of depression and sudden cardiac death involves an arrhythmic mechanism. It is unknown whether treatment of the depressive episode will reduce the associated increase in cardiac mortality.

However, before one can consider studying this question, it needs to be established that there is a safe and effective antidepressant treatment for the post-MI depressed patient. The tricyclic antidepressants (TCAs) have been the most systematically studied with respect to cardiovascular effects, and it has been documented that the tricyclics (1) increase heart rate, (2) induce orthostatic hypotension, (3) slow intraventricular cardiac conduction, and (4) suppress VPDs.[3] Although TCAs can cause significant complications in depressed patients with cardiac disease, their robust efficacy combined with knowledge

that forewarns the clinician as to when problems are likely to occur had led to the belief that, in most cases, the use of TCAs in patients with heart disease was a "relatively" safe procedure with a favorable risk-benefit ratio.

However, the results of the cardiac arrhythmia suppression trials (CAST) suggest that this conclusion be revised.[4,5] The hypothesis of the CAST studies was that suppression of post-MI VPDs would decrease mortality. Contrary to expectations, patients treated with drugs with class 1C (encainide hydrochloride or flecainide acetate) or class 1A (moricizine) antiarrhythmic activity had an increased mortality rate compared with placebo-treated patients. The mechanism by which the antiarrhythmics induce this increased mortality rate has not been definitively established. To date, most evidence points to an interaction between drugs with class 1 antiarrhythmic activity and ischemic myocardium, which results in an increased vulnerability to ventricular fibrillation.[6-8] Thus, patients with ischemic heart disease treated with a class 1A or 1C antiarrhythmic drug may be at risk when their next ischemic episode occurs. Because TCAs are class 1A antiarrhythmic drugs, similar in effect to quinidine and moricizine, it is both reasonable and prudent to assume that TCA treatment carries a similar risk.[9]

Given the probable risk associated with TCA treatment in patients with ischemic heart disease, the obvious question is whether the selective serotonin reuptake inhibitors (SSRIs) are a safe and effective alternative. The available data on the cardiovascular effects of the SSRIs are quite limited.[10-14] It has been reported that the SSRIs slightly decrease heart rate, do not routinely slow intracardiac conduction, do not affect supine or standing systolic or diastolic blood pressure, and do not induce orthostatic hypotension. However, these findings are compromised by methodological problems in data collection and their applicability is limited because the sample studied consisted of predominantly medically healthy patients with depression and, specifically, patients free of cardiac disease.

To date, there is only one study of the cardiovascular effects of an SSRI, fluoxetine, in the treatment of depressed patients with significant cardiac disease.[15] In that study, 27 patients with major depression and left ventricular impairment and/or conduction disease and/or ventricular arrhythmia were treated openly with fluoxetine for 7 weeks at a maximum dose of 60 mg/d. Fluoxetine induced a small reduction in heart rate, but did not have a statistically significant effect on blood pressure, ejection fraction, ventricular arrhythmia, or conduction intervals. However, the study included patients with multiple types of cardiac disease and did not specifically address the issue of risk in depressed patients with ischemic heart disease.

In this article, we report the first prospective double-blind study comparing the safety and efficacy of an SSRI, paroxetine, with a TCA, nortriptyline hydrochloride, in depressed patients with ischemic heart disease.

METHODS

This study was conducted at 4 sites simultaneously (College of Physicians and Surgeons, New York, NY; University of Pittsburgh Medical Center, Pittsburgh, Pa; Yale-New Haven Hospital, New Haven, Conn; and Vanderbilt University Medical Center, Nashville, Tenn). This study was approved by the internal review boards for the protection of human subjects at all 4 sites. To be included in the study, patients had to (1) meet *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria for major depressive disorder, unipolar subtype, with a score of 16 or greater on the 17-item Hamilton Rating Scale for Depression (HRSD); (2) have ischemic heart disease; and (3) be capable of, and willing to, sign informed consent to participate in a protocol studying the cardiovascular safety of antidepressant medication. Patients were considered to have ischemic heart disease if they had had an MI, coronary artery bypass graft surgery, or coronary angioplasty, or had a positive stress test, or angiographic evidence of a 75% or greater luminal narrowing of a major coronary artery or one of its primary branches. Patients were excluded from the study if they had an MI within the past 3 months, a baseline QTc interval of 460 milliseconds or greater, unstable or crescendo angina, or were receiving drugs with class 1 antiarrhythmic activity or warfarin.

