Review Article

Cardiovascular Effects of Antidepressants and Mood Stabilizers

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Abstract

Depression is a serious disorder in today's society, with the estimates of lifetime prevalence being as high as 21% of the general population in some developed countries. As defined by the American Psychiatric Association, depression is a heterogeneous disorder often manifested with symptoms at the psychological, behavioral, and physiological levels. Such patients are often reluctant to take synthetic antidepressants in their appropriate doses due to their anticipated side effects including inability to drive a car, dry mouth, constipation, and sexual dysfunction. As a therapeutic alternative, effective herbal drugs may offer advantages in terms of safety and tolerability, possibly also improving patient compliance. The advent of the first antidepressants, Monoamine Oxidase Inhibitors (MAOIs) and Tricyclic Antidepressants (TCAs), in the 1950s and 1960s represented a dramatic leap forward in the clinical management of depression. The subsequent development of the Selective Serotonin Reuptake Inhibitors (SSRIs) and the Serotonin Norepinephrine Reuptake Inhibitor (SNRI) venlafaxine in the past decade and a half has greatly enhanced the treatment of depression by offering patients medications that are as effective as the older agents but are generally more tolerable and safer in an overdose. The introduction of atypical antidepressants, such as bupropion, nefazadone, and mirtazapine, has added substantially to the available pharmacopoeia for depression. Nonetheless, rates of remission tend to be low and the risk of relapse and recurrence remains high. One of the concerns regarding the safety of antidepressant is its potential risk of cardiotoxicity and cardiovascular side effects. In this review, we will focus on the cardiovascular side effects of different types of antidepressants.

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Depression may be the most common serious illness with which a primary care physician is faced. It represents about 15 percent of office visits to the primary care physician.[1] Depression is a major public health problem, as more and more people are affected by it.[2] Approximately two to three percent of males and four to nine percent of females have depression at any one time. According to statistics from the National Institute of Mental Health, ten million Americans suffer from depression each year.[3] The annual direct cost of depression is estimated to be 12.4 billion dollars. Indirect cost, which includes time lost from work, is approximately 30 billion dollars. This makes the total cost of depression more than 40 billion dollars per year. Of course, the cost in human suffering is untold. Appropriate treatments could help over 70% of those with serious depression; but unfortunately, not everyone with depression seeks help.[4] Without treatment, symptoms can last for weeks, months, years, or even a lifetime. Approximately, 15% of patients with a major depressive disorder eventually commit suicide, resulting in 16,000 deaths every year. Most suicides are in the elderly. Studies

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have shown that all of the various antidepressants are equally effective if given in adequate doses. The big differences are the side effects and, in particular, their cardiovascular side effects.[5]

Selective serotonin reuptake inhibitors

The SSRIs have superseded the TCAs as the first-line agents for treating the cardiac patient with major depressive disorder.[6] Their efficacy is comparable to that of the older TCAs; they are better tolerated, safer in overdose, and have less pharmacological action on the heart.[7] The data thus far suggest that the SSRIs have minimal cardiovascular effects and a large margin of safety in treating patients with even severe heart disease. The SSRIs have little anticholinergic, antihistaminic, or noradrenergic activity and appear to inhibit platelet aggregation.[8]

In healthy patients, the SSRIs have no adverse effects on cardiac contractility or conduction; and there is no evidence of cardiotoxicity in overdose. In cardiac populations, they do not appear to cause significant ECG or blood pressure changes, although they can slow the heart rate.[9] Only rarely do they produce a clinically significant degree of sinus bradycardia. Because the SSRIs interfere with platelet aggregation, they can increase bleeding time. The SSRIs do have the potential to interact with a number of medications used in cardiac patients.[10] They inhibit hepatic cytochrome P450 isoenzymes, a series of isoenzymes involved in the oxidative metabolism of many drugs.[11] These include lipophilic beta blockers (e.g., metoprolol, propranolol); calcium channel blockers; type IC antiarrhythmics; angiotensin-converting enzyme (ACE) inhibitors; anticonvulsants; antihistamines; benzodiazepines; TCAs; codeine; and warfarin. The SSRIs can, therefore, raise the blood levels of these other agents when coadministered.[12] Caution should be exercised when giving SSRIs to patients on these medications, and in particular the prothrombin time of patients receiving both warfarin and an SSRI should be monitored closely. Because the SSRIs are highly protein bound, they may displace other protein-bound drugs when coadministered, thereby increasing their bioavailability. This interaction can occur with warfarin and digitoxin, but it does not appear to be clinically significant in magnitude.[13]

Because both depression and myocardial infarction (MI) enhance platelet activation, the period of post-MI depression poses excessive risks for thrombotic events. In a recent controlled analysis of 281 patients with acute coronary syndrome (ACS) with or without depression, patients with combined ACS and depression showed the highest levels of platelet factor 4, beta-thromboglobulin, and platelet/endothelial cell adhesion molecule-1 compared with ACS patients without depression or healthy controls. The use of SSRIs to treat depression in patients with coronary heart disease (CHD) or congestive heart failure (CHF) confers additional antiplatelet effects beyond the effect of aspirin.

