Review Articles

Cardiovascular Considerations in Antidepressant Therapy: An Evidence-Based Review

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Abstract

There is a definite correlation between cardiovascular diseases and depressive disorders. Nevertheless, many aspects of this association have yet to be fully elucidated. Up to half of coronary artery disease patients are liable to suffer from some depressive symptoms, with approximately 20% receiving a diagnosis of major depressive disorders. Pharmacotherapy is a key factor in the management of major depression, not least in patients with chronic diseases who are likely to fail to show proper compliance and response to non-pharmacological interventions. Antidepressants are not deemed completely safe. Indeed, numerous side effects have been reported with the administration of antidepressants, among which cardiovascular adverse events are of paramount importance owing to their disabling and life-threatening nature. We aimed to re-examine some of the salient issues in antidepressant therapy vis-à-vis cardiovascular considerations, which should be taken into account when prescribing such medications.

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Introduction

A definite correlation exists between cardiovascular diseases (CVD) and depressive disorders, yet many aspects of this relationship have remained challenging. Up to 50% of patients with coronary artery disease (CAD) suffer from some depressive symptoms and approximately 20% of them have a diagnosis of major depressive disorder (MDD).[1, 2] On the other hand, it has been demonstrated that depressed patients are more vulnerable to experience myocardial infarction even after controlling their pure cardiovascular risk factors.[3, 4] Moreover, significantly higher risk of mortality due to cardiovascular events has been reported in patients suffering from psychiatric disorders such as depression.[5, 6] The diagnosis of depression can be difficult in people with CVD as depressive symptoms such as fatigue and low energy are common in people with CVD and may also be a side effect of some drugs used to treat CVD such as beta blockers. The diagnosis may be further complicated in such patients by their responses to their disease, which may include denial, avoidance, withdrawal, and anxiety.[1, 2]

According to the World Health Organization (WHO) reports, ischemic heart disease is now the leading cause of death worldwide and by 2030, depression will have the

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greatest burden among diseases in terms of years lost due to disability.[7] Besides impairing patients' quality of life, depression has profound negative effects on the long-term prognosis of individuals with any type of cardiovascular disorder.[8, 9] These facts further underscore the importance of the proper treatment of depression in patients with CVD.

Pharmacotherapy plays a key role in the management of major depression, especially in patients with chronic diseases who do not usually show proper compliance and response to non-pharmacological interventions.[10-12] The overall number of prescriptions containing at least one antidepressant agent has considerably increased in recent decades.[13] However, antidepressants are not thought to be completely safe drugs and numerous side effects have been reported with their administration, among which cardiovascular adverse events are of special importance because of their disabling and life-threatening nature.[14-17] Serious complications such as arrhythmia or sudden cardiac death can even occur in individuals with no prior history of cardiovascular problems.[18] Apparently, patients with CVD are more susceptible to encounter such adverse events, which can negatively affect the course of their cardiac disease as well. Many of these unfavorable reactions with antidepressants can be prevented by increasing the knowledge of physicians and patients about basic processes and clinical cautions in this regard. Given these challenges, we aimed to review some of the most important issues in antidepressant therapy with regard to cardiovascular considerations that should be kept in mind when prescribing such medications.

Antidepressants categories and their cardiovascular side effects

Although antidepressants are commonly used in clinical setting, numerous negative effects of antidepressants on the cardiovascular system have been reported to date, including bradycardia, tachycardia, hypertension, hypotension, orthostatic hypotension, electrocardiogram (ECG) changes, electrolyte abnormalities, reduced cardiac conduction and output, arrhythmias, and sudden cardiac death.[15] A summary of the essential basic and clinical considerations in the administration of different classes of antidepressants is presented first. Because of its prevalence and life-threatening consequences, arrhythmia is then further discussed in a separate section. Antidepressant agents are classified as first or second generation: first-generation antidepressants include monoamine oxidase inhibitors (MAOIs) and tricyclic/tetracyclic antidepressants (TCAs) and second-generation antidepressants include selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants.