After signing informed consent, the patients were evaluated by a supervising cardiologist (A.G., M.N., M.S.F.). Patients had to be clinically stable without medication changes for 2 weeks before they entered the placebo period. During a 2-week placebo period, baseline cardiac testing was conducted, including a 24-hour continuous electrocardiogram (ECG) recording, 12-lead ECG at the beginning and end of the placebo period, weekly supine and standing blood pressure measurements, and a multigated radionuclide angiogram. Conduction intervals were determined from the ECG recording. Heart rate, rhythm, and heart rate variability were determined from 24-hour continuous ECG recording. At the end of the placebo period, if the patient had complied with the study procedures and continued to meet inclusion and exclusion criteria including an HRSD score of 16 or greater, the patient was randomized by permuted blocks of 10 to treatment with either paroxetine or nortriptyline for a double-blind 6-week medication trial.

Dosing Schedule

For patients younger than 65 years, the initial dose of paroxetine was 20 mg/d for the first 3 weeks, whereas for patients 65 years and older paroxetine was started at 10 mg/d for the first week and increased to 20 mg for weeks 2 and 3. If at the end of week 3 the patient did not meet criteria for response, defined as a 50% reduction in baseline HRSD score and total HRSD score of 8 or less, the paroxetine dose was increased to 30 mg at week 4 and, if necessary, to 40 mg at the end of week 5.

The nortriptyline dose was begun at 25 mg for the first 2 days and increased to 50 mg on day 3. On day 7, a plasma level was measured and the dose adjusted, if necessary, to achieve a nortriptyline plasma level between 304 and 456 nmol/L (80-120 ng/mL). This level was targeted to increase the likelihood that patients would achieve a nortriptyline plasma level within the therapeutic range of 190 to 570 nmol/L (50-150 ng/mL).

To maintain the medication blind, a double dummy technique was used; patients were either taking active paroxetine in the morning and nortriptyline placebo at night or taking paroxetine placebo in the morning and active nortriptyline at night. To ensure that the treating physician and other raters remained unaware of drug administration, the nortriptyline dose was adjusted by a physician who was not otherwise involved in the study. Because the nortriptyline dose might be increased or decreased to achieve the therapeutic plasma level, the blind was maintained by selecting, on a random basis, patients receiving active paroxetine to have their nortriptyline placebo increased or decreased to mimic the dose adjustments for patients receiving active nortriptyline. If at the end of weeks 3 and 4 the patient had not met criteria for response, the treating physician increased the dose of paroxetine by 1 pill. Therefore, the dose was in reality increased if the patient was taking paroxetine, but if the patient had been randomized to nortriptyline, this action increased the number of paroxetine placebo tablets. Medication compliance was monitored by weekly pill counts and by plasma level measurements.

Cardiac Assessment During Medication Treatment

Patients received active medication for 6 weeks; supine and standing blood pressure readings were recorded weekly, and

12-lead ECGs and 24-hour continuous ECG recordings were repeated at the end of weeks 2 and 6 of medication treatment.

Criteria for Drug Discontinuation

Trial medications were stopped due to an adverse cardiac event if (1) there was a greater than 50% increase in the QRS interval from baseline, (2) the QRS interval exceeded 180 milliseconds in patients with bundle-branch block at baseline, (3) the QTc interval exceeded 500 milliseconds, (4) the patient developed orthostatic hypotension of such severity that there was a postural blood pressure decline of 50 mm Hg or greater or the patient was unable to maintain a standing position because of symptoms associated with a postural blood pressure decline of 25 mm Hg or greater, or (5) the patient developed a proarrhythmic effect as defined by the criteria of the Cardiac Arrhythmia Pilot Study.[16] Additionally, the supervising cardiologist discontinued medication if the patient developed a cardiovascular event documented by blood pressure measurement, ECG, cardiac enzyme levels, or 24-hour continuous ECG recording.

