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Treating Depression in Patients with Ischaemic Heart Disease

Which Agents are Best to Use and to Avoid?

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Abstract

There are a number of dimensions to the complex relationship between cardiovascular disease and affective disorders including: (i) patients with depression are at an increased risk of dying from sudden cardiovascular death compared with the general population; (ii) patients with depression over the course of a lifetime have a higher rate of symptomatic and fatal ischaemic heart disease compared with a control group without depression; and, (iii) patients after either a myocardial or a cerebrovascular infarction who are depressed have a higher mortality rate than their medically comparable nondepressed counterparts.

The deleterious impact of depression on the prognosis of cardiac disease and the suggestion that treatment of depression may reduce cardiac mortality has led clinicians to seek safe and effective treatment for patients with comorbid depression and ischaemic disease.

Though they are robustly effective, the tricyclic antidepressants are type 1A antiarrhythmic agents and presumably carry the same risk in patients with ischaemic disease as treatment with other type 1 antiarrhythmics such as moricizine. Short term studies of the safety of other antidepressant agents, specifically amfebutamone (bupropion) and the selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs) fluoxetine, paroxetine and sertraline, suggest that these medications have a benign cardiovascular profile in patients with depression and pre-existing cardiac disease. However, given the methodological limitations of study design and the relatively small number of patients included, it is premature to conclude that SSRIs are a 'safe' treatment in patients with heart disease.

Thus, clinicians must still make treatment decisions on a case by case basis, considering the type and severity of depression and cardiovascular disease, as well as what is known about the cardiovascular effects and therapeutic profile of the different classes of antidepressant medications.

Clinicians have long struggled over the treatment of depression in patients with cardiac disease. It used to be believed that the frequency of this clinical problem simply reflected the expected comorbid occurrence of 2 relatively prevalent illnesses, especially in the older population. However, evidence from different types of studies strongly suggest that the comorbidity of depression and ischaemic heart disease is not serendipitous, but rather inevitable.

The first association observed between depression and cardiovascular disease was that depressed patients have a higher than expected rate of sudden cardiovascular death. The first, and still perhaps the most definitive data supporting this clinical observation, comes from the work of Malzberg published in 1937.[1] This study was designed to compare the mortality rate of patients hospitalised for melancholia with the mortality rate for the general population, controlling for age by comparing groups of patients to the general population according to decade. Malzberg reported that the death rate was 6 times greater in patients with melancholia compared with the general population and this was consistent across the age span of 40 to 75 years. Cardiac disease accounted for 40% of all deaths reported in the depressed patients and the rate of cardiac death in patients was 8 times greater than the corresponding rate in the general population. The Malzberg study remains very influential because the data were collected in an era when there was no specific somatic treatment for depression and, therefore, the mortality rates represent the natural course of the illness.

The finding of an increased cardiac mortality rate in depressed patients compared with a control population has subsequently been reported by a number of investigators in both the US and Europe.[2,3] However, a question as to whether depression is an independent risk factor for cardiac mortality was raised by the observation that depression increases both the likelihood that an individual smokes and failure if that individual attempts to quit smoking.[4] Thus, it was hypothesised that the association found between depression and cardiovascular mortality is primarily the result of a behaviour (smoking) that is associated with depression, but does not reflect a direct pathophysiological relationship between depression and cardiac disease.

In an attempt to resolve this question, a number of investigators have reanalysed epidemiological data sets to determine whether the increase in cardiovascular mortality in depressed patients is still significant after controlling for known cardiovascular risk factors such as smoking, family history, bodyweight, etc. Of the 6 studies using this methodological approach, five have found a significant increase in the rate of symptomatic and fatal ischaemic heart disease in depressed patients even after controlling for medical risk factors.[5]

1. The Influence of Depression on the Prognosis of Cardiac Disease

A number of studies have reported a higher than expected incidence of depression in patients with ischaemic heart disease, particularly in the patient who has recently had a myocardial infarction. About 20% of patients who are eligible for angioplasty or who are in the post–myocardial infarction period, meet criteria for the depressive syndrome.[6,7] One study reported that in a follow-up interview 3 months after myocardial infarction, 44% of patients who were initially diagnosed as depressed still met the criteria for a diagnosis of depression.[7]