MAOIs (Tranylcypromine, Phenelzine, Moclobemide, Selegiline, etc.) were the first antidepressant drugs used in clinical practice. Even though MAOIs are effective in improving depressive symptoms, various unfavorable side effects and drug interactions significantly limit their clinical application.[19] These agents can affect different neurotransmitter systems. Since a period of time is needed to establish such neurotransmitter disturbances, cardiovascular adverse events are usually seen 12-24 hours after MAOIs have reached their toxic levels.[16] Hypotension and tachycardia are frequently experienced under MAOIs use;[20] this phenomenon should be particularly watched in elderly patients who have more vulnerability to cardiovascular events and usually take multiple drugs affecting the cardiovascular system like antihypertensive medications. A hypertensive crisis can occur when tyramine-containing foods such as aged cheese are ingested along with MAOIs, which is due to epinephrine, norepinephrine, and dopamine release.[21] In more detail, tranylcypromine can lead to symptomatic hypotension or a mild decrease in diastolic blood pressure.[22] High doses of Phenelzine may cause acute myocarditis, and the manifestations of Phenelzine toxicity include agitation, seizure, tachycardia, and hypertension. However, hypotension has been reported as well.[23] Moclobemide overdoses can result in QTc prolongation, predisposing to ventricular tachyarrhythmia and torsade de points (TdP).[24]

TCAs (Imipramine, Amitriptyline, Nortriptyline, Desipramine, Amoxapine, Clomipramine, Doxepin, Maprotiline, etc.) were the first-line treatment for depression before the introduction of SSRIs, but their application has been restricted in recent decades mainly because of cardiovascular adverse events.[25, 26] Although nowadays they are not prescribed to that extent, TCAs are still widely used particularly when patients do not respond to SSRI therapy.[27] Cardiovascular complications of TCAs have been reported not only in patients with CVD but also in people with no prior history of cardiac diseases.[28]

Through making delay in phase 0 of depolarization and impairing the electrical conduction in His-Purkinje fibers as well as in atrial and ventricular myocytes, TCAs can slow conduction velocity, which is presented on the ECG by prolonged PR, QRS, and QT intervals.[29] This delay is due to the inhibition of the fast sodium channels by TCAs and can be critical particularly in those with previous conduction defects, patients receiving class 1 antiarrhythmic agents, or in case of TCA consumption with high doses.[30, 31] In overdose ranges, this delayed conduction may even cause complete heart block or ventricular reentry arrhythmia, which can ultimately lead to death.[32, 33] It has also been demonstrated that depressed patients who are taking TCAs and have a baseline conduction defect, particularly a bundle branch block, are at increased risk for developing symptomatic atrioventricular (AV) block.[31] Moreover, TCAs can reduce heart rate variability (HRV) and cause different cardiac arrhythmias such as ventricular fibrillation, ventricular premature beats, and reentry arrhythmias.[34-37]

At therapeutic levels, TCAs are able to block alpha-adrenergic receptors and reduce systemic vascular resistance. Therefore, they may cause hypotension or orthostatic hypotension, especially in case of dehydration or concurrent use of antihypertensive medications.[17] Sinus tachycardia has been also reported under TCAs use which is due to the significant inhibition of central cholinergic neurotransmission.[35] In summary, TCAs are not obviously the first-line choice for treating depression in patients suffering from CVD. Because of the serious unfavorable effects and potential cardiotoxic nature of TCAs, these agents should be prescribed cautiously not only in patients with CVD but also in individuals without prominent cardiovascular complaints. Accordingly, close monitoring of patients receiving TCAs with particular attention to cardiovascular markers seems to be mandatory.