Statistical Analysis

To determine the effectiveness of randomization, the paroxetine and nortriptyline groups were examined for age, sex distribution, initial severity of depressive illness, and cardiac parameters, including baseline heart rate, blood pressure, ejection fraction, conduction intervals, and VPD frequency. To determine whether paroxetine or nortriptyline caused significant cardiovascular effects, 2-tailed paired *t* tests were performed comparing mean measures at the end of the placebo period with means at week 2 and week 6 for both drugs independently. Comparisons were made for supine and standing systolic and diastolic blood pressure; orthostatic decline; heart rate (as determined by 24-hour continuous ECG recordings); radial pulse in the supine position and after 1 minute standing; PR, QRS, and QTc intervals; and ventricular arrhythmia in patients with 6 or more VPDs an hour at baseline. The SD of all normal R-R intervals during a 24-hour period (SDNN) and the absolute difference between successive R-R intervals greater than 50 milliseconds expressed as a percentage of all heart periods (pNN50) were also compared by 2-tailed paired *t* tests.

RESULTS

Ninety-two patients met inclusion and exclusion criteria and entered the placebo phase of the study. Eleven patients who began the placebo phase were not randomized to drug because of noncompliance: 3 for not taking placebo medication, 4 for not returning for clinic visits, and 4 for not completing the cardiovascular testing. Eighty-one patients were randomized to drug treatment, 41 to paroxetine and 40 to nortriptyline. Demographic characteristics and cardiac status at baseline are reported in Table 1.

Table 1.—Demographic and Cardiovascular Status at Randomization*

	Paroxetine Group (n=41)	Nortriptyline Group (n=40)
Age, mean±SD, y	58±11	58±13
Male	36 (88)	31 (78)
Recurrent depression	40 (73)	27 (67)
HRSD score at baseline, mean±SD	24±1	22±1
Duration of IHD, mean±SD, y	6.7±7.6	5.8±5.4
History of MI	25 (61)	29 (73)
Previous coronary bypass surgery	15 (37)	14 (35)
Previous coronary angioplasty	17 (42)	16 (41)
Classification for angina†		
I, asymptomatic	24 (59)	21 (53)
II, symptomatic with moderate activity	13 (33)	17 (42)
III, symptomatic with mild activity	3 (8)	2 (5)
IV, symptomatic at rest	0	0
Left ventricular ejection fraction, mean±SD, %	58±14	60±14
Abnormal left ventricular wall motion	11 (27)	10 (25)
Cardiovascular medications		
β-Blockers	14 (34)	13 (33)
ACE inhibitors	9 (22)	5 (13)
Calcium channel blockers	26 (63)	24 (60)
Vasodilators	16 (39)	16 (40)

*Data are number (percent) of patients, unless otherwise specified. HRSD indicates Hamilton Rating Scale for Depression; IHD, ischemic heart disease; MI, myocardial infarction; and ACE, angiotensin-converting enzyme.
†New York Heart Association classification.

Medication Treatment and Response

The mean (±SD) dose of study medication at end point was 22±5 mg/d for paroxetine and 74±30 mg/d for nortriptyline. At week 6, the range of nortriptyline plasma level was 152 to 836 nmol/L (40-220 ng/mL); 81% of patients had a plasma level between 190 and 570 nmol/L (50-150 ng/mL), the established therapeutic plasma level range for nortriptyline.

In the intent-to-treat analysis, defining response as a 50% reduction in the HRSD score and a final HRSD score of 8 or less, 61% (25/41) of paroxetine-treated patients and 55% (22/40) of nortriptyline-treated patients were classified as responders. Ninety percent (37/41) of paroxetine-treated patients completed the medication trial and 68% (25/37) were responders. Sixty-five percent (26/40) of nortriptyline-treated patients completed the medication trial and 85% (22/26) were responders.

