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REVIEW ARTICLE

The Cardiovascular Effects of Newer Antidepressants in Older Adults and Those With or At High Risk for Cardiovascular Diseases

Lauren M. Behlke[1] · Eric J. Lenze[1] · Robert M. Carney[1]

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Abstract

Depression is common in older adults and those with cardiovascular disease. Although selective serotonin reuptake inhibitors generally have been shown to be safe to treat depression in these patients, it is important to identify additional antidepressants when selective serotonin reuptake inhibitors are not effective. This qualitative narrative review summarizes what is known about the cardiovascular side effects of some of the newer antidepressants. Twelve novel non-selective serotonin reuptake inhibitor antidepressants were identified from the literature: venlafaxine, desvenlafaxine, duloxetine, milnacipran, levomilnacipran, mirtazapine, bupropion, vilazodone, vortioxetine, agomelatine, moclobemide, and ketamine–esketamine. A search restricted to publications written in English was conducted in PubMed and Google Scholar with the following search criteria: the specific antidepressant AND (QT OR QTc OR "heart rate" OR "heart rate variability" OR "hypertension" OR "orthostatic hypotension" OR "cardiovascular outcomes" OR "arrhythmia" OR "myocardial infarction" OR "cardiovascular mortality") AND (geriatric OR "older adults" OR "late life depression" OR "cardiovascular disease" OR "hospitalized" OR "hospitalized"). The recommended use, dosing ranges, cardiovascular effects, and general advantages and disadvantages of each of the drugs are discussed. Levomilnacipran and vilazodone have not received enough study to judge their safety in older patients or in those with, or at high risk for, cardiovascular disease. There is at least some evidence for possible adverse events with each of the other newer antidepressants that could be of concern in these patients. Nevertheless, with careful administration and attention to the potential adverse reactions for each drug, these may provide safe effective alternatives for older adults and patients with cardiovascular disease who do not respond to selective serotonin reuptake inhibitor antidepressants. However, more research on the safety and efficacy of these drugs in these specific patient populations is urgently needed.

1 Introduction

Depression is common in medically vulnerable populations, including older adults and those with chronic medical illnesses such as cardiovascular disease (CVD). For example, the point prevalence of major depression is between 15 and 20% for patients with coronary heart disease (CHD) [1, 2], compared with about 5% in the general population [3]. In addition to its negative effect on the quality of life, depression is associated with an increased risk for medical morbidity in persons with heart disease [4, 5]. A recent scientific advisory from the American Heart Association recommended that depression be recognized as a risk factor

Key Points

It is important to identify safe and effective antidepressants when selective serotonin reuptake inhibitors are not effective in treating depression in older adults and those with cardiovascular disease.

There are few high-quality studies evaluating the cardiovascular effects of the newer antidepressants in these patients and more careful research is needed.

Nevertheless, we conclude that, with careful attention to the potential adverse events and contraindications that have been associated with each of these drugs, there are second-line antidepressants that may provide safe effective alternatives for older adults and patients with cardiovascular disease who do not respond to selective serotonin reuptake inhibitors.

✉ Robert M. Carney
carneyr@wustl.edu

[1] Department of Psychiatry, Washington University School of Medicine, 4320 Forest Park Avenue, Suite 301, Saint Louis, MO 63108, USA

for adverse medical outcomes including mortality in patients with an acute coronary syndrome [6]. Given this elevated risk of medical morbidity and mortality, identifying and effectively treating depression in persons with or at high risk for CVD, including older adults, is imperative. However, some antidepressants have cardiovascular side effects that may add to rather than reduce the risk for cardiac events. Tricyclic antidepressants (TCAs), for example, can cause orthostatic hypotension, slow cardiac conduction, increase heart rate, and decrease heart rate variability. Evidence-based psychotherapies such as cognitive behavioral therapy or interpersonal psychotherapy have been shown to be effective treatments for depression [7], but they may not be available to many, may not be covered by insurance, and may not be fully utilized even when available. Thus, finding safe and effective antidepressants for use in vulnerable populations remains a high priority.

There are challenges in determining the safety of antidepressants in vulnerable populations, including older adults and those with or at risk for CVD. Much of what we know about the cardiovascular effects of antidepressants comes from observational studies of the safety of antidepressants in older adults or those with heart disease. In a review of 22 of these studies, Biffi and colleagues [8] identified 99,367 incident cases of cardiovascular endpoints. Unexpectedly, they found a 24% *increased* risk for cerebrovascular disease in those individuals who were receiving selective serotonin reuptake inhibitors (SSRIs). They also found a 29% increased risk of incident CHD in those receiving TCAs compared with individuals who were not receiving any antidepressants. However, Biffi et al. reported that they were often unable to reliably distinguish between the effects of antidepressants and the effects of depression itself, a source of bias particularly in observational studies termed "confounding by indication." Most studies included in this review did not consistently assess depression using accepted methods, and even when they did, potential bias in who received an antidepressant, the dose of antidepressant prescribed, or the factors that led to its selection (e.g., depression severity, history of prior episodes or prior treatments) makes it difficult to interpret these results. Thus, it is unclear whether this elevated risk is due to antidepressants, to depression itself, or both. Confounding by indication is a common problem in observational studies of antidepressants and medical events [9]. Dragioti and colleagues [10] identified 45 meta-analyses of observational studies evaluating the relationship between antidepressant use and a variety of adverse medical events (cardiovascular events were not included). Even when a relationship was reliable and medically/biologically plausible, Dragioti and colleagues were often unable to completely rule out confounding by indication.

