AMERICAN COLLEGE of CARDIOLOGY

Current Updates Regarding Antidepressant Prescribing in Cardiovascular Dysfunction

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Expert Analysis

Major depressive disorder (MDD) is one of the most debilitating health conditions in the world that often requires lifelong treatment and close monitoring. The World Health Organization now reports MDD to be the universal leading cause of disability.[1] Untreated MDD has been associated with an increased risk of suicide, decreased quality of life and increased risk of cardiovascular related mortality.[2] The increased cardiovascular disease (CVD) risk can also be attributed to other factors, including physical inactivity, poor medication adherence, smoking, obesity and other major comorbidities such as diabetes and hypertension (HTN).[3] There is also a high prevalence of MDD in patients with pre-existing CVD. Up to 45% of patients with coronary artery disease (CAD), including those with stable CAD, unstable angina or myocardial infarction suffer from clinically significant depressive symptomatology.[4] The following review will discuss the treatment of MDD related to CVD and evaluate antidepressant use in relation to the updated guideline recommendations regarding the treatment of heart failure (HF) and HTN.

As MDD is associated with worsening cardiovascular outcomes, it is imperative to treat the patient's MDD appropriately. When choosing a treatment plan for the acute phase of MDD, options include psychotherapy, pharmacotherapy or a combination best suited for the patient. Pharmacologically, antidepressants have been the mainstay of treatment and are among the most frequently prescribed medications worldwide. Antidepressants are comprised of several different classes including: selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).[5] Both TCAs and MAOIs have fallen out of favor and are now reserved for treatment resistant depression due to their side effect profiles and safety concerns. The TCAs are associated with arrhythmogenic activity which may be a result from the potent blockade of cardiac sodium and potassium channels. Additionally, the TCAs affect cardiac contractility and have even been linked to worsening of ischemic heart disease and sudden cardiac death, and thus should be avoided completely in patients at risk of a serious arrhythmia and those with CAD.[6]

Several studies have suggested that SSRIs may potentially reduce the risk of thrombotic events, but their role in CVD remains controversial.[7] One study attempted to answer this question in order to quantify the relationship between commonly used antidepressants and cardiovascular

outcomes. Results from the meta-analysis showed no evidence that SSRI users were at a higher risk of developing acute heart disease; however, significant between-study heterogeneity was observed. The authors also found a 29% increased risk of acute heart disease comprising coronary heart disease, acute myocardial infarction, ischemic heart disease and sudden death when TCAs were used.[3] A separate meta-analysis evaluated the risk of coronary heart disease (CHD) readmission rates in patients diagnosed with both CHD and depression using SSRIs compared to placebo or no intervention. Results of the meta-analysis indicated that there were no significant differences in mortality risk or CHD admission rates between groups; however, there was a significant difference in depressive symptomatology when SSRIs were present in the medication regimen.[8] A third meta-analysis sought to summarize the data regarding antidepressant efficacy and tolerability in depressed patients with CAD. The findings from the meta-analysis showed that treatment with SSRIs resulted in significant therapeutic effects without increased rates of discontinuation.[9] A systematic review looked at the effect of SSRIs, SNRIs and TCAs on the outcomes of mortality, cardiovascular function and depression.[10] This review demonstrated that antidepressants were not associated with an increased mortality rate and were well tolerated in this population. However, there was not enough evidence to conclude whether they offered significant effects for the improvement of depression or cardiac outcomes.[10] Collectively, these studies support antidepressant treatments in CVD and the results are reflective of the outcomes frequently encountered in clinical practice.