Cardiovascular Variables

The cardiovascular effects of paroxetine and nortriptyline are presented in Table 2. Paroxetine induced a statistically significant 4–beat per minute decrease in heart rate at week 2 that was no longer apparent by week 6, and paroxetine induced a 4–mm Hg increase in the supine systolic blood pressure at week 6. Paroxetine had no other significant effects on blood pressure, nor any effect on cardiac conduction. There was an increase in SDNN at week 2, which was not sustained by week 6, and no evidence of an effect on the high-frequency component as represented by the pNN50 at either week 2 or week 6.

Nortriptyline induced a statistically significant 11% increase in 24-hour heart rate and a 12% increase in supine and standing pulse rates that were sustained throughout the treatment trial. There was a significant decline in standing systolic blood pressure at week 2 and, although the magnitude of that decline persisted throughout the medication trial, statistical significance was no longer present at week 6. There was no effect on cardiac conduction. Nortriptyline induced a significant decrease in SDNN that was present by week 2 and sustained through week 6, and a decrease in the pNN50 at week 2 and week 6 that approached statistical significance ($P<.06$).

Because 13 analyses were performed, the question arises whether a correction for multiple comparisons is warranted. There are many reasons to argue that a correction factor is not necessary or even appropriate. However, a reasonable approach is to present the results with and without the use of a correction factor. When a Bonferroni correction for multiple comparisons is used, the only results that remain statistically significant for either medication are the increase in 24-hour heart rate and increase in su-

Table 2.—Medication Effect of Paroxetine and Nortriptyline*

	Paroxetine Group			Nortriptyline Group		
	Baseline	Week 2	Week 6	Baseline	Week 2	Week 6
No. of patients	41	38	37	40	36	26
Heart rate, beats/min	73 (10)	69† (5)†	72 (6)	75 (11)	82 (16)‡	83 (7)‡
Pulse rate, supine	66 (10)	64 (10)§	67 (10)	70 (12)	79 (14)‡	78 (14)‡
Pulse rate, standing	74 (11)	73 (12)	76 (11)	77 (14)	86 (16)‡	86 (16)‡
Blood pressure, mm Hg						
Systolic, supine	133 (15)	135 (18)	137 (15)†	141 (19)	140 (14)	141 (16)
Systolic, standing	129 (20)	129 (20)	129 (16)	138 (21)	130 (16)‖	132 (20)
Diastolic, supine	76 (9)	77 (11)	78 (11)	78 (10)	80 (9)	81 (6)
Diastolic, standing	76 (13)	78 (15)	78 (13)	80 (11)	79 (10)	78 (13)
Conduction intervals, ms						
PR	165 (30)	159 (9)	164 (11)	168 (33)	171 (11)	173 (18)
QRS	100 (18)	99 (6)	100 (5)	101 (15)	102 (6)	104 (11)
QTc	420 (22)	417 (16)	419 (14)	427 (22)	434 (20)	416 (19)
Heart rate variability						
SDNN	112 (37)	127 (23)§	111 (27)	112 (19)	98 (42)‖	96 (16)‖
pNN50	6.4 (10)	6.8 (5)	6.3 (4)	6.5 (9)	4.2 (7)	4.1 (7)
VPDs/h in patients with >6 VPDs/h at baseline [n]	91 (169) [16]	. . .	107 (215) [13]	50 (50) [10]	. . .	38 (61) [9]

*Data are mean (SD). Comparisons were analyzed by 2-tailed paired *t* test, baseline vs week 2, baseline vs week 6. SDNN indicates SD of all normal R-R intervals; pNN50, R-R intervals greater than 50 milliseconds expressed as percentage of all heart periods; and VPDs, ventricular premature depolarizations.
†$P<.03$.
‡$P<.001$.
§$P\leq.05$.
‖$P<.01$.

pine and standing pulse rate induced by nortriptyline.

Discontinuation of Medication Due to Adverse Events

Two patients were discontinued from paroxetine treatment because of adverse events: 1 patient had intractable diarrhea and the other developed unstable angina. The patient with angina was a 53-year-old man with a previous history of MI who reported severe chest pain during the fourth week of treatment. Coronary angiography revealed a 90% occlusion of the circumflex artery, and the patient underwent angioplasty with good result. The cardiologist made the decision to restart treatment with paroxetine immediately following the angioplasty, but for purposes of this report, the patient is considered to have had an adverse event that required discontinuation of medication.