Some observational studies have either failed to find a relationship between antidepressant use and cardiac outcome [11], or found that patients receiving antidepressants may actually be at a *lower* risk for cardiac events. A large cohort study by Coupland and colleagues [12] determined depression status in all of the participants. During a 5-year follow-up, no significant associations were found between general antidepressant use and incident myocardial infarction (MI). However, in the first year of follow-up, those patients who received an SSRI had a *reduced* risk of MI (adjusted hazard ratio [HR] 0.58, confidence interval [CI] 0.42–0.79) compared with those who received no antidepressants. No significant associations were found between antidepressant class or individual antidepressant drugs and the risk of either stoke or transient ischemic attack. Antidepressant class was not significantly associated with arrhythmia over the 5-year follow-up, but the risk was significantly increased in the first 28 days of treatment with TCAs (HR 1.99, CI 1.27–0.59–0.92). Fluoxetine was associated with a *reduced risk* of arrhythmia (0.74, CI 0.59–0.92) over 5 years. Citalopram was not significantly associated with a risk of arrhythmia, even at higher doses (HR 1.11, CI 0.72–1.71, for doses $\geq$ 40 mg/day), although the sample size was relatively small and other studies have reported at least a modest dose-related increase in the corrected QT (QTc) interval with citalopram and escitalopram [13, 14]. A US Food and Drug Administration meta-analysis found that citalopram produced the most QTc prolongation of any SSRI, in a dose-dependent relationship, and recommended that doses of > 20 mg/day be avoided in older adults aged > 65 years, and > 40 mg be avoided in all patients. Dose-related QTc prolongation with escitalopram has led Health Canada and the UK Medicines and Healthcare products Regulatory Agency, but not the US Food and Drug Administration (FDA), to recommend dose limitation to 10 mg/day in older adults [15] (https://www.gov.uk/drug-safety-update/citalopram-and-escitalopram-QT-interval-prolongation). One criticism of these recommendations, however, is that they narrow the dose range of citalopram, as many patients respond better to doses 30 mg or greater, and escitalopram in which a dose of 20 mg is often more effective than 10 mg, and some controversy remains about this dosage recommendation [16]. It is not recommended that patients receiving a stable dose of these medications have dose reductions unless electrocardiogram (ECG) monitoring suggests a prolonged QTc [17].

Randomized placebo-controlled clinical trials of antidepressants can address some of the inadequacies of observational studies. However, there are limitations to what we can learn about cardiovascular side effects or the longer term risk of cardiac events even from randomized clinical trials. First, older adults and patients with comorbid medical or psychiatric disorders are often excluded or underrepresented in clinical trials. Thus, the patients who may be most vulnerable to the side effects or longer term medical effects of a drug are usually not well represented in the trial. Second, the

length of follow-up in standard clinical trials is necessarily limited, as it would be unethical to continue to treat patients who have current major depressive disorder with a placebo for an extended period. While many cardiovascular effects of a drug occur shortly after beginning the regimen, cardiac events that require accumulative exposure of the drug may not appear for weeks, months, or even years after beginning treatment. Finally, even with randomization, potential confounders need to be compared between groups, especially in smaller trials where important factors may not be balanced. Studies of high-risk populations, including older adults, those with stable CHD, or those post-acute coronary syndrome or post-stroke, tend to have smaller sample sizes, thus random assignment does not assure that all relevant factors will be equally distributed. Nevertheless, with the high prevalence of depression, especially in older adults and those with CVD, it is important to consider carefully the evidence for the safety and efficacy of these drugs, especially in these populations.

Selective serotonin reuptake inhibitors are thought to be relatively safe even in the most vulnerable populations. As a class they are the best-studied antidepressants in older adults and in those with CVD. A number of SSRI antidepressants have been tested in randomized clinical trials in patients with depression with CHD, including citalopram, fluoxetine, and sertraline [18–21] None of the trials reported an increased rate of cardiovascular side effects or cardiovascular events compared to placebo. A meta-analysis of studies of SSRI antidepressants to treat depression in patients with CHD reported a modest positive effect on depression, but no difference in mortality or CHD hospitalizations between intervention and control groups in the randomized trials [22]. However, there were modest reductions in hospitalizations and mortality when non-randomized studies were included in this analysis.

Overall, the evidence from clinical trials and observational studies suggests that SSRIs can be safely administered to patients with stable CHD, although sample sizes in clinical trials are generally too small to detect an effect on relatively rare events. Nevertheless, SSRIs in general appear to be safe and at least modestly effective in treating depression in patients with or at risk for CVD. However, many patients do not respond to SSRIs, and even fewer achieve remission. Thus, it may be necessary to consider alternatives in patients who do not respond to SSRIs.

We undertook a qualitative narrative review of the literature to summarize what is known about the cardiovascular side effects of the newer non-SSRI antidepressants. We focused on those novel non-SSRI antidepressants that are approved for use, and are likely to come to the attention of cardiologists, gerontologists, and other readers of this journal. Drugs that are used purely as augmentation agents such as atypical antipsychotics were excluded. Our search included studies of the antidepressants in patients being treated for anxiety disorders as well as those receiving treatment for depression. Studies of the antidepressants when used for other indications were considered only if they provided additional information.

Twelve novel non-SSRI antidepressants were identified: venlafaxine, desvenlafaxine, duloxetine, milnacipran, levomilnacipran, mirtazapine, bupropion, vilazodone, vortioxetine, agomelatine, moclobemide, and ketamine–esketamine. Both clinical trials and observational studies were included in the review, owing to the paucity of randomized controlled trials for many of the antidepressants. A search was conducted in PubMed and Google Scholar for each of these antidepressants with the following search criteria: the specific antidepressant AND (QT OR QTc OR "heart rate" OR "heart rate variability" OR hypertension OR "orthostatic hypotension" OR "cardiovascular outcomes" OR "cardiovascular mortality" OR "arrhythmia" OR "myocardial infarction") AND (geriatric OR "older adults" OR "elderly" OR "old age" OR "late life depression" OR "cardiovascular disease" OR "hospitalized" OR "hospitalised" OR "inpatient"). Studies were only included if they were available in English, and if they reported data for each antidepressant separately and not as part of a group or class of antidepressants. The search was not restricted by publication date and includes publications up to July 2020.

2 Serotonin Norepinephrine Inhibiting Antidepressants

2.1 Venlafaxine

Venlafaxine is a serotonin norepinephrine reuptake inhibitor (SNRI), increasing both serotonin and norepinephrine signaling [23]. This drug is generally prescribed in the once-daily extended-release (ER) formulation and is typically started at 37.5–75 mg/day, and then titrated based on response and tolerability. The FDA-approved dose range is 37.5–225 mg/day; 150 mg is typically considered a moderate dose, while 225–300 mg is considered high and should be used only when 150 mg is insufficiently effective. Advantages of venlafaxine include its once-daily dosing and lack of effects on the metabolism of other drugs [24]. One disadvantage is that because the dosing range is wide (37.5–300 mg), it can be difficult to achieve an individually optimal dose in real-world settings such as primary care [25].