The most important consequence of depression in the patient with ischaemic heart disease was illustrated in a study by Frasure-Smith et al.[8] This study identified a group of patients who met the

DSM-III[9] criteria for major depressive illness in the post–myocardial infarction period. Most striking was that the patients with depression had a significantly higher rate of cardiac mortality in the 6 months after myocardial infarction compared with their nondepressed counterparts who had cardiac disease of comparable severity. By 18 months after myocardial infarction, approximately 17% of patients with a diagnosis of depression had died a cardiac death compared with only 3% of comparable cardiac patients without depressive symptomatology.[10]

2. Cardiovascular Safety of Tricyclic Antidepressants

Considering the deleterious impact of depression on the prognosis of cardiac disease and data from studies that suggest that treatment of depression may reduce cardiac mortality,[11] it is compelling to find a safe and effective treatment for depression in patients with ischaemic disease. The most studied antidepressants with respect to cardiovascular effects are the tricyclic antidepressants. The systematic investigation of the therapeutic plasma concentration of tricyclic antidepressants in patients with or without cardiac disease has established a number of cardiovascular effects; tricyclic antidepressants: (i) increase heart rate; (ii) induce orthostatic hypotension; (iii) slow intraventricular cardiac conduction; and, (iv) have type 1A antiarrhythmic activity.[12] Until recently, the robust efficacy of the tricyclic antidepressants in the treatment of depression in combination with a knowledge of the adverse cardiac effects of tricyclic antidepressants which forewarn the clinician to expect trouble, and the suggestion that the treatment of depression can reduce the associated increase in cardiac mortality, led to the conclusion that in most circumstances there was a favourable risk-benefit ratio for tricyclic antidepressant treatment in depressed patients with heart disease. However, data from clinical trials of the safety of antiarrhythmic drugs have indicated that this conclusion needs to be revised.[13]

In the late 1980s, the US National Heart, Lung and Blood Institute initiated a series of multicentre cardiac arrhythmia suppression trials (CAST) to determine whether the common practice of suppressing ventricular premature depolarisations following myocardial infarction did, in fact, decrease cardiac mortality. The first of these studies, known as CAST I, was prematurely discontinued after only 2 years because treatment with 2 of the 3 antiarrhythmic drugs being tested, encainide and flecainide was associated with a significant excess of deaths compared with placebo-treated control participants.[14] Since encainide and flecainide are both type 1C antiarrhythmics, it was hoped that this finding of increased mortality might not apply to the third drug used in the trial, moricizine, a drug with type 1A antiarrhythmic action. Therefore, a second study, CAST II, that compared moricizine with placebo was subsequently initiated. However, this study was prematurely discontinued as well when it became clear that moricizine also induced an increased mortality comparable with that seen with encainide and flecainide.[15]

Subsequently, other studies have indicated that antiarrhythmic drugs may carry a risk of increased mortality not only in patients with ventricular arrhythmias after myocardial infarction, but also when these compounds are used in patients with a broader range of ischaemic disease.[16,17] Although the mechanism by which antiarrhythmics induce mortality in patients with ischaemic disease has not been definitively established, recent data suggest that there is an interaction between the antiarrhythmic drug and ischaemic myocardia such that when an ischaemic event occurs, the presence of an antiarrhythmic drug increases the probability of ventricular fibrillation.[18] If this suspicion proves correct, it would imply that the risk of using type 1A or 1C antiarrhythmic drugs increases proportionately with the severity of the ischaemic heart disease. Tricyclic antidepressants have type 1A antiarrhythmic action similar to moricizine. Therefore, unless specific information to the contrary becomes available, it would be prudent to assume that tricyclic antidepressants carry a similar risk of in-

creased mortality if given to depressed patients with ischaemic heart disease.

3. Cardiovascular Effects of Nontricyclic Antidepressants

Given that it would be preferable to avoid the use of tricyclic antidepressants in depressed patients with ischemic heart disease, the obvious question is whether other types of antidepressants may prove to be safe and effective alternatives in this patient population.

