Cardiovascular Effects of Antidepressant Drugs: Updated

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The cardiovascular effects of tricyclic antidepressants (TCAs), including the propensity of these agents to be fatal in overdose, have been well described. It has been established further that even at therapeutic doses the TCAs may have untoward cardiovascular effects in the context of underlying ischemic heart disease. By comparison, the selective serotonin reuptake inhibitors (SSRIs) as a class are less likely to affect cardiovascular parameters in depressed patients who are otherwise healthy. Importantly, the SSRIs in overdose situations are enormously safer than TCAs and rarely have been associated with cardiotoxic effects when ingested alone. More recently, the safety and efficacy of several of the SSRIs have been evaluated in patients with existing ischemic heart disease. Although the studies have involved a limited number of patients, the available data suggest that SSRIs are not associated with adverse cardiovascular effects in these patients and are safer than TCAs in the treatment of depression in patients with heart disease. The prevalence of cardiovascular disease and the evidence that comorbid depression with cardiovascular disease (for example, following myocardial infarction) increases the risk of mortality underscore the importance of understanding the cardiac effects of antidepressants and the need for effective antidepressants that are free of adverse cardiovascular effects. At present, the SSRIs should be considered first-line agents for the treatment of depressed patients with cardiovascular illness, particularly ischemic heart disease. Among the SSRIs, those with a lower potential for causing pharmacokinetic drug interactions generally are preferred.

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Shortly after the antidepressant efficacy of the first tricyclic compounds became apparent, reports appeared describing overdose fatalities with these new drugs. Within a few years, it was clear that the vast majority of these overdose deaths were cardiovascular in nature. When imipramine first was marketed, the vast majority of drug-related suicide attempts involved barbiturate overdoses. However, by the late 1960s and early 1970s, benzodiazepines had replaced barbiturates as the most commonly used sedative, hypnotic drugs, and tricyclic antidepressants (TCAs) had replaced barbiturates as the most commonly ingested drugs in suicide attempts. By the late 1970s, 1500 to 2000 individuals a year killed themselves in TCA overdoses.[1]

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CARDIOVASCULAR EFFECTS OF TCAs

Although the cardiovascular risks of TCAs in overdose were evident by the mid-1960s, the implications of the cardiovascular effects of TCAs at usual therapeutic levels was not evident for more than a decade. In the mid-1970s, for example, some National Institute of Mental Health (NIMH) reviewers of our original grant proposal to study the cardiovascular effects of TCAs maintained that these compounds had no cardiac effects at usual therapeutic levels. A decade of work subsequently established that their cardiovascular effects were, in fact, limited as long as depressed patients remained free of cardiovascular disease.[2] In otherwise healthy depressed patients, the cardiovascular complications are more or less restricted to orthostatic hypotension, which most likely causes falls in 2% to 3% of treated patients. The frequency of orthostatic hypotension rises modestly in elderly patients; however, the adverse consequences of falling increase dramatically in the elderly. Fortunately, the risk is not the same across all of the TCAs. Nortriptyline, although not free of this risk, appears to be significantly less likely to result in falls than imipramine, desipramine, clomipramine, or amitriptyline.[3]

All TCAs have been shown to delay cardiac conduction and increase heart rate; however, in otherwise healthy adult patients, these effects seldom, if ever, are of any clinical significance. In children, the story is somewhat

more complex. Here, this class of drugs regularly produces sustained elevation of blood pressure, and there persists a suspicion that treatment with TCAs, especially desipramine, can, on rare occasions, result in sudden death.[4]

In adults, the safety of the TCAs changes significantly in patients with overt heart disease. The frequency of orthostatic hypotension increases. In part, this may result from interactions with other drugs, but the change is particularly dramatic in patients with left ventricular impairment. Here, several studies have observed the development of orthostatic falls in as many as 50% of patients.[5,6] Another problem recognized many years ago is that the moderate prolongation of conduction characteristic of TCAs can become problematic in patients who already have conduction disease, especially bundle branch block,[7] since the TCA-induced delay could easily result in symptomatic rhythm disturbances and even death.