At low doses, venlafaxine acts primarily to increase serotonin, while its effect on norepinephrine appears to occur primarily at higher doses (150 mg/day or higher) [26, 27]. There have been concerns regarding its effect on increasing blood pressure, especially supine diastolic blood pressure [28], an effect likely related to its noradrenergic properties.

Because of its effect on noradrenergic signaling, it is particularly important to study its cardiovascular effects in at-risk populations.

An early open-label study of older adults suggested that orthostatic hypotension, not hypertension, could be of concern with venlafaxine in a geriatric population [29]. Electrocardiograms were not obtained in this study. Another open-label, observational, prospective 6-month trial of 75–150 mg/day of ER venlafaxine in 1190 adults aged 69–99 years demonstrated a statistically significant *decrease* in mean systolic and diastolic blood pressure, as well as heart rate [30]. However, changes in ECGs were not measured. In contrast, other 6-month open-label trials of 75–225 mg/day of ER venlafaxine in 59 older adults aged 60–92 years and 97 older adults aged 80–90 years did not demonstrate a change in blood pressure or heart rate [31, 32]. However, again, ECGs were not evaluated in these studies. A 3-month open-label trial that included doses up to 300 mg/day of ER venlafaxine in 62 older adults (mean age 74.5 ± 7.5 years) noted that 50% of participants developed orthostatic hypotension. Furthermore, there was a significant decrease in standing diastolic blood pressure. This trial also noted a mean increase in heart rate of 3.5 beats per minute, and found that 2 out of 40 participants had "QTc interval prolongation", which was conservatively defined as a QTc interval ≥ 440 ms. No participants had a QTc interval ≥ 470 ms [33].

A recent secondary analysis of ECG changes during an open-label multi-center trial of venlafaxine in 169 older adults aged ≥ 60 years with depression demonstrated that there was no change in QTc from baseline in venlafaxine doses up to 300 mg daily [34]. The QTc interval was also not associated with the serum venlafaxine concentration, suggesting that therapeutic doses of venlafaxine do not prolong the QTc interval in older adults. Another recent study examining ECG and serum venlafaxine concentrations came to the same conclusion [25].

As SSRIs have been studied more extensively in vulnerable populations, an appropriate question is whether the cardiovascular effects of venlafaxine are different from those of commonly used SSRIs. A 2004 randomized trial compared 6 months of treatment with venlafaxine vs citalopram in 151 participants aged ≥ 65 years. There were no changes in mean systolic or diastolic blood pressure or pulse rate during venlafaxine or citalopram treatment, and there were no statistically significant differences between the treatments except for pulse rate, which was slightly greater in the citalopram group at 8 weeks [35]. Electrocardiograms were not evaluated in this study.

A 2006 randomized controlled trial compared 8 weeks of treatment of venlafaxine vs fluoxetine vs placebo in 300 older adults (mean age 71 ± 5 years). There were comparable numbers of treatment-emergent hypertension in each group. The authors did not specifically comment on orthostatic hypotension [36]. In this trial, ECGs were obtained for participants at the beginning and end of the trial, but the results from the ECGs were not reported. A retrospective cohort study of older adults (median age 75 years) compared cardiovascular events between 48,876 patients who were prescribed venlafaxine and 41,238 who were prescribed sertraline [37]. They documented cardiovascular events for a median of 105 days. After controlling for baseline comorbidities, demographics, and other medications, they found that patients taking venlafaxine had a lower risk of heart failure compared with those taking sertraline. However, they found that patients without a history of CVD had no differences in heart failure risk compared to those taking sertraline, but patients with CVD had a decreased risk of heart failure with venlafaxine compared with sertraline. Higher doses of venlafaxine were associated with a higher incidence of adverse cardiac events than lower dose venlafaxine, but depression severity was not controlled for and thus confounding by indication remains a potential explanation for these findings. This retrospective cohort also did not investigate vital signs or ECG changes.

Overall, the risk for venlafaxine-induced hypertension in older adults appears low. However, there may be an increased risk for the development of orthostatic hypotension. There do not appear to be significant changes in ECG parameters even at high doses in the therapeutic range. Further research is needed to determine the cardiovascular effects in other vulnerable patients, especially those with pre-existing CVD.

2.2 Desvenlafaxine

Desvenlafaxine is an SNRI and the active metabolite of venlafaxine [38]. One potential advantage of using desvenlafaxine over venlafaxine is to circumvent cytochrome P450 (CYP)2D6-dependent metabolism. This may reduce adverse side effects in patients who are genetically poor metabolizers, or in those receiving medications that interact with the CYP2D6 system [39].

Desvenlafaxine has recently become available as a generic in the USA, thus its price is expected to continue to drop in that country. It is a once-daily medication, and it does not affect the metabolism of other drugs. The starting dose of desvenlafaxine is the same as the suggested effective dose at 50 mg, but patients who do not adequately respond to 50 mg can be up-titrated to 100 mg daily (http://labeling.pfizer.com/showlabelingaspx?id=497). It is available as 25-, 50-, and 100-mg ER tablets. Because desvenlafaxine is a metabolite of venlafaxine, there is likely some overlap in the cardiovascular effects of venlafaxine and desvenlafaxine. However, it is important to elucidate what

cardiovascular effects may be specific to desvenlafaxine in at-risk populations.

The literature regarding the cardiovascular effects of desvenlafaxine in vulnerable populations is far smaller than that of venlafaxine. One 2010 open-label trial studied 100 or 200 mg/day of desvenlafaxine for up to 6 months in 52 older adults aged 65–87 years. Increased blood pressure was reported in five participants (10%), and three patients stopped the drug because of hypertension. Two patients developed orthostatic hypotension. However, there was no placebo group to compare rates of these events. Mean resting heart rate increased by 3.1 beats per minute by the end of the trial. In terms of ECG effects, one patient developed a prolonged QTc, another developed bradycardia, and one had increased premature ventricular contractions. However, without a control group it is not possible to relate these events to the drug, particularly in this older population that may be prone to spontaneous ECG changes. An important caveat of this open-label trial is that the authors of the paper are all associated with the pharmaceutical company that developed and sold desvenlafaxine initially as Pristiq (Wyeth, under Pfizer) [40].