SSRIs (Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Sertraline, Paroxetine, etc.) are the first-line antidepressant agents in most cases because of their more acceptable safety profile and wider margins of nontoxic levels compared with other antidepressant classes. Cardiovascular adverse events are usually mild and are unlikely to occur with SSRIs at therapeutic doses.[26] Nevertheless, orthostatic hypotension, mild bradycardia, and conduction abnormalities such as QT interval prolongation have been reported under SSRIs use.[33, 34] Most cases of SSRI-induced QT interval prolongation and subsequent TdP are seen in patients with underlying vulnerabilities such as congenital long QT syndrome, recent myocardial infarction, hypokalemia, hypomagnesemia, or in case of drug overdose.[38-41]

Interestingly, it has been suggested that SSRIs may even have some benefits for the cardiovascular system through complex mechanisms. SSRIs users have been shown to experience lower rates of myocardial infarction compared with the other types of antidepressant, particularly TCAs.[42] SSRIs interfere with platelet activation and aggregation by inhibiting serotonin uptake into platelets and subsequently decrease the risk of ischemic heart events.[42, 43] Evidence shows that this category of antidepressants can normalize or at least improve some abnormalities of platelet function indices in patients with ischemic heart diseases.[42, 44] However, SSRIs inhibitory effects on platelet activation and aggregation may theoretically lead to impaired hemostasis and abnormal bleeding.[45] This point should be carefully noted in prescribing these agents for patients with underlying hemostatic abnormalities or those on anticoagulation therapies.

SSRIs should not be assumed to be completely safe from cardiovascular point of view. Although these are usually first-line antidepressant agents, a growing number of reports are emerging on cardiovascular complications due to SSRIs use, the most important of which are arrhythmias and syncope.[18, 46-48] Vasoconstriction and consequent myocardial ischemia (Prinzmetal's angina) has been reported in connection with SSRIs use.[49] SSRIs can cause QT interval prolongation, but they do not usually lead to life-threatening arrhythmias in therapeutic doses.[50] Among SSRIs, Citalopram is known to have the highest cardiotoxic capacity in a dose-dependent fashion.[51] A wide range of conduction disturbances and arrhythmias has been reported vis-à-vis Citalopram intake, including sinus bradycardia and tachycardia, left and right bundle branch block, supraventricular tachycardia, ventricular fibrillation, and QTc prolongation.[52-57] In summary, SSRIs are unlikely to cause serious cardiovascular adverse events when used in recommended dosage ranges, but further studies with anterograde observations are warranted to clarify their precise cardiovascular safety profile.

SNRIs (Venlafaxine, Desvenlafaxine, Reboxetine, Duloxetine, etc.) have many similarities with SSRIs in terms of basic mechanisms of action and clinical side effects. In addition to serotonin, SNRIs also inhibit the reuptake of norepinephrine from the synaptic cleft, resulting in increased neurotransmission. Increased levels norepinephrine and serotonin can accelerate cardiac sympathetic activity, leading to a mild increase in heart rate and systemic blood pressure. Apparently, excessive sympathetic stimulation may cause dangerous tachyarrhythmias and/or hypertensive crisis.[16] Blood pressure monitoring is recommended in patients receiving SNRIs, particularly Venlafaxine, since elevation in blood pressure has been reported in epidemiological studies.[55, 56] Venlafaxine is also suspected to cause QTc prolongation at toxic levels through its blocking effect on sodium channels,[57-60] but high doses of Reboxetine have not been associated with QTc prolongation in healthy subjects.[61]

Atypical antidepressants (Mirtazapine, Agomelatine, Bupropione, Nefazodone, Trazodone, etc.) are some individual medications with unique modes of action which are usually prescribed for patients who do not respond to first-line treatment or cannot tolerate their side effects. In general, these agents show minimal cardiovascular side effects. Mirtazapine is an antagonist of both α_2-adrenergic and serotonin receptors but has no impact on cholinergic system or rapid sodium channels. In overdoses, this medication may cause moderate hypotension and can affect patients' heart rate.[62, 63] Trazodone has some minimal anticholinergic activity and in acute overdoses may cause QT prolongation and impaired atrioventricular conduction.[64] When used in high doses, Trazodone may result in orthostatic hypotension as well.[65]

Arrhythmia: a serious adverse event

Arrhythmias are one of the most critical and important side effects of antidepressant agents. Different categories of antidepressants, particularly TCAs, provoke various types of arrhythmias through complex processes involving voltage-gated sodium, potassium, and calcium ion channels in cardiac

myocytes and conduction system.[66-68] Of note, the results of a recently published large-scale epidemiological study estimated the risk of sudden cardiac death and ventricular arrhythmia to be 3.3/1000 person-years after antidepressant exposure.[17]