Another potential problem has become apparent that was not originally appreciated. In 1977, it was first reported that TCAs were class I antiarrhythmic drugs.[8] Originally this was thought to be beneficial in that if a depressed patient also had a ventricular arrhythmia, these compounds would seem likely to improve both conditions. In the late 1980s, to almost everyone's surprise, studies revealed that, although the usual class I drugs (which block sodium channels) were powerful antiarrhythmics, their long term use *increased* rather than decreased mortality.[9] It gradually became clear that, although these class I antiarrhythmic drugs under usual conditions suppress ventricular arrhythmia, they regularly become proarrhythmic when cardiac tissue becomes anoxic. This has proven to be true with quinidine, flecainide, encainide, and moricizine. Although no study has been conducted specifically to test whether, under anoxic conditions, a TCA would increase mortality, because the action of TCAs on the heart is so similar to other class I antiarrhythmics, it would be prudent to assume they would carry the same risk in patients with ischemic heart disease.[10]

Considering the problems associated with class I antiarrhythmics and the conduction and orthostatic effects, TCAs probably should never be the initial treatment in a depressed patient with cardiac disease, especially ischemic disease. The TCAs remain potent antidepressant drugs and under certain conditions their use in depressed patients with heart disease might still be warranted; however, one would need to balance carefully the risks and benefits for each individual patient.

OVERDOSE EXPERIENCE WITH SSRIs

The initial concern that TCAs might have cardiotoxic properties came from experience with these drugs in overdose. One of the dramatic differences between the TCAs and the selective serotonin reuptake inhibitors (SSRIs) is that SSRIs are remarkably less likely to be life-threatening even when ingested in fairly dramatic overdoses.[11] There is a propensity to wonder whether an SSRI ingested alone ever can cause death, and the answer is clearly yes. However, it is important to remember that for many years TCA usage resulted in 1500 to 2000 overdose deaths per year. Although the prescribing information for all SSRIs alludes to rare occurrences of fatal overdoses with these drugs, there are only 2 well-documented deaths reported in the literature from ingestion of SSRIs alone during the decade since they were introduced: one with fluoxetine[12] and the other with citalopram.[13] In both cases the patients ingested what would amount to a 6-month supply of drug at the usual dose of 20 mg per day.

Overdose cases can be informative about potential cardiovascular problems at normal therapeutic levels. This was certainly true for the TCAs for which conduction delays and arrhythmia were absolutely characteristic of overdose, even when only moderately severe. With SSRIs there is no similar clear signal. Most SSRI overdoses result in no significant clinical symptomatology; however, when symptoms develop following ingestion of large doses of SSRIs, the most common serious event is seizure—not cardiotoxicity.

The majority of cases in which SSRI ingestion was associated with mortality involved the coingestion of either alcohol or benzodiazepines; however, without more detailed descriptions of pathologic findings in deaths following SSRI overdose, it is not possible to establish the mechanism of toxicity. It is conceivable that the seizurogenic qualities of the SSRIs in overdose, combined with the effect of alcohol and benzodiazepine withdrawal to lower the seizure threshold, could produce status and death. It has been reported in some cases of mixed SSRI/alcohol/benzodiazepine overdoses that QRS or QT prolongations have occurred. However, status itself can result in such prolongations, and, as a result, it is unclear if the cardiac changes are a direct effect of the drug or secondary to seizures.

There are 2 large reported series of overdose cases with SSRIs. One regional group of the U.S. Poison Control Center reported 234 fluoxetine cases,[14] and, similarly, a Swedish Poison Information Centre reported 159 cases of citalopram ingestion.[15] The 2 studies involved over 400 overdoses, and both are notable for the lack of fatalities. Curiously, the citalopram overdose cases reported in the Swedish study involved, on average, a considerably higher level of ingestion. Five of the Swedish cases were known to have ingested more than 1900 mg (about 100 times the usual daily dose), and all of these patients had either seizures or conduction delays (wide QRS) or both. Of 18 cases in which 600 mg–1900 mg of citalopram was ingested, 6 experienced QRS widening and seizures.

None of the fluoxetine cases reported in the U.S. series involved ingestion of more than 1500 mg of drug, and none showed QRS widening, although seizures occurred

in 2 of the 7 cases in which 600 mg–1200 mg of fluoxetine was ingested. Thus, even in cases of rather substantial SSRI overdose, except for tachycardia and occasional QRS widening, there is little evidence for cardiovascular toxicity. The most common serious problem, if any serious problem at all arises, is seizures. Although less evidence is available with either paroxetine or sertraline, the story would seem to be the same.

CARDIOVASCULAR EFFECTS OF SSRIs

Although the relative lack of toxicity in SSRI overdose is reassuring, the ultimate test of safety comes only from treating depressed patients with coexisting cardiovascular disease. Until very recently, no such studies were available. Some information was available from studies with each of the SSRIs in which cardiovascular measures were obtained in otherwise healthy depressed patients.[16–19] These studies frequently showed a very modest slowing of pulse rate, but no influence on either resting or postural blood pressure and no influence on PR, QRS, or QT_c intervals. Measures of cardiac contractility or irritability were not likely to be informative in patients with healthy hearts and were not obtained.