Consequently, SSRI use may modify the dose or the need for aspirin or other antiplatelet medications.[14]

Tricyclic antidepressants

TCAs were previously the mainstay of antidepressants pharmacotherapy and remain effective agents that are still widely employed. However, their multiple cardiovascular side effects and their potential lethality in overdose are disadvantages in patients with cardiac disease. TCAs act on adrenergic and serotoninergic neurons in the central nervous system and, in the periphery, have anticholinergic properties. They also have quinidine-like effects and produce alpha-adrenergic receptor blockade.[6,13,15]

Orthostatic hypotension is one of the most common reasons for discontinuation of tricyclic antidepressant treatment. Orthostatic hypotension can occur with all of the tricyclic drugs, but it is less pronounced with nortriptyline.[6,15] It has been suggested that orthostatic hypotension is caused by α1-adrenergic blockade; however, the postural reflex is primarily affected. Resting supine blood pressure may be unaffected or may be raised. Orthostatic hypotension is most likely to occur or is most severe in patients who have preexisting orthostatic hypotension.

Desipramine has been reported to raise supine blood pressure in younger patients, although it is not clear this effect is limited to that age group. This effect may be similar to that reported for venlafaxine (Effexor).[16]

Tachycardia occurs with all tricyclic drugs, not just the more anticholinergic agents. Both supine and postural pulse changes can occur. Patients do not accommodate to the pulse rise, which can persist for months. Tachycardia is more prominent in younger patients who appear more sensitive to the sympathomimetic effects of these agents and is one of the most common reasons for drug discontinuation in this age group.[17]

The effect of tricyclic antidepressants on cardiac conduction has been a subject of great interest. Cardiac arrhythmia is the principle cause of death following overdose. As a result, for many years there was great concern about the use of tricyclic antidepressants in patients with heart disease. The effect of these agents has now been well described. These agents have type I antiarrhythmic qualities, or quinidine-like effects. Apparently, through inhibition of Na+, K+-adenosine triphosphatase (ATPase), the tricyclic compounds stabilize electrically excitable membranes and delay conduction, particularly His-ventricular conduction.[18]

At therapeutic blood concentrations, tricyclic drugs can have beneficial effects on ventricular excitability. Alternatively, in patients with preexisting conduction delay, the tricyclic antidepressants can further delay conduction and cause heart block. The QTc interval is regarded as the best index of those who might be vulnerable to this effect. Patients with

a QTc interval of 450 milliseconds or more are at increased risk and are not candidates for tricyclic antidepressant treatment. The risk of cardiac toxicity is further increased by high blood concentrations. For example, first-degree atrioventricular heart block is increased with imipramine plasma concentrations above 350 ng/mL and is increased more than 30-fold in patients with plasma concentrations above 450 ng/mL.[15,19]

Tricyclic drugs do not appear to adversely affect cardiac contractility or cardiac output. Studies using radionuclide angiography indicate no adverse effect of imipramine or doxepin on cardiac output, even in patients with diminished left ventricular ejection fractions. Severe orthostatic hypotension is reported to be common in these patients.[20]

Recently, another possible hazard of tricyclic drugs was suggested. Based on the report of the Cardiac Arrhythmia Suppression Trial (CAST) studies, which found that type I antiarrhythmic drugs given following myocardial infarction actually increased the risk of sudden death, Alexander Glassman, Steven Roose, and Thomas Bigger suggested that the tricyclic drugs might pose similar risks. Thus, a clinician considering the long-term use of tricyclic drugs in patients with ischemic heart disease needs to weigh this possible risk against possible benefits.[21]

Other antidepressants

Bupropion, a non-TCA that acts on both the dopamine and norepinephrine systems, causes less hypotension than the TCAs; does not affect cardiac conduction or contractility; and is safely used in patients with cardiac disease. It does not exacerbate ventricular arrhythmias or conduction block in patients with these conditions. An additional benefit of bupropion in cardiac patients is that it is apparently effective in smoking cessation. An increased incidence of seizures is seen at higher doses, and bupropion may occasionally elevate blood pressure and heart rate, although rarely to a clinically significant degree. Because it inhibits the cytochrome P450 isoenzymes, bupropion can raise the levels of beta blockers and type 1C antiarrhythmics when administered concurrently.[22]