The QT interval of the ECG is generally accepted as the predictive parameter for predisposition to arrhythmia. In healthy individuals, the mean QTc length is approximately 400 milliseconds (ms). QT interval prolongation (longer than 500 ms) may result in "R on T phenomenon" in some special situations, causing TdP.[69, 70] TdP is a life-threatening polymorphic ventricular tachyarrhythmia and usually presents with seizure, dizziness, or syncope, predisposing to ventricular fibrillation and sudden cardiac death. Some antidepressants can bind to cardiac inward-rectifier potassium ion channels and block the efflux of potassium from cardiac myocytes, leading to the prolongation of repolarization phase and QT interval.[66, 71, 72] Within the tricyclic and tetracyclic categories of antidepressants, Imipramine, Amitriptyline, Nortriptyline, Desipramine, Maprotiline, and Doxepin may cause considerable QTc prolongation, while the administration of Clomipramine, Mirtazapine, and Trazodone lead to a mild prolongation.[73, 74] Fortunately, there is no report of QTc abnormality with SSRIs or SNRIs use in their therapeutic doses.[74] However, QTc prolongation has been reported in some cases of Fluoxetine, Citalopram, and Venlafaxine intake when used by toxic dosages or in patients with additional risk factors.[41] Similarly, TCAs, Citalopram, Fluoxetine, Paroxetine, and Mirtazapine have been reported to cause TdP most often in patients with other risk factors, at toxic levels, or in combination with other TdP-causing medications.[41, 73, 75] It has been shown that some antiarrhythmic agents such as Quinidine, Sotalol, Flecainide, and Propafenone can cause QT prolongation, leading to TdP themselves and the overall risk of such event is interestingly much lower with antidepressants compared with these antiarrhythmic medications.[76, 77] Factors which increase the risk of QT prolongation occurrence and consequent TdP include female gender, age over 65 years old, bradycardia, myocardial hypertrophy, congenital long QT syndrome, hypomagnesemia, hypokalemia, and hepatic or renal failure.[76, 77]

In addition to the ECG markers, HRV is known as a relatively more reliable predictor of arrhythmia occurrence, particularly in some specific patients such as those with CAD, chronic heart failure, and diabetes mellitus.[78, 79] Cardiac arrhythmias may develop in a person with a normal ECG, but HRV almost always shows some degrees of abnormality before arrhythmia occurrence.[80] HRV is defined as the standard deviation of interbeat intervals. Variability in the heart rate is regulated by autonomic innervations and a high degree of beat-to-beat variability is seen in a normal functioning heart. This HRV provides a protective mechanism against many assaults such as myocardial infarction and heart failure.[81] HRV has been shown to be reduced in patients suffering from depression.[82, 83] However, it is not clear whether this reduction in HRV is secondary to depression itself or the effects of antidepressant medications.[84, 85] Interestingly, it has been shown that HRV has a negative relationship with the severity of depressive symptoms and severely depressed patients show lower HRV than those with mild to moderate depression.[86] Even more striking, low HRV negatively mediates the impact of depression on patients' survival after major cardiac events such as myocardial infarction.[87]

Among antidepressant agents, TCAs markedly reduce HRV through their profound impact on adrenergic and cholinergic systems.[88] Although further research is needed to define the precise impact of different antidepressant classes on HRV, it has been demonstrated that SSRIs such as Sertraline cause either no changes or a mild increase in HRV.[89] Although Paroxetine has some anticholinergic activity in addition to being an SSRI, patients receiving this medication do not show any significant change in their HRV.[90]