The only potential problem that could be documented from early clinical experience with SSRIs was a very occasional report of severe sinus bradycardia.[20] These reports have occurred with all of the SSRIs, and no clear mechanism has been established. Paradoxically, there also are infrequent reports of supraventricular tachycardia, particularly with fluoxetine.[21] However, the reports of tachycardia are so rare that it is not obvious that these cases are drug-induced.

Use of SSRIs in Patients With Cardiovascular Disease

In 1996, the first systematic studies of SSRIs in patients with preexisting cardiac disease have appeared. The first of these studies examined 27 inpatients with both serious depression and serious, but stable, cardiovascular disease, who were treated with fluoxetine.[22] These patients had conduction disease, arrhythmia, impaired contractility, or some combination of the 3 conditions. In most cases, these symptoms were the result of ischemic heart disease. However, none of the patients was less than 4 months post–myocardial infarction. These patients were started on fluoxetine 20 mg/day and, after 2 weeks, if they could tolerate it, were raised to 60 mg/day. The average dose after 6 weeks actually reached 50 mg/day. In spite of this unusually high dose in a group of patients who averaged 77 years of age, almost no cardiovascular effects and certainly no evidence of cardiac harm were seen. Pulse rate did slow slightly as had been reported previously, but that slowing did not increase even though the average blood level almost quadrupled between weeks 2 and 6. There were negligible effects on both resting and postural blood pressure and no evidence of orthostatic hypotension, even in patients with impaired left ventricular function (in whom TCAs are particularly problematic). There was no effect of fluoxetine treatment on conduction, even in patients with preexisting conduction disease. In those patients with ventricular ectopy at baseline, there was no evidence of either proarrhythmic or antiarrhythmic activity. The one surprise was that among those patients with evidence of impaired cardiac contractility at baseline, ejection fraction improved during treatment with fluoxetine. The improvement—though modest—was clinically significant; however, since the finding was post hoc and because the number of patients with baseline impairment of ejection fraction was small, replication is needed.

The second study in depressed patients with heart disease involved 40 patients treated with paroxetine compared with 40 treated with nortriptyline.[23] All were outpatients who suffered from chronic but stable cardiovascular disease. Both the degree of cardiac impairment and the severity of depression were less than that in the patient population exposed to fluoxetine. Those issues notwithstanding, the cardiovascular effects of paroxetine were very similar to those observed with fluoxetine. As with fluoxetine treatment, there was observed a modest (4 beat per minute) decrease in heart rate at 2 weeks among patients treated with paroxetine. The dose of paroxetine also was raised after 2 weeks—but only by 50%. Thus, a less dramatic increase in blood levels was observed, compared with the fluoxetine study. Somewhat surprisingly, the initial bradycardia observed at week 2 had disappeared by week 6, and heart rate returned essentially to baseline values even though the paroxetine dose was higher. As with fluoxetine, there was no influence of paroxetine on resting systolic or diastolic blood pressure, nor evidence of orthostatic hypotension. Similarly, there was no evidence of intracardiac conduction delays. The study's authors further noted that, compared with nortriptyline, paroxetine was associated with a lower incidence of adverse cardiovascular effects.[23]

Effects of SSRIs on Platelet Activity

While the paroxetine study did not measure drug effects on left ventricular function, it did include measures of platelet function. An increasing awareness of the role thrombus formation plays in the onset of myocardial infarction and an increasing awareness of the association between depression and ischemic heart disease have led to increased attention to issues of platelet function. The marked effect of SSRIs on platelet serotonin has been known for some time, although the effect of SSRIs on platelet function had not been investigated previously. In the paroxetine study, the Pittsburgh site elected to examine platelet factor 4 and β-thromboglobulin. Both proteins are extruded when the platelet shifts into an activated or more "sticky" state, and a rise in levels of these proteins is associated with increased readiness of the platelet to aggregate.

Pollock and Laghrissi-Thode made 2 striking observations: prior to treatment, depressed cardiac patients had markedly elevated levels of these 2 proteins compared with nondepressed cardiac patients, and, when depressed patients were treated with paroxetine but not with nortriptyline, these levels returned significantly toward control values.[24,25] The baseline elevations in these markers of platelet activation are consistent with recent epidemiologic data indicating that not only are depressed individuals more likely to die of cardiovascular disease, but they are also more likely to develop a first myocardial infarct than their nondepressed counterparts.[26] In this study, the reduction in platelet stickiness observed with paroxetine treatment was in addition to the contribution of aspirin, which most of these patients were receiving to reduce the propensity of their platelets to aggregate. There are some data with citalopram to suggest that this characteristic is a general property of the SSRI drugs and not unique to paroxetine.