Venlafaxine affects the reuptake of both serotonin and norepinephrine. It appears to have few cardiovascular actions and no effect on the ECG. At higher doses, venlafaxine has been associated with an elevation in blood pressure and pulse. Unlike the SSRIs, it does not inhibit cytochrome P450 isoenzymes and is not highly protein bound; it may, therefore, be useful in patients on cardiac medications.[13,23]

Duloxetine, the newest serotonin and norepinephrine reuptake inhibitor (SNRI), has not been studied in patients with cardiovascular disease. For now, we can only assume that we should manage it as we manage venlafaxine, with one important difference. Unlike venlafaxine, duloxetine does not raise blood pressure at high doses.[12]

Trazodone, a triazolopyridine antidepressant, is often used in low doses as a hypnotic. Cardiovascular complications from trazodone are rare. It has few, if any, antiarrhythmic properties, although it has rarely been associated with heart block and ventricular arrhythmias. Because of its weak alpha-adrenergic blockade, it may also produce orthostatic hypotension. Nefazodone, a closely related drug, can also occasionally produce orthostatic hypotension and has significant P450 isoenzyme inhibition. Therefore, nefazodone can increase the levels of concurrently administered calcium channel blockers, quinidine, and lidocaine.[12]

Mirtazapine is a tetracyclic antidepressant with a complex mechanism of action. It has not been studied in patients with cardiovascular disease; but in noncardiac populations, it does not affect blood pressure or cardiac conduction. It has no anticholinergic activity, but it may increase the heart rate slightly.[12]

Psychostimulants, such as dextroamphetamine and methylphenidate, are used to treat depression in medically compromised and elderly patients. These agents tend to be used when depression is life threatening, when immediate treatment response is crucial (because they have a rapid onset of action), and in depressions with prominent anergia and apathy. Although there is considerable clinical support for their use, empirical evidence of their sustained efficacy over time is lacking. Serious cardiovascular side effects such as tachycardia, hypertension, and arrhythmias are relatively rare; still, caution must be exercised when administering these medications to patients with significant hypertension, tachycardia, or ventricular ectopy, and blood pressure and heart rate should be monitored.[12]

Mood stabilizers

Lithium exerts minimal cardiotoxicity at therapeutic doses in most patients and can be used safely in cardiac disease if initiated at a low dose, increased gradually, and monitored carefully.[24] Clinically significant, cardiovascular side effects of lithium are rare; they may include sinus node dysfunction and increases in ventricular irritability. Benign, reversible T wave changes (including inversion and flattening) are common with lithium administration and are not clinically significant. The major toxic effects of lithium are neural (confusion, sedation), and the primary concern in cardiac patients is lithium toxicity resulting from decreased renal clearance or hypovolemia.[25] This is of concern in patients with CHF, and it is exacerbated by their diuretics and restricted sodium intake. Sodium depletion decreases renal clearance of lithium. In the kidney, lithium is filtered out at the glomerulus and then reabsorbed in the proximal tubules. Sodium depletion, such as with diuretics, causes an increased proximal reabsorption

of sodium, and lithium is reabsorbed more efficiently at the same time. A given lithium dose, thus, results in a higher blood level. Lithium may still be administered to the patient on diuretics, but levels must be monitored and dosage may need to be reduced. The elderly also require lower lithium doses because of a decline in the glomerular filtration rate. On rare occasions, lithium may worsen arrhythmias in patients with sinus node dysfunction.[24-25]

Anticonvulsants

These drugs are increasingly prescribed to stabilize the mood of patients with bipolar disorder (manic-depressive illness). Their use in cardiac patients has not yet been systematically studied. Carbamazepine has quinidine-like effects and can aggravate heart block, and it may also exacerbate CHF. Carbamazepine can also produce hyponatremia, and this effect is potentiated by other causes of hyponatremia such as diuretics and CHF.[24]

Valproate, albeit not yet studied widely in cardiac populations, does not appear to have adverse cardiac effects. It can, however, lower the platelet count, decrease fibrinogen levels, and increase the prothrombin time. Lamotrigine is increasingly used in refractory depression and appears to have no significant cardiac effects and no impact on the cytochrome P450 system. Topiramate may have a role in the treatment of mania and anxiety. It is renally excreted, and care must be taken to ensure adequate hydration.[22]

Conclusion

Depression is an international public health issue with impairment in social and occupational functioning, increased psychiatric and medical comorbidity, and an increased risk of mortality among depressed individuals as consequences. Although SSRIs may not work as well as TCAs in severe depression and/or melancholia, generally SSRIs are superior to the TCAs in terms of side-effects and, in particular, cardiovascular adverse effects.

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