3.1 Amfebutamone (Bupropion)

Amfebutamone (bupropion) was the first nontricyclic antidepressant to be systematically studied in depressed patients with cardiac disease. A report on 36 depressed patients with congestive heart failure and/or conduction disease and/or ventricular arrhythmias treated with amfebutamone concluded that the agent: (i) did not affect heart rate; (ii) infrequently caused an elevation in supine systolic blood pressure; (iii) did not adversely affect left ventricular function; (iv) induced systematic orthostatic hypotension in only 1 out of 36 patients; and, (v) did not significantly prolong conduction or induce degrees of atrioventricular block in patients with patients with pre-existing bundle branch block.[19] Although it does appear that there may be patients who cannot tolerate a tricyclic antidepressant because of adverse cardiac effects who can be safely and effectively treated with amfebutamone, it remains possible that amfebutamone may have significant cardiovascular effects that were not detected because of the relatively small sample size in this study.

3.2 Selective Serotonin Reuptake Inhibitors

Given their established effectiveness and generally favourable adverse effect profile, both of which have contributed to their widespread use, perhaps the more important question is whether the selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs) carry less cardiovascular risk than the tricyclic antidepressants. To date there have been 3 studies of SSRI treatment in depressed patients with serious cardiovascular disease.

The first study examined the use of fluoxetine in 27 patients who met DSM-III[9] criteria for depression and who had heart failure and/or conduction disease and/or ventricular arrhythmias.[20] Patients were entered into a 7-week open treatment study in which they received fluoxetine in an escalating dose from 20 to 60 mg/day (the mean dosage at the end of 7 weeks was 54 mg/day). The mean age of the patients was 73 ± 9 years, 74% of the patients were male and 45% had a history of previous myocardial infarction. Fluoxetine induced a statistically significant decrease in heart rate of 5 beats/min, but did not affect either systolic or diastolic supine or standing blood pressure, cardiac conduction, or ventricular ectopic activity. A surprising finding was a statistically significant, albeit small, increase in the ejection fraction of patients with pre-existing left ventricular impairment. However, this study included only 12 patients with an ejection fraction below 50%. Therefore, it would seem prudent to defer concluding that SSRIs have a beneficial effect on left ventricular function until this finding is replicated.

In this study, the fluoxetine dose was 20 mg/day for 2 weeks, 40 mg/day for 2 weeks, and then 60 mg/day for the last 3 weeks. Cardiovascular assessments were done at week 2 and week 7. Given the administration schedule and the long half-life of the parent compound and active metabolite, norfluoxetine, it is not surprising that the mean plasma concentration of fluoxetine plus norfluoxetine was 4 times greater at week 7 than at week 2. However, there were no significant cardiovascular findings that emerged at week 7 that were not evident at week 2. Perhaps most important in terms of the cardiovascular safety of fluoxetine was the absence of patients who had to withdraw from treatment because of adverse cardiac events. Thus, in this series of 27 patients with depression and cardiovascular disease, fluoxetine was a relatively safe and well tolerated treatment and was associated with

fewer adverse cardiovascular effects than has been reported for tricyclic antidepressants.

There has been 1 prospective randomised, controlled trial comparing an SSRI, paroxetine, to a tricyclic antidepressant, nortriptyline, in depressed patients with ischaemic heart disease.[21] In this study, patients were randomised to a 6 week trial of either a therapeutic plasma concentration of nortriptyline or paroxetine at a dosage of up to 30 mg/day. The study included 81 patients (40 randomised to receive nortriptyline and 41 randomised to receive paroxetine) with a mean age of 58 ± 13 years, 80% male and 68% of whom had a previous myocardial infarction although not within the past 3 months. Patients met DSM-III[9] criteria for unipolar depression and the baseline Hamilton Depression Rating Scale (HAM-D)[22] mean score was 23 ± 1.

In this clinical trial, both drugs proved to be effective for the treatment of depression. Using a remission criteria of a final HAM-D score of ≤8, the intent-to-treat remission rate was 60% in the paroxetine-treated group and 55% in the nortriptyline-treated group, and the completer remission rate was 65% in the paroxetine group compared with 85% in the nortriptyline group. With respect to cardiovascular effects, nortriptyline demonstrated the expected cardiac profile of a tricyclic antidepressant, specifically a mean 11% increase in heart rate, a decrease in orthostatic blood pressure and suppression of ventricular arrhythmia. In contrast, paroxetine did not have any clinically significant sustained effect on heart rate, diastolic or systolic supine or standing blood pressure, cardiac conduction or ventricular ectopic activity. In any safety study, a critical result is the rate of serious adverse cardiac events. In this study, the rate of documented cardiac events that required an intervention by the cardiologist and discontinuation of study drug was 17% (8/40) in the nortriptyline-treated patients compared with only 2% (1/41) in the paroxetine-treated patients.