Indeed, the putative antiplatelet activity of SSRIs possibly could explain the occasional episode of bleeding that has been reported with these agents. However, in patients who are post-infarction or at risk for other thrombotic diseases, an SSRI effect to reduce platelet "stickiness" might serve a beneficial function.

Use of SSRIs Post–Myocardial Infarction

Evidence also has been accumulating that patients experiencing depression in the immediate post-infarction period are at markedly increased risk for death. The 1993 study by Frasure-Smith and colleagues in particular raised the issue of treating depression in the immediate post-infarction period.[27] However, treatment of these patients with TCAs would be of concern because of the TCAs' class I antiarrhythmic activity. It is not yet clear whether another antidepressant would be less troublesome. The SSRIs are a reasonable choice because of their widespread use and their lack of obvious toxicity. However, even the 2 studies just described, with fluoxetine and paroxetine, avoided including patients within 4 to 6 months of infarction.

The only data available in the immediate post-infarction period are from a pilot study of 26 patients treated with sertraline.[28] These patients were identified as depressed while still hospitalized after an infarction, and treatment began, on average, within 1 month of infarction. In spite of focusing on this high-risk period, again there was no evidence of harm. As in the other studies, neither blood pressure (supine or standing) nor conduction measures showed any evidence of change. Unlike the fluoxetine and paroxetine study groups, the post-infarction population was followed for 12 rather than 6 weeks. One difference between the studies' findings was that sertraline-treated patients never showed any evidence of bradycardia. As was observed in the fluoxetine study, sertraline-treated patients showed an increase in ejection fraction over the course of the study. However, this observation is harder to interpret since the initial measure generally was made within 2 weeks after infarction, and, if the patient survives, the pump function of the heart often will show evidence of recovery. The same is true of ventricular arrhythmia. Arrhythmia is not uncommon in the post-infarction period and, again, if the patient survives, the incidence often decreases over time. In fact, this was observed in the sertraline study. To determine whether the antiarrhythmic effect or the improvement in ejection fraction is the result of sertraline treatment or whether such changes merely reflect recovery in patients who survive infarction would require a placebo-controlled group. Nevertheless, it is encouraging that patients could tolerate an SSRI in the immediate post-infarction period without difficulty.

There had been some question about the effect of a serotonergic drug on a patient with a recently injured coronary artery. Serotonin in healthy coronary arteries produces vasodilation; however, serotonin injected in human coronary arteries with evidence of intimal damage results in vasoconstriction.[29] It is not clear to what extent administering an SSRI may increase free serotonin levels in circulating blood, especially blood reaching the coronary arteries. The accepted wisdom has been that, at least initially, SSRIs increase serotonin in the synaptic cleft and that, because reuptake is blocked, some of the excess will find its way into the plasma. Ordinarily a large fraction of that plasma serotonin is taken up into platelets, but the SSRIs block this uptake as well as that in the cleft. The largest source of this excess serotonin comes from the gut, and, although platelet reuptake is reduced, this serotonin-rich blood enters the liver via the portal circulation before reaching the general circulation. The liver is rich in monoamine oxidase (MAO) and can readily deaminate serotonin. Thus, it remains unclear to what degree serotonin in the general circulation actually rises. One of the few reports that attempted to measure the level of circulating serotonin after SSRI treatment found it to be reduced rather than increased.[30] Whatever happens and regardless of theoretical considerations, it is reassuring that no clinical evidence of coronary vasoconstriction following SSRI treatment was observed.

Taking this information together certainly suggests that the SSRIs as a class are safe in depressed patients with heart disease. However, it is important to recognize that the total number of patients in the 3 studies described here is only 96, and of that number, only 26 are patients in the immediate post-infarction period. Ninety-six patients do not establish safety. There is a wide variety of cardiac pathology, and what may be safe in one situation may not be safe in another. For example, it is not understood why very occasionally patients taking SSRIs develop severe bradycardia. In general, it would seem that SSRIs slow the heart a few beats per minute and that, after a few weeks, even this modest slowing seems to diminish or disappear. Interestingly, in overdose, the characteristic effect on heart

rate is not bradycardia, but rather tachycardia. Rare cases of supraventricular tachycardia have been reported at normal therapeutic levels of these drugs. Why these rare deviations in heart rate occur remains unclear, and whether this might pose a problem for patients with unrecognized sinus node disease also is uncertain. For the vast majority of patients, however, even those with heart disease, rate changes are not a problem with SSRIs.