Depression has been shown to be an independent risk factor for mortality in CVD, especially in patients diagnosed with HF. An estimated one out of every five patients diagnosed with HF will also struggle with MDD, which can more than double the mortality risk for those individuals.[11,12] Despite advances in the management for HF, optimal therapeutic management in patients who concurrently suffer from MDD should be considered. Thus, with the emergence of updated HF management guidelines, one must analyze the recommendations and how they affect current treatments for MDD. One important element to always consider when designing a therapeutic regimen for patients with concurrent MDD and HF is the potential for drug interactions. In HF patients, the initial treatment options include an angiotensin converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB) plus a beta-blocker and diuretic as needed. The 2017 American College of Cardiology/American Heart Association/Heart Failure Society of America Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure introduced new therapeutic options for the treatment of acute and chronic HF: ivabradine, a sinoatrial (SA) node modulator and valsartan/sacubitril, an angiotensin receptor-neprilysin inhibitor. Ivabradine is indicated to decrease hospitalization rates in patients who have HF with a left ventricular ejection fraction ≤35% and a heart rate ≥70 bpm, despite being on appropriate standard therapy.[13] Ivabradine blocks the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel which is responsible for the cardiac pacemaker If current, consequently reducing heart rate.[14,15] Electrophysiology studies show that ivabradine also prolongs the PR interval and uncorrected QT interval. Concomitant use of ivabradine with QT prolonging agents must be approached with caution, as such combinations have the potential to induce Torsades de pointes.[14] Many of the commonly utilized antidepressants may also prolong the QT interval. These medications include SSRIs, such as citalopram, escitalopram and fluoxetine as well as

SNRIs such as venlafaxine. Citalopram and fluoxetine produce the highest risk when combined with ivabradine.[16] TCAs, such as amitriptyline and imipramine, in addition to trazodone, a weak serotonin and norepinephrine reuptake inhibitor, have also been shown to prolong the QT interval. It is recommended to avoid concurrent use of ivabridine with these agents or, if unavoidable, employ an extensive QT monitoring strategy. Other antidepressant options, namely bupropion or mirtazapine may be considered since they carry minimal to no risk of QT prolongation.

Valsartan/sacubitril is a guideline recommended option for HF management. This medication serves as an alternative therapy to ACE-Is and ARBs to further reduce morbidity and mortality in patients with chronic symptomatic HF with reduced ejection fraction NYHA Class II or III. Valsartan/sacubitril has a unique mechanism via the inhibition of neprilysin, a neutral endogenous enzyme that degrades several vasoactive peptides and decreases the breakdown of angiotensin, a potent vasoconstrictor.[17,18] Sacubitril is a prodrug activated by esterases that acts by antagonizing neprilysin receptors, subsequently increasing the level of these substances to promote cardiac relaxation, vasodilation, diuresis and natriuresis. The most common adverse effects seen in the trials with valsartan/sacubitril were angioedema and hypotension.[19,20] Patients currently treated for depression with certain agents such as MAOIs, including phenelzine or selegiline, or the SNRI duloxetine, while concomitantly being treated with valsartan/sacubitril may be more susceptible to hypotension due to additive blood pressure lowering effects. However, such combinations can still be utilized with close monitoring.

Depression is also very common in HTN and other chronic diseases and is frequently associated with adverse health outcomes, poor quality of life and excessive use of healthcare resources.[21] The release of the 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults makes it exceedingly prudent for practitioners to know if the treatment recommendations for HTN have the potential to interact with already existing MDD regimens. Antihypertensive drug therapy includes first-line agents belonging to four therapeutic classes: thiazide diuretics, calcium channel blockers (CCBs), ACE-Is and ARBs. The update recommends chlorthalidone as the preferred thiazide diuretic over hydrochlorothiazide in relation to its prolonged half-life and evidence of CVD risk reduction.[22] Chlorthalidone exerts its diuretic effect on the body by inhibiting the reabsorption of sodium and chloride in the cortical segment of the ascending loop of Henle, thus leading to more cases of electrolyte imbalance (e.g., hyponatremia) compared to hydrochlorothiazide.[22,23] Hyponatremia, especially in certain patient populations (e.g., elderly, chronic kidney disease), can potentially be exacerbated by concurrent use with SSRIs and SNRIs. Although there is a <1% chance of occurrence,[16] SSRIs and SNRIs may induce a syndrome of inappropriate antidiuretic hormone secretion, a condition characterized by over-secretion of the hormone vasopressin, leading to impaired water excretion.[24,25,26,27] While concomitant use of chlorthalidone with these two medication classes is not contraindicated, appropriate monitoring should be implemented if a patient presents with signs and symptoms of hyponatremia.