There may also be concern regarding increasing blood pressure, as there has been for venlafaxine. However, the literature is lacking in studies specifically examining the cardiovascular effects of desvenlafaxine in vulnerable populations. While the effects could be similar to those of venlafaxine, in which orthostatic hypotension is likely a greater concern, there is not enough evidence to determine if this is the case.

2.3 Duloxetine

Duloxetine is an SNRI that has been approved for depression, diabetic peripheral neuropathy, and fibromyalgia [41]. Venlafaxine, with a 30:1 serotonin transporter to norepinephrine transporter relative binding affinity, is considered noradrenergic only at higher doses (150 mg or above), while duloxetine with a 10:1 serotonin:norepinephrine relative affinity is considered more balanced [24]. Duloxetine is available as a generic and is prescribed once daily, typically starting at 30 mg and titrating to 60–120 mg daily according to response and tolerability. Advantages of duloxetine include effects on pain and (modestly) on improving memory; a disadvantage is that it inhibits CYP2D6 and 2B6, particularly at high doses, thus it can interfere with the metabolism of other drugs such as some opiates and bupropion [42].

An important potential cardiovascular property of duloxetine found in in vitro studies is its ability to block the cardiac sodium channel Nav1.5, which has been associated with prolonged QT [43]. Another in vitro study found that duloxetine inhibited the hERG K channel, which is implicated in drug-induced QTc prolongation [44]. However, clinical trials in healthy participants have not found an effect of duloxetine on QTc [45]. In terms of the noradrenergic properties of duloxetine, it has been shown to increase heart rate slightly and minimally increase systolic blood pressure in healthy adults, but these changes were not deemed to be clinically meaningful in these participants [46]. Thus, while clinical trials in healthy volunteers have suggested the cardiovascular safety of duloxetine, its in vitro properties suggest that there could be adverse cardiovascular effects in vulnerable populations.

A 2004 open-label trial investigated 80–120 mg/day of duloxetine administered over 1 year to 101 adults aged ≥ 65 years with depression. The study found no changes in blood pressure from baseline. There was an incidence of low standing systolic blood pressure in 5 of 96 (5.2%) participants, but there were no other potentially clinically meaningful blood pressure or ECG changes. Overall, duloxetine was well tolerated in this population [47]. A 2008 randomized placebo-controlled trial of 60 mg/day of duloxetine in 311 adults aged ≥ 65 years with depression over 9 weeks reported a statistically significant decrease in orthostatic blood pressure of about 3 mmHg in patients receiving duloxetine compared with those receiving placebo. However, there were no differences in treatment-emergent orthostatic hypotension or other effects on blood pressure, and there was no change in QTc interval [48]. A 2014 randomized placebo-controlled trial of 60 and 120 mg/day over 24 weeks in 299 older adults aged 65–89 years with major depressive disorder investigated the impact of shorter vs longer term cardiovascular effects (12 weeks vs 24 weeks). All participants taking duloxetine received 60 mg/day during the initial acute phase (12 weeks), and dosage escalation to 120 mg/day was only an option for participants during the continuation phase (12–24 weeks) who did not show symptom responses in the acute phase with 60 mg/day. Diastolic blood pressure showed a greater increase from baseline in the duloxetine vs placebo group at 12 weeks (+ 1.89 mmHg vs − 1.58 mm Hg), but this difference was not statistically significant at 24 weeks. Similarly, there was a difference in orthostatic diastolic blood pressure change in duloxetine vs placebo groups at 12 weeks (− 0.94 mmHg vs + 2.28 mmHg), but at 24 weeks this difference was only marginally significant. There was no difference in the resting heart rate at 24 weeks, but there was a small but statistically significant increase at 24 weeks in the duloxetine group (+ 2.1 bpm vs − 0.87 bpm). Importantly, cardiovascular effects were not compared between the 60- and 120-mg/day dosages. There was one serious adverse event in the duloxetine group. A patient fell, fractured a hip, and was determined to be hypotensive. Electrocardiogram changes were not measured in this study [49].

A 2019 review and meta-analysis of adverse effects of antidepressants found that SNRIs, but not SSRIs, had a higher rate of adverse events compared with placebo [50]. Specifically, they noted that duloxetine significantly

increased the risk of falls in older adults. One potential mechanism for this is orthostatic hypotension, which is of particular concern in geriatric populations. Overall, these clinical trials suggest that duloxetine does not cause hypertension but may lead to orthostatic hypotension in some high-risk patients. However, the cardiovascular effects overall seem minimal in older adults.

Duloxetine is also indicated for the treatment of generalized anxiety disorder. As anxiety and depression are commonly comorbid, studies of duloxetine and anxiety in vulnerable populations are also of interest. One randomized controlled trial of 291 adults aged ≥ 65 years with generalized anxiety disorder compared 10 weeks of 30–120 mg/day of duloxetine with placebo [51, 52]. There were no differences in systolic blood pressure or ECG markers. There was a statistically significant increase in sitting diastolic blood pressure from baseline compared with placebo (0.3 mmHg vs − 1.7 mm Hg) and in sitting pulse rate (1.8 vs − 1.3 bpm). However, these changes were not considered clinically significant. There was no significant difference in the fall rate between the groups. This study supports the cardiovascular safety of duloxetine in older adults treated for generalized anxiety disorder, which is an important consideration in patients with anxious depression.

Because of its approval for the treatment of diabetic peripheral neuropathy, duloxetine has also been studied in patients who have diabetes mellitus and CVD. Importantly, these studies often excluded participants with depression, thus these results cannot be extrapolated to a depressed population per se. However, they can still offer valuable insight into the risk of duloxetine in patients with CVD. A 2008 randomized placebo-controlled trial of 60 or 120 mg/day of duloxetine in 1024 adults aged ≥ 18 years with type 1 or type 2 diabetes and diabetic peripheral neuropathy without depression investigated the efficacy as well as cardiovascular adverse events and vital signs in participants with and without pre-existing CVD [53]. The study included an acute treatment phase of 12–13 weeks, followed by an optional open-label continuation of treatment with a 12-month follow-up. In patients with a history of CVD, heart rate increased significantly by 2.75 bpm in the duloxetine 120-mg/day group compared with placebo. However, there were no changes in blood pressure in the acute phase and no other changes in vital signs in the follow-up phase. There were also no differences in cardiovascular adverse events between patients with and without CVD who were taking duloxetine, and there were no increased events with duloxetine compared to placebo. Electrocardiograms were obtained, but they did not analyze differences in QTc between cardiovascular groups because of a low incidence of QTc abnormalities (1/635 in duloxetine group and 2/314 in placebo group). Duloxetine was well tolerated in this sample of patients with CVD.