Other Cardiovascular Effects of SSRIs

The SSRIs show no propensity to produce either systolic or diastolic hypertension. In contrast, both bupropion and venlafaxine in adults and TCAs in children and adolescents can raise blood pressure.[31] Most importantly, and in marked contrast to the TCAs and MAOIs, the SSRIs show no proclivity to produce orthostatic hypotension. This appears true even in those with impaired left ventricular function at baseline. Again, in contrast to the TCAs, there has been no evidence of conduction prolongation by SSRIs in either the large data sets collected by the manufacturers in essentially healthy patients or in the limited number of cases with preexisting conduction disease. Conduction changes have been reported in a small number of very severe overdose ingestions of SSRIs. However, even in those limited cases, at least some of the changes may be secondary to seizures that are reported to occur in SSRI overdose situations.

Similar to the TCAs, there has been no evidence of SSRIs causing harm to the pump function of the heart. In a post hoc analysis, there was even the suggestion that patients with impaired left ventricular ejection fraction at baseline improved following SSRI treatment, but this is an observation that needs replication. The influence, if any, of SSRIs on arrhythmia is the most difficult to establish. This is because the only patients that are informative are those who suffer both depression and arrhythmia. In addition, ventricular arrhythmia is inherently a highly variable condition, so to make any evaluation certainly requires an unusually large sample. The number of patients studied to date is quite limited, and any statement at this time must be guarded. Nevertheless, the data available show no evidence of any antiarrhythmic activity and, even in massive overdoses, SSRIs have not been associated with malignant arrhythmia.

DRUG-DRUG INTERACTIONS WITH SSRIs

While the use of SSRIs for the treatment of depression in cardiac patients generally appears to be safe, it is important to remember that these patients frequently will be receiving other medications for their conditions. The potential for SSRIs to cause pharmacokinetic drug-drug interactions is therefore of concern, and the risk is not the same for all agents.[32] For example, fluoxetine and paroxetine are highly potent inhibitors of the P450 2D6 isozyme, which is responsible for the metabolism of a number of cardiovascular medications. In contrast, sertraline and fluvoxamine are nearly an order of magnitude less potent than fluoxetine and paroxetine in 2D6 inhibition, and citalopram and venlafaxine are at most only weak inhibitors of 2D6. With respect to the 2C19 isozyme, fluvoxamine is a highly potent inhibitor, whereas fluoxetine and sertraline are moderate inhibitors, paroxetine is a mild inhibitor, and citalopram and venlafaxine cause minimal or no inhibition. Thus, in selecting an antidepressant for the treatment of a depressed cardiac patient, an SSRI with a lower potential for causing pharmacokinetic drug interactions generally is preferred.

COMMENT

It is clear that the use of SSRIs in cardiac patients is associated with considerably less risk than the use of TCAs. There is little or no information available on other antidepressant drug classes in patients with overt cardiac disease. Neither venlafaxine nor mirtazapine have been studied in populations with known heart disease. Bupropion has been examined in depressed patients with stable but significant heart disease and no problems with conduction, contractility, or orthostatic hypotension were observed.[33] There was some evidence of antiarrhythmic activity. The only obvious concern with bupropion involved the occasional occurrence of significant elevation of blood pressure; however, only 27 patients in total were studied. Even with the SSRIs, for which 3 different studies have looked at a total of 96 patients with comorbid heart disease, the power to see a problem—if one exists—is quite limited. This is particularly true for the period following myocardial infarction, for which only a pilot study with 26 patients treated with a single drug, sertraline, has been conducted. Although the available information is limited, both the commonness of cardiovascular disease in later life and the strong evidence that depression after a heart attack greatly increases the risk of death make the need for antidepressant drugs that can be used safely in this group imperative. To determine whether treating depression after a heart attack will reduce the risk of mortality, it is essential first to prove that there are antidepressant drugs that are both safe and effective in this clinical population.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin), citalopram (Celexa), clomipramine (Anafranil), desipramine (Norpramin and others), flecainide (Tambocor), fluoxetine (Prozac), imipramine (Tofranil and others), mirtazapine (Remeron), moricizine (Ethmozine), nortriptyline (Pamelor and others), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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