In today's developed world where the leading cause of mortality is CVD, selecting an appropriate pharmacological treatment for individuals with concomitant CVD and MDD is essential.[28]

Providers must weigh the risks versus benefits on a case-by-case basis while considering a patient's comorbidities and past medical history. With the advent of updated HTN and HF guidelines, it is vital to be cognizant of how these new recommended medications might interact with first- and second-line antidepressant agents. As more research is conducted regarding these new recommendations, healthcare providers must always keep in mind the safety, tolerability, efficacy and patient's preference when determining an optimal treatment for this patient population.

Table 1: Antidepressant Use in Cardiovascular Dysfunction

Authors	Journal, Year of Publication	Article	Number of Studies Evaluated	Purpose of Meta-Analysis	Findings
Biffi A, et al.	*Eur J Clin Pharmacol*, 2017	Use of Antidepressants and the Risk of Cardiovascular and Cerebrovascular Disease: A Meta-Analysis of Observational Studies	22 observational studies	Review associations between antidepressant use and CV outcomes	No evidence that SSRI users were at a higher risk of developing acute heart disease but significant between-study heterogenicity was observed. There was 29% increased risk of acute heart disease found for using TCAs.
Dowlati Y, et al.	*Can J Psychiatry*, 2010	Efficacy and Tolerability of Antidepressants for Treatment of Depression in Coronary Artery Disease: A Meta-Analysis	4 RCTs	Summarize the data on the efficacy and tolerability of antidepressant treatment for depression in CAD	Treatment with SSRI antidepressants resulted in significant therapeutic effects without increasing the rates of discontinuation.

Pizzi C, et al.	*Am J Cardiol*, 2011	Meta-Analysis of Selective Serotonin Reuptake Inhibitors in Patients with Depression and Coronary Heart Disease	6 RCTs	Summarize evidence on the effects of SSRI versus placebo or no antidepressants in all-cause mortality and readmission for CHD in patients with CHD and depression.	No significant difference in mortality risk or CHD admission rates compared to controls. There was a significant decrease in depressive symptomatology, CHD admission and mortality rates when SSRIs were present in the medication regimen.
Rajeswaran T	*International Journal of Psychiatry in Clinical Practice*, 2017	The Effect of Antidepressant Medications in the Management of Heart Failure on Outcomes: Mortality, Cardiovascular Function and Depression—a Systematic Review	3 RCTs 2 cohorts	Determine whether the use of antidepressants could improve outcome in patients with HF and concomitant depression.	Antidepressants are not associated with increased mortality rate and well tolerated in this population. Not enough evidence to conclude whether they offer significant effects for improvement of depression or cardiac outcomes.

Table 2: Antidepressant Use in Heart Failure

Caution with Concomitant Ivabradine	Caution with Concomitant Valsartan/Sacubitril
Citalopram	Duloxetine
Escitalopram	Phenelzine
Fluoxetine	Selegiline
Venlafaxine	*Monitor blood pressure for possible hypotension
Tricyclic Antidepressants (e.g., amitriptyline, imipramine)	
Trazodone	
*QT interval monitoring may be recommended if any of the agents listed above are used in combination with Ivabradine	

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Clinical Topics: **Arrhythmias and Clinical EP, Cardiovascular Care Team, Dyslipidemia, Heart Failure and Cardiomyopathies, Prevention, Vascular Medicine, Implantable Devices, EP Basic Science, SCD/Ventricular Arrhythmias, Atrial Fibrillation/Supraventricular Arrhythmias, Lipid Metabolism, Statins, Acute Heart Failure, Heart Failure and Cardiac Biomarkers, Hypertension, Smoking**

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