Overall, duloxetine may have some risk of orthostatic hypotension in older adults, but it has not demonstrated adverse effects on ECG parameters or other cardiovascular adverse events in older populations or in those with CVD. Further studies are needed to evaluate the cardiovascular safety of duloxetine in patients with depression and CVD.

2.4 Milnacipran

Milnacipran is an SNRI that is FDA approved for the treatment of fibromyalgia but is occasionally used to treat depression [54]. It is a twice-a-day medication, usually dosed at 100 mg per day (50 mg twice a day), with a maximum dosage of 200 mg per day [55] (https://www.accessdata.fda.gov/drugsatfddocs/label/2012/022256s013lbl.pdf). The serotonergic-noradrenergic ratio for milnacipran is approximately equivalent (1:1) for serotonin and norepinephrine reuptake inhibition [56].

Although there is evidence that milnacipran does not affect ECG parameters such as QTc in medically well individuals [57], there is minimal literature regarding its cardiovascular effects in vulnerable populations. A 1998 randomized trial compared 75–100 mg/day of milnacipran to imipramine in the treatment of depression in 219 older adults aged 65–93 years [58]. Postural hypotension was found to occur more often in the imipramine group than the milnacipran group. Both groups had a slight increase in heart rate and a slight decrease in systolic blood pressure. There were no significant changes in the QTc interval in either group. This suggests that milnacipran has a favorable cardiovascular profile compared with the TCA imipramine in older adults (particularly with regard to orthostatic hypotension). However, TCAs are not recommended in older adults because of their cardiovascular effects, thus milnacipran having a lower incidence of postural hypotension compared with imipramine does not necessarily mean it is free of risk. Further research is required to better elucidate the potential effects of milnacipran on cardiovascular parameters in vulnerable populations.

2.5 Levomilnacipran

Levomilnacipran is an SNRI that has been approved for treatment of depression [59]. It is an active enantiomer of milnacipran [60]. It is available as an ER once-daily medication, at 40–120 mg daily. Like milnacipran, the serotonergic-noradrenergic ratio of levomilnacipran is approximately equivalent (1:1) for serotonin and norepinephrine reuptake inhibition [56].

In clinical trials with medically healthy adults, levomilnacipran increased systolic and diastolic blood pressure, pulse, and the QTc interval by a small but statistically significant degree. However, the increase in QTc

in this population was not deemed clinically significant [61]. There are no studies of the cardiovascular effects of levomilnacipran in older adults, adults with CVD, or adults who have been medically hospitalized. Given the findings in healthy adults, it is possible that clinically significant cardiovascular effects occur in at-risk patients taking levomilnacipran. More work is needed to determine the safety of levomilnacipran in vulnerable populations.

3 Atypical Monoaminergic Antidepressants

3.1 Mirtazapine

Mirtazapine is an antidepressant that increases serotonergic and noradrenergic signaling via a unique mechanism. It is a centrally-acting alpha-2 antagonist as well as a blocker of serotonin 5-HT_2 and 5-HT_3 receptors [62]. Mirtazapine is available as a generic medication, and it is prescribed once daily at night because it tends to be sedating because of its anti-histaminergic properties. It is typically started at 7.5–15 mg daily and titrated to 30–60 mg daily. It does not affect the metabolism of other drugs.

A perceived advantage by some patients is the immediate effects of mirtazapine on sleep and appetite mediated through its anti-histaminergic effects. Depending on the patient, this may be advantageous or disadvantageous, and it sometimes leads to mirtazapine being under-dosed because its sleep and appetite effects occur more rapidly and at lower doses (7.5–15 mg) than its antidepressant dose (typically 30 mg or higher).

Because mirtazapine use has been associated with weight gain, it is often prescribed to aid in populations with medical comorbidities that cause them to be underweight. Studies have suggested that mirtazapine is safe overall in vulnerable populations treated with mirtazapine for off-label use, such as weight gain in older adults [63] and cancer-related symptomology [64]. While they note a common side effect is dizziness, which could be related to orthostatic hypotension, the cardiovascular effects of mirtazapine in these populations have not been systematically studied to our knowledge. In addition, as weight gain can lead to metabolic effects that are cardiovascular risk factors, it is particularly important to determine the cardiovascular safety of mirtazapine in patients for whom weight gain could be medically problematic.

A 2002 randomized controlled trial comparing 15–45 mg/day of mirtazapine to the SSRI paroxetine in 255 adults aged ≥ 65 years with depression over 16 weeks found no clinically significant changes in ECG or vital signs from baseline in the mirtazapine group, and no differences compared to the paroxetine group [65]. There were no reports of hypotension. Studies investigating the effect of mirtazapine in a geriatric population are otherwise lacking.

There are, however, some studies investigating the cardiovascular effects of mirtazapine in other at-risk populations. A nested randomized controlled trial within the MIND-IT trial investigated the efficacy and safety of 15–45 mg/day of mirtazapine over 24 weeks in 331 adults hospitalized with an MI who also had depression. They found no differences in blood pressure, heart rate, or change in QTc or QRS interval with mirtazapine relative to placebo [66]. These findings suggest that mirtazapine may be safe in patients with a recent cardiac event and a history of CVD, at least in the short term. A small retrospective cohort study investigated the effect of mirtazapine on sudden cardiac death and ECG changes (QTc, arrhythmias) in 61 medically hospitalized patients who received mirtazapine after a psychiatric consultation [67]. In this study, mirtazapine was initiated at an average dose of 9.8 mg/day and up titrated to a mean dose of 13.5 mg/day, below the effective antidepressant dose of ≥ 30 mg. There were no significant changes from baseline in ECG parameters and no cardiac events in these patients receiving low-dose mirtazapine.

There appears to be minimal cardiovascular adverse effects of mirtazapine in patients who are older, hospitalized, or have CVD. However, there have only been a few studies with relatively small numbers of patients, and the effect of mirtazapine has not been studied for longer than 24 weeks in these populations.