Antidepressant therapy in cardiovascular patients

Heart Failure

The prevalence of depressive disorders is estimated to be up to 50% in patients with heart failure (HF).[91, 92] Independent of HF severity, depression leads to higher mortality rates and a significant decline in the patients' prognosis and quality of life.[93] Some factors are known to increase the risk of developing depression in patients with HF, including female gender, young age, comorbid chronic obstructive pulmonary disease (COPD), higher functional class by the time of diagnosis based on New York Heart Association (NYHA) functional classification, and significant deterioration of NYHA functional class within the first year of diagnosis.[93-94]

It has been proven that amelioration of depressive symptoms has beneficial advantages on the survival of patients who suffer from both HF and depression. Patients who respond to antidepressant therapy within the first year of treatment have shown to experience significantly lower rates of morbidity and mortality.[95] In terms of antidepressant agents, SSRIs seem to be the first choice in patients with HF. However, the results of a large-scale randomized placebo-controlled clinical trial showed that Sertraline administration was safe but not efficient for improving depression in these patients.[96, 97] Despite the negative effects of depression on the clinical course of HF, some controversial evidence indicates worsening of the patients' prognosis (increase in cardiovascular hospitalization and mortality rate) after receiving treatment with antidepressant medications.[98, 99] Comparing the prognosis of patients with HF who were treated with either SSRIs or TCAs showed that the

coadministration of beta blockers with TCAs was associated with lower mortality than with SSRIs.[99] More research is required to clarify such relationships; be that as it may, current evidence highlights the importance of considering specific issues in choosing antidepressants for patients suffering from HF.

Acute Coronary Syndrome

Evidence shows that the occurrence of acute coronary syndromes (ACS) doubles the risk of developing MDD in affected individuals.[100] Depression has several negative consequences in patients who have experienced ACS such as decreasing their compliance with cardiac rehabilitation and medications intake as well as increasing their mortality and rehospitalization rates.[101] Abnormal levels of various substances such as serotonin, norepinephrine, and dopamine have been proposed as a probable basic mechanism in the association between ACS and MDD. On the one hand, deficits in such neurotransmitters are attributed to the pathophysiology of depression. On the other hand, several lines of evidence shows that these abnormalities are involved in the stiffening and narrowing of arteries as well as increased endothelial reactivity seen in the different types of CAD.[44] Moreover, depression leads to various dysfunctions in the immune system and neuroendocrine pathways. These changes predisposes vessel plaques to be unstable and along with hemodynamic factors may eventually result is plaque rupture, thrombosis, and subsequent ACS.[44]

Choosing the best strategy to treat depression in patients with ACS is still a big challenge and we face a relative inconsistency in the literature in this regard. Due to serious cardiovascular events reported with TCAs use, this class of antidepressants is totally contraindicated in patients with ACS.[31, 102] Like the majority of CVDs, SSRIs constitute the first-line antidepressants prescribed for patients suffering from a coexistent ACS.[103] In addition to their antidepressant activity, SSRIs are believed to have some cardioprotective properties through blocking the serotonin reuptake during platelet aggregation and subsequent antithrombotic effects.[104] Citalopram or Sertraline have been suggested to be the first-choice antidepressant agents for patients with CAD.[105, 106] In addition to these two SSRIs, Fluoxetine is recommended to be used in improving post-myocardial infarction depression.[107] Finally, it has been demonstrated that SSRIs use in patients with depression who experience acute myocardial infarction may also decrease their cardiovascular-related morbidity and mortality rates.[108]

Conclusion

Several lines of evidence indicate that different cardiovascular considerations should be inspected in patients who need to take antidepressant medications. Since there is no robust clinical guideline yet, patients should be individually evaluated with respect to their potential risks and benefits from antidepressant therapy. The ECG is recommended to be definitely performed before and after starting treatment, particularly in patients with pre-existing cardiac diseases and/or risk factors. Periodical monitoring with the ECG is also required to detect probable QT prolongation or other substantial ECG abnormalities indicative of increased risk of serious arrhythmias. Moreover, patients should be closely monitored for the manifestations and laboratory abnormalities of fluid/electrolyte disturbances. Further basic and clinical studies are warranted to reach a relative consensus in selecting appropriate antidepressant regimen for each patient and subsequently avoid life-threatening cardiovascular adverse events due to depression treatment.

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