The third study of an SSRI in depressed patients with cardiac disease directly addressed the issue of the safety and efficacy of medication in the treatment of depression in the immediate post–myocardial infarction period. In this study, patients meeting criteria for major depression within 30 days of an acute myocardial infarction and who had an ejection fraction >35% were treated with placebo for 1 week and then open label sertraline, 50 to 200 mg/day, for 16 weeks.[23] The sample included 26 patients, mean age 57 ± 12 years, 58% male, mean baseline ejection fraction 49%, and mean baseline HAM-D score of 19 ± 6. Sertraline proved to be an effective antidepressant in this sample; the mean baseline HAM-D score decreased from 19 ± 6 at baseline to 9 ± 2 at the end-point. Sertraline did not induce any significant effect on heart rate, supine or standing diastolic or systolic blood pressure. The completion rate for the medication trial was 73% (19/26) and, most importantly, of the 7 patients who prematurely discontinued the medication trial, none did so because of a significant adverse cardiac event.

The results of these 3 studies of SSRIs have been consistent and, at this point, all data suggest that the SSRIs have a benign cardiovascular profile in depressed patients with pre-existing cardiac disease. However, based on these studies alone, it is premature to conclude that the SSRIs are a 'safe' treatment in patients with ischaemic heart disease. First, and most importantly, these studies included a relatively small number (n = 94) of patients and there may be infrequently occurring, but important, adverse cardiovascular events which these studies did not have the power to detect. Secondly, these studies were all acute medication trials; there are no data on the cardiovascular safety of SSRIs when given over the extended period of time necessary for the treatment and prophylaxis of depressive illness. Thirdly, because of their effect on the cytochrome P450 (CYP) system, the SSRIs have potential for drug-drug interactions, with some variations among the individual compounds depending on inhibition of specific CYP isoenzymes, e.g. 2D6, 3A4. This is particularly important in patients with cardiac disease who are often receiving multiple medications, some of which have a narrow margin of safety. Though the studies of

fluoxetine, paroxetine and sertraline treatment in cardiac patients on multiple medications did not report instances of drug-drug interactions, the clinician should still be vigilant to the possibility of this type of adverse event. Fourthly, the question of whether the cardiovascular effects of other SSRIs are similar or different to those established for fluoxetine, paroxetine and sertraline cannot be answered. There may be important, but as yet unrecognised differences between the SSRIs with respect to cardiovascular effects.

4. Conclusion

In making treatment decisions for a patient who has both a depressive illness and ischaemic heart disease, the clinician must consider the risk-benefit ratio of any intervention. With respect to the risk side of the equation, the SSRIs appear safer than the tricyclic antidepressants. However, with respect to therapeutic benefit, the SSRIs and tricyclic antidepressants do not have equivalent efficacy in all depressed patients. There are some types of depression, specifically melancholia, for which the tricyclic antidepressants have better established efficacy than the SSRIs.[24] Furthermore, any discussion of treatment options for a depressed patient should include consideration of electroconvulsive therapy (ECT). Though ECT is a relatively benign procedure in healthy depressed patients, to date only 1 study has reported on the effects of ECT in a large series of patients with cardiac disease.[25] ECT was given to 40 patients with depression and significant cardiac impairment, many of whom could not tolerate tricyclic antidepressants; the therapeutic outcome was favourable and the adverse events minimal, including no mortality. However, the assessment of cardiac effects was on a short term basis only, and therefore conclusions about safety must be restrained. Therefore, the treatment of the depressed patient with heart disease remains a challenge to the clinician, who must still make treatment decisions on a case by case basis, taking into account the type and severity of depression as well as the type and severity of the cardiovascular disease, and the established cardiovascular effects and therapeutic profile of the various antidepressant medications.

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