Concerns regarding mirtazapine in older adults have been raised from the findings of a 2015 matched case–control study of older adults in Swedish national registries that investigated the relationship between the risk of all-cause mortality and prescriptions for a variety of antidepressants [68]. The investigators also examined how all-cause mortality relating to each antidepressant compared to their reported cardiovascular risk as measured by QTc-prolonging ability. They included persons aged 65 years and older who died outside the hospital between 2008 and 2013 and compared them to age and sex-matched alive controls, resulting in data being used from 904,246 unique individuals. After adjusting for sociodemographic factors and medical comorbidities, the odds ratio for all-cause out-of-hospital mortality for mirtazapine was the highest of all antidepressants investigated at 1.67. However, this study is limited by possible confounding by indication. Mirtazapine is often used for its off-target effects of aiding sleep and weight gain in patients with other medical or psychiatric disorders. Additionally, this study did not directly investigate cardiovascular risk, but instead examined all-cause out-of-hospital mortality as a proxy. Because of these limitations, the results of this study should be interpreted cautiously and highlight a need for more large-scale randomized clinical trials of mirtazapine in older populations.

3.2 Bupropion

Bupropion is an antidepressant, also used to facilitate smoking cessation, that increases dopaminergic and norepinephrine signaling via inhibition of dopamine and norepinephrine reuptake [69]. It is available as a generic and is typically prescribed as a once-daily ER formulation, and not the sustained-release formulation that is twice daily and more difficult to adhere to. The usual starting dose is 150 mg, with effectiveness for depression at 300–450 mg. It has a different side-effect profile than the SSRIs. Because of its combined noradrenergic and dopaminergic activity, it is associated with side effects that can be described as "stimulant-like" and include wakefulness and reduced appetite. This can be advantageous or disadvantageous, depending on the patient. There are two main disadvantages for bupropion use: it tends not to be effective for treating anxiety, which is common in depression (and cardiac disease), and it is a strong inhibitor of the liver enzyme CYP2D6, which metabolizes many drugs. It also causes neurotoxic side effects at high doses, including seizures in young people (rarely) and falls in older adults [70]. Despite these disadvantages, it is commonly used and is popular as an alternative to SSRIs in those who do not respond to or tolerate SSRIs, and as an augmentation agent for those with insufficient response [71].

Similar to concerns with SNRIs, the increased noradrenergic signaling could affect cardiovascular parameters, particularly in vulnerable populations. A population of particular concern is smokers with CVD, as bupropion has also been FDA approved to aid in smoking cessation.

A 3-week open-label trial investigated the efficacy and safety of bupropion 350–600 mg/day in 36 inpatients who had both depression and cardiac disease (congestive heart failure, bundle branch blocks, or multiple premature ventricular contractions on ECGs) [72]. These patients were mostly older adults with a mean age of 69 years (±9 years), although they included some younger patients (range 49–86 years of age). Patients experienced a statistically significant increase from baseline in mean supine systolic (+5 mmHg) and diastolic (+3 mmHg) blood pressure. There was no change in standing blood pressure. There was, however a significant increase in orthostatic blood pressure, with blood pressure dropping a mean of 4 mmHg upon standing. One patient had an orthostatic drop of 40 mmHg and fell, leading to discontinuation of bupropion. There was no impact on resting heart rate and no significant ECG changes. While the increase in supine blood pressure and the orthostatic drop in blood pressure were relatively small, this may be of concern in a high-risk population. However, the uncontrolled open-label design of this study makes it impossible to draw causal conclusions.

In another study of bupropion, a randomized placebo-controlled trial investigated the efficacy and safety of 150–300 mg/day over 13 weeks in 418 older adults with depression aged 65–96 years [73]. The study did not find any clinically significant vital sign changes between the groups treated with bupropion or placebo, and there were no differences in adverse events. In this study, ECGs were not evaluated. Bupropion was well tolerated and appeared to be safe from a cardiovascular standpoint. However, the 13-week timeframe is relatively short, thus it does not provide information concerning the long-term cardiovascular effects of bupropion in this population.

While the literature regarding cardiovascular safety of bupropion in vulnerable populations with depression is not comprehensive, there is additional literature focusing on the safety of bupropion for smoking cessation in patients with CVD and chronic obstructive pulmonary disease. Three randomized placebo-controlled trials investigated the efficacy and safety of acute (7–12 weeks) treatment with bupropion 300 mg/day in 151–626 adults with CVD with a 1-year follow-up of smoking abstinence and cardiovascular safety evaluations [74–76]. None of these trials found an effect for bupropion on blood pressure or resting heart rate in this population. One of the studies found a statistically significant increase in non-fatal cardiovascular adverse events occurring >30 days after stopping the study drug in the bupropion group vs the placebo group [75]. The other two clinical trials did not find any difference in cardiovascular adverse events between the groups. However, changes in ECGs were not evaluated in these trials.

Another randomized placebo-controlled clinical trial focused on only major adverse cardiac events (death, MI, unstable angina) in 392 adult smokers who had been hospitalized with an acute MI and treated with 9 weeks of 300 mg/day of bupropion, plus a 1-year follow-up [77]. There were no differences between bupropion and placebo groups in total adverse cardiovascular events, or in the subcomponents of death, MI, or unstable angina. Vital signs or ECGs were not evaluated in this trial.

An important point regarding these bupropion clinical trials in smokers with CVD is that they excluded participants who had a diagnosis of depression. Even so, these results are reassuring for the safety of the short-term use of bupropion in certain high-risk populations. The data are lacking, however, with regard to long-term cardiovascular effects for the treatment of depression in high-risk individuals.

3.3 Vilazodone

Vilazodone is a newer antidepressant with a unique mechanism of action that classifies it as a serotonin partial agonist and reuptake inhibitor. Vilazodone increases serotonergic signaling via two mechanisms. First, it functions as an SSRI. Second, it is a partial agonist for the 5-HT_{1A} receptor [78].

Vilazodone is currently patent protected, thus it is more expensive than generic drugs. It is usually started at 10 mg daily and typically follows a fixed titration schedule of up to 40 mg/day. A theorized advantage of vilazodone is that it could have a quicker onset of action and fewer sexual side effects. However, these assertions have not been studied in head-to-head studies with other comparable antidepressants such as SSRIs [79]. A disadvantage compared to SSRIs is that it can cause more nausea [80].