Ten patients discontinued nortriptyline treatment. Three patients had noncardiac adverse events: 2 patients had intractable constipation and 1 patient had persistent myoclonic jerks. Seven patients had adverse cardiovascular events: 4 patients developed sinus tachycardia (>120/min), 1 patient experienced severe angina associated with ST-segment changes on ECG, and 2 patients had asymptomatic increase in their ventricular ectopy that met criteria for a proarrhythmic effect. There was a significantly greater rate of dropout due to adverse cardiovascular events in the nortriptyline group compared with the paroxetine group (2-tailed Fisher exact test, $P<.03$).

COMMENT

Paroxetine and nortriptyline were both effective treatment for depressive illness in this group of patients with ischemic heart disease. With respect to cardiovascular parameters, paroxetine did not have a significant effect on heart rate, blood pressure, conduction intervals, or ventricular arrhythmia. Thus, paroxetine did not demonstrate class 1 antiarrhythmic activity. Consistent with previous reports, nortriptyline induced a statistically significant increase in heart rate,[17-19] but did not cause other frequently reported effects, such as decrease in ventricular ectopy[20] and prolongation of PR, QRS, and QTc intervals.[21] The mean frequency of VPDs per hour did decrease in the nortriptyline-treated patients, and the failure to demonstrate a statistically significant antiarrhythmic effect is probably attributable to the small number of patients with arrhythmia included in this study. Prolongation of cardiac conduction is a well-established effect of TCA treatment.[22] However, nortriptyline is used at a lower dose than other TCAs and has been reported not to induce the same degree of conduction delay.[21] Nonetheless, in patients with preexisting conduction disease, nortriptyline has been reported to have the same potential as other TCAs to cause adverse effects on cardiac conduction such as 2:1 atrioventricular block.[21] Nortriptyline produced orthostatic hypotension at week 2 that was no longer significant at week 6; the loss of significance may be due to the number of dropouts that occurred by week 6, which limited power to demonstrate a sustained orthostatic effect.

Nortriptyline induced an increase in all 3 measures of heart rate. The finding that the increase in supine pulse rate is comparable to the increase in pulse rate after 1 minute standing implies that the heart rate increase is not positional, ie, not exclusively or even primarily a response to the orthostatic decline induced by nortriptyline. Furthermore, the baseline measure and subsequent increase in 24-hour heart rate was essentially equivalent to the radial pulse rate, indicating that the clinician can obtain a reliable measure of heart rate increase induced by nortriptyline by measuring radial pulse.

The increased heart rate associated with nortriptyline treatment in this study and with TCAs in general[22,23] may be especially important in patients with ischemic heart disease. There was no evidence of attenuation of this effect during the 6 weeks of this medication trial or in previous studies. If the heart rate increase is in fact a persistent effect, then any conclusions about its potential consequence must consider that patients who respond to a TCA for a depressive episode continue with the medication for a minimum of 6 months, and that many patients who have recurrent depressive illness require lifetime medication for prophylaxis. It has been established that in patients with ischemic heart disease there is a positive correlation between heart rate and mortality, ie, patients with higher heart rates have increased mortality.[24-26] The increase in heart rate induced by TCAs may cause an increase

in cardiac work and, if so, have an insidious, but significantly detrimental effect that would not be appreciated in a study that evaluated adverse events after only 6 weeks of drug exposure.

Determining the effect of medication on indexes of heart rate variability is a relatively new and potentially important method of evaluating cardiac safety. The SDNN reflects the interplay and balance between sympathetic and parasympathetic input on the cardiac pacemaker. A high degree of heart rate variability has been demonstrated in compensated hearts with good cardiac function, whereas heart rate variability is significantly decreased in patients with severe coronary artery disease or congestive heart failure. Kleiger et al[27] demonstrated that SDNN was a predictor of long-term survival in patients after MI.[27] After adjusting for other significant cardiac parameters, eg, baseline ejection fraction, rales in a coronary care unit, frequency of ventricular premature complexes, or New York Heart Association classification, SDNN emerged as the most significant predictor of mortality. In 808 patients followed up for a mean of 31 months, the relative risk of mortality was 5.3 times higher in the group with low heart rate variability compared with the group with normal heart rate variability.