In terms of cardiovascular safety, so far it has been well tolerated in clinical trials. In patients with depression who were otherwise healthy, there was no effect of vilazodone on vital signs or on QTc [81]. There have been no studies to our knowledge examining the cardiovascular safety of vilazodone in older adults, patients with CVD, or hospitalized patients. While the safety in healthier populations is reassuring, there is always the risk that an adverse effect emerges in one of these populations. Further research is needed to determine the cardiovascular safety of vilazodone in high-risk populations.

3.4 Vortioxetine

Vortioxetine has a novel mechanism of action that does not fit well with previously defined antidepressant classes. It increases serotonin signaling via a variety of mechanisms, leading to a description of vortioxetine as a "multimodal serotonin modulator". It acts as an antagonist, agonist, and partial agonist at a variety of serotonin receptors. Importantly, it functions to block serotonin reuptake while simultaneously acting as an agonist on both presynaptic and postsynaptic 5-HT_{1A} receptors. This functions to decrease the negative feedback from serotonin to further increase serotonergic signaling. Vortioxetine is also an antagonist for 5-HT_3 receptors, which is thought to decrease nausea [82]. Through these pre- and post-synaptic serotonin effects, it has been shown to increase extracellular acetylcholine, norepinephrine, dopamine, and histamine in animal models. While the exact mechanism for the antidepressant effectiveness of vortioxetine remains unknown, it is claimed to be novel and potentially related to its post-synaptic effects [83]. Importantly, clinical trials in otherwise healthy adults with depression did not show an effect for vortioxetine on vital signs or ECG changes in short-term trials, or longer trials that lasted up to a year [84].

One randomized placebo-controlled clinical trial investigated the efficacy and safety of 5 mg/day of vortioxetine in 452 older adults aged 65–88 years with depression over 8 weeks. They found no differences in vital signs or ECG parameters during this time [85]. While the results of this trial are promising for the treatment of older adults, this study needs to be replicated with treatment continued for a longer period of time and in higher doses (as the full dose range has a maximum of 20 mg and only 5 mg was tested here) to further test the safety of vortioxetine in a geriatric population.

Vortioxetine has not been studied in other vulnerable populations, such as those with CVD or patients who have been hospitalized for other medical conditions. Future research will need to investigate the cardiovascular safety of vortioxetine in these high-risk populations.

3.5 Agomelatine

Agomelatine is an antidepressant that has a unique mechanism via melatonin and serotonergic receptors. Specifically, it is an agonist at the melatonin MT_1 and MT_2 receptors and an antagonist at the serotonin 5-HT_{2C} and $_{2B}$ receptors [86, 87]. Its unique mechanism via melatonin is thought to impact depression through modulation of circadian rhythm signaling, targeting the sleep disturbances in depression [86]. It is considered to have a favorable side-effect profile, without the weight gain, sexual side effects, or discontinuation syndrome seen with antidepressants such as SSRI/SNRIs. As a side note, most cardiologists are familiar with cardiac valvulopathy found to occur with agonists of 5-HT_{2B}, such as fenfluramine [88]. However, this effect is specific to agonists of 5-HT_{2B} receptors, not antagonists such as agomelatine.

A 2013 randomized controlled trial of 222 older adults aged ≥ 65 years examined the effect of 25 or 50 mg/day of agomelatine compared to placebo over 8 weeks [89]. There were no clinically relevant changes in heart rate, blood pressure, or ECG parameters. Agomelatine has also been studied in adults with CVD. However, these studies were open-label without a placebo control. A 2014 trial investigated the efficacy and tolerability of 6 weeks of 25 or 50 mg/day of agomelatine in 88 adults aged 45–60 years with CVD [90]. From baseline to the end of the trial, there were no changes in blood pressure or heart rate. Electrocardiograms were not evaluated in this trial. A larger 2017 open-label trial of 896 participants aged 18–65 years with CVD studied depressive symptoms and cardiovascular parameters with treatment of 25 or 50 mg/day of agomelatine over 12 weeks [91]. Throughout the trial, there was a statistically and clinically significant decrease in blood pressure and heart rate, which was considered clinically tolerable. However, a major confounder of this open-label trial was that participants were also being seen by a cardiologist and treated with cardiotropic medications during the trial, which likely affected the participant's heart rate and blood pressure. Electrocardiograms were also not evaluated in this trial.

From the limited number of trials examining agomelatine in vulnerable populations, it appears to be safe from a cardiovascular perspective in older adults and adults with CVD. Studies of greater duration would add to the evidence of cardiovascular safety for older adults, and studies designed

as randomized controlled trials that also include ECG evaluations would be valuable future studies for agomelatine use in adults with CVD.

3.6 Moclobemide

Moclobemide is a monoamine oxidase inhibitor (MAO-I) that has a more favorable side-effect profile than other drugs in its class. Typically, a major concern with MAO-I antidepressants is the potential to induce a hypertensive crisis when patients taking an MAO-I consume food rich in tyramine, such as wine and cheese. Moclobemide is unique in that it is a reversible inhibitor [92], whereas most MAO-Is are irreversible. Thus, moclobemide will not have the same risk of a tyramine-induced hypertensive crisis, which has been demonstrated pre-clinically and clinically [92, 93]. While moclobemide can be a valuable antidepressant option with less risk than other MAO-Is, it is important to investigate whether it is also safe in populations that are more vulnerable to cardiovascular side effects.

The efficacy and safety of moclobemide in elderly patients was studied in two randomized controlled trials. A 1995 randomized controlled trial compared 7 weeks of treatment with moclobemide (400 mg/day), nortriptyline, and placebo in 109 older adults aged 60–90 years with depression. There were no changes in blood pressure or ECGs with moclobemide vs placebo [94]. The investigators noted a significantly greater incidence of orthostatic hypotension with nortriptyline vs placebo, but not with moclobemide. Notably, however, they were unable to detect an antidepressant effect in this trial, and suggested that a higher dose may be needed for efficacy in this population. Therefore, while this trial suggests cardiovascular safety in older adults, it is not clear that this safety extends to higher doses that may be needed to achieve an antidepressant effect.