In this study, paroxetine had no effect on SDNN or pNN50, whereas nortriptyline appeared to decrease variability. The results may be intriguing, but any conclusions would be speculative and premature. It has been reported that depressive illness itself affects heart rate variability[28-30]; thus, studies are needed that effectively distinguish the impact of medication from the impact of illness. Nonetheless, it may be important that nortriptyline and other TCAs appear to diminish variability. In adolescents and young adults, TCAs significantly reduce the high-frequency component (an anticholinergic effect of the drug) and thus increase the ratio of low to high frequency.[31] Indeed, it has been hypothesized that sudden death reported in children taking desipramine may result from drug-induced alterations in parasympathetic-sympathetic balance that increase the vulnerability to ventricular arrhythmia.[32]

Perhaps, most important, the high rate of serious adverse events associated with nortriptyline in this study further documents that despite their potent antidepressant efficacy, TCAs are relatively toxic in depressed patients with heart disease. In contrast, paroxetine demonstrated comparable antidepressant efficacy but a significantly lower rate of adverse events. It may be premature to consider paroxetine a "safe" medication in patients with ischemic heart disease on the basis of this study alone. First, a relatively small number of patients were studied, and there may be infrequently occurring but important adverse cardiovascular events that this study did not have the power to detect. Second, the patients in this study had documented, significant, but stable ischemic heart disease and only mild impairment of left ventricular function. It is not known what effect paroxetine might have in patients with more severe cardiovascular disease, eg, patients with ejection fractions below 0.30. Third, although 67% of the study sample had a previous MI, patients were excluded if they had an MI within the past 3 months. Therefore, this study cannot comment on the safety of paroxetine in the immediate post-MI period.

When making treatment decisions for a patient who has both depressive illness and ischemic heart disease, the clinician must consider the risk-benefit ratio of any intervention. The results of this study contribute important new information to the evaluation of risk, and are consistent with other data that suggest that SSRIs are safer than TCAs in the treatment of depressed patients with heart disease. Nonetheless, our knowledge is far from complete, and clinicians must still make treatment decisions for this patient population on a case-by-case basis, taking into account the type and severity of depression as well as the type and severity of cardiovascular disease and the established cardiovascular effects of the various antidepressant medications.

This work was supported by funds from SmithKline Beecham Pharmaceuticals.

References

1. Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction: impact on 6-month survival. *JAMA.* 1993;270:1819-1825.
2. Frasure-Smith N, Lesperance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. *Circulation.* 1995;91:999-1005.
3. Roose SP, Glassman AH. Cardiovascular effects of tricyclic antidepressants in depressed patients with and without heart disease. *J Clin Psychiatry.* 1989;50(suppl):1-18.
4. Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med.* 1989;321:406-412.
5. Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med.* 1992;327:227-233.
6. Bigger JT Jr. Implications of the Cardiac Arrhythmia Suppression Trial for antiarrhythmic drug treatment. *Am J Cardiol.* 1990;65:3D-10D.
7. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo: the Cardiac Arrhythmia Suppression Trial. *N Engl J Med.* 1991;324:781-788.
8. Greenberg HM, Dwyer EM Jr, Hochman JS, Steinberg JS, Echt DS, Peters RW. Interaction of ischaemia and encainide/flecainide treatment: a proposed mechanism for the increased mortality in CAST I. *Br Heart J.* 1995;74:631-635.
9. Glassman AH, Roose SP, Bigger JT Jr. The safety of tricyclic antidepressants in cardiac patients: risk/benefit reconsidered. *JAMA.* 1993;269:2673-2675.
10. Cooper GL. The safety of fluoxetine: an update. *Br J Psychiatry.* 1988;153(suppl 3):77-86.
11. Kuhs H, Rudolf GAE. Cardiovascular effects of paroxetine. *Psychopharmacology.* 1990;102:379-382.
12. Fisch C. Effect of fluoxetine on the electrocardiogram. *J Clin Psychiatry.* 1985;46(3, pt 2):42-44.
13. Wernicke JF. The side effect profile and safety of fluoxetine. *J Clin Psychiatry.* 1985;46(3, pt 2):59-67.
14. Upward JW, Edwards JG, Goldie A, Waller DG. Comparative effects of fluoxetine and amitriptyline on cardiac function. *Br J Clin Pharmacol.* 1988;26:399-402.
15. Roose SP, Glassman AH, Attia E, Woodring S, Giardina EGV, Bigger JT Jr. Cardiovascular effects of fluoxetine in depressed patients with heart disease. *Am J Psychiatry.* In press.
16. Cardiac Arrhythmia Pilot Study (CAPS) Investigators. The Cardiac Arrhythmia Pilot Study. *Am J Cardiol.* 1986;57:91-95.
17. Vohra J, Burrows GD, Sloman G. Assessment of cardiovascular side effects of therapeutic doses of tricyclic anti-depressant drugs. *Aust N Z J Med.* 1975;5:7-11.
18. Freyschuss U, Sjoqvist F, Tuck D, Asberg M. Circulatory effects in man of nortriptyline, a tricyclic antidepressant drug. *Pharmacol Clin.* 1970;2:68-71.
19. Ziegler VE, Co BT, Biggs JT. Plasma nortriptyline levels and ECG findings. *Am J Psychiatry.* 1977;134:441-443.
20. Giardina EGV, Barnard JT, Johnson LL, Saroff AL, Bigger JT Jr, Louie M. The antiarrhythmic effect of nortriptyline in cardiac patients with ventricular premature depolarizations. *J Am Coll Cardiol.* 1986;7:1363-1369.
21. Roose SP, Glassman AH, Giardina EGV, Walsh BT, Woodring S, Bigger JT Jr. Tricyclic antidepressants in depressed patients with cardiac conduction disease. *Arch Gen Psychiatry.* 1987;44:273-275.
22. Kantor SJ, Glassman AH, Bigger JT Jr, Perel JM, Giardina EGV. The cardiac effects of therapeutic plasma concentrations of imipramine. *Am J Psychiatry.* 1978;135:534-538.
23. Giardina EGV, Bigger JT Jr, Glassman AH, et al. Desmethylimipramine and imipramine on left ventricular function and the ECG: a randomized crossover design. *Int J Cardiol.* 1983;2:375-385.
24. Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA. Heart rate and cardiovascular mortality: the Framingham Study. *Am Heart J.* 1987;113:1489-1494.
25. Gillum RF, Makuc DM, Feldman JJ. Pulse rate, coronary heart disease, and death: the NHANES I Epidemiologic Follow-up Study. *Am Heart J.* 1991;121:172-177.
26. Dyer AR, Persky V, Stamler J, et al. Heart rate as a prognostic factor for coronary heart disease and mortality: findings in three Chicago epidemiologic studies. *Am J Epidemiol.* 1980;112:736-749.
27. Kleiger RE, Miller JP, Bigger JT Jr, et al. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol.* 1987;59:256-262.
28. Roose SP, Dalack GW, Woodring S. Death, depression, and heart disease. *J Clin Psychiatry.* 1991;52(suppl 6):34-39.
29. Yeragani VK, Pohl RB, Balon R, et al. Effect of imipramine treatment on heart rate variability measures. *Biol Psychiatry.* 1992;26:27-32.
30. Carney RM, Saunders RD, Freedland KE, Stein P, Rich MW, Jaffe AS. Association of depression with reduced heart rate variability in coronary artery disease. *Am J Cardiol.* 1995;76:562-564.
31. Walsh BT, Giardina EGV, Sloan RP, Greenhill L, Goldfein J. Effects of desipramine on autonomic control of the heart. *J Am Acad Child Adolesc Psychiatry.* 1994;33:191-197.
32. Schroeder JS, Mullin AV, Elliott GR, et al. Cardiovascular effects of desipramine in children. *J Am Acad Child Adolesc Psychiatry.* 1989;28:376-379.