A larger 1996 randomized controlled trial examined the effect of 6 weeks of moclobemide 400 mg/day vs placebo in 726 elderly patients aged 60–90 years with depression and decreased cognitive function [95]. There was no difference in blood pressure, heart rate, or ECG parameters between the moclobemide and placebo groups. This study was able to detect an antidepressant effect of moclobemide at the dose of 400 mg/day. These findings are reassuring for the cardiovascular safety of moclobemide in an elderly population. However, moclobemide has not been studied in patients with CVD, and a particular concern would be in patients with baseline hypertension. Future studies focusing on this group of patients would greatly contribute to the understanding of cardiovascular safety of moclobemide in vulnerable populations.

3.7 Ketamine and Esketamine

Several non-monoaminergic drug types are being studied for repurposing as antidepressants, reflecting the high rate of depression that does not respond to typical monoaminergic antidepressants. These non-monoaminergics include neurosteroids, ketamine (and its S-enantiomer, esketamine), and psychedelics. This section describes ketamine and esketamine, as the latter drug was recently approved by the FDA for the indication of treatment-resistant depression.

Ketamine has been used as an anesthetic since the 1960s [96], but has been increasingly studied for its antidepressant properties since a landmark paper in 2000 demonstrated a rapid-onset antidepressant effect [97]. While ketamine is an antagonist of the *N*-methyl-D-aspartate receptor, which likely plays an important role in its anesthetic and analgesic properties, it also affects many other receptors and channels such as alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and calcium channels. The precise mechanism of its antidepressant effect remains unclear [96]. An important cardiovascular effect of ketamine is its ability to transiently increase blood pressure and heart rate. This led to an FDA label for anesthetic ketamine that includes a contraindication in patients for whom an increase in blood pressure would constitute a "serious health hazard" (https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/016812s039lbl.pdf).

A 2018 systematic review of the side effects of ketamine use for depression noted that 38% of the 60 studies noted acute changes in cardiovascular status, specifically blood pressure and heart rate increase [98]. The review noted that most cardiovascular effects occurred during administration of ketamine or shortly thereafter, with most resolving within 90 min of administration. A 2018 case series described the blood pressure effects of 684 0.5-mg/kg ketamine infusions given over 40 min to 66 patients with treatment-resistant depression and a mean age of 57 years [99]. Peak blood pressures were recorded at 30 and 40 min, with an average increase in systolic blood pressure at 30 min of + 3.28 mmHg and a diastolic increase of + 3.17 mmHg. After 30–40 min, blood pressure gradually decreased through the end of vital sign monitoring (70 min after infusion began, 30 min after infusion ended). Patients with baseline hypertension had a greater increase in systolic blood pressure than those without baseline hypertension (+ 6.31 mmHg vs + 2.26 mmHg). However, at 70 min, normotensive patients had an average diastolic blood pressure that was 1.56 mmHg higher than patients with baseline hypertension. Patients aged older than 60 years had higher systolic and lower diastolic blood pressures at the start and throughout the infusion compared with patients aged younger than 60 years. Older patients had a slightly higher increase in systolic blood pressure at 30 min (+ 2.27 vs + 1.42 mmHg). About 9% of the infusions

were associated with clinically significant increases in blood pressure, defined as an increase in systolic blood pressure of > 30 mmHg and in diastolic blood pressure of > 15 mmHg. Importantly, no infusions had to be stopped because of unstable vital signs in this large case series.

A randomized controlled trial in 16 adults aged ≥ 60 years evaluated the effects of ketamine for depression. However, this pilot study investigated the efficacy and safety of 0.1–0.5 mg/kg of ketamine given subcutaneously over 2 weeks and followed for 6 months [100]. The investigators reported a transient increase in blood pressure with a peak concentration 4 h following subcutaneous administration. There were no serious adverse events reported. Electrocardiograms were not evaluated.

Other studies have investigated the safety and efficacy of ketamine in different at-risk populations. One particularly complex group that has been studied is patients receiving hospice care. One open-label trial studied the efficacy and safety of 0.5 mg/kg of oral ketamine over 28 days in eight patients receiving hospice care who had depressive symptoms, one of whom had a cardiovascular primary diagnosis [101]. This study found no changes in blood pressure, and there were no adverse cardiovascular events. There have also been case reports of ketamine in intravenous and intramuscular formulations given to patients with metastatic cancer and depression. These patients did not experience vital sign changes with ketamine administration [102, 103]. Electrocardiogram changes were not evaluated in these trials in hospice care patients. While ketamine has an exciting potential as a novel antidepressant, there are clear reasons to be concerned regarding its cardiovascular safety in vulnerable populations [104].

In 2019, the FDA approved the S-enantiomer of ketamine, esketamine, for treatment-resistant depression. While intravenous ketamine is used off-label for treatment-resistant depression, the esketamine nasal spray is the first ketamine formulation FDA approved for depression. Because of concerns regarding blood pressure, the FDA label for the esketamine nasal spray includes contraindications for patients who have cerebral aneurysms, arteriovenous malformations, or a history of intra-cerebral hemorrhage (https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211243lbl.pdf).

A randomized placebo-controlled trial investigated the efficacy and safety of 28, 56, or 84 mg of esketamine intranasal spray twice weekly for 4 weeks in 138 adults aged ≥ 65 years with depression [105]. The trial investigators reported a transient elevation in mean blood pressure in participants receiving esketamine that peaked at 40 min post-treatment and resolved in 2 h in about 80% of participants. Treatment-emergent acute hypertension, defined as systolic blood pressure of ≥ 80, was observed in both esketamine and placebo groups in a minority of patients. In the esketamine group, 2/72 (2.8%) demonstrated treatment-emergent acute systolic hypertension compared with 1/65 (1.5%) in the placebo group. There was a slightly greater difference between groups in diastolic treatment-emergent acute hypertension, defined as a diastolic blood pressure ≥ 100 mmHg. This was seen in 7/72 (9.7%) of the esketamine group and 3/65 (4.6%) in the placebo group. However, statistical analyses comparing the differences between groups in frequencies of treatment-emergent acute hypertension were not conducted. For elevations in diastolic blood pressure, there was one participant in each group who reached a diastolic blood pressure of ≥ 105 mmHg, while no patients in either group reached a diastolic blood pressure of ≥ 110 mmHg. One participant discontinued esketamine treatment because of blood pressure increases, while none left the placebo group. Overall, this suggests that esketamine can cause increased blood pressure in older adults, and this increase may be clinically significant in a minority of patients. However, with respect to other cardiovascular parameters, esketamine was well tolerated, as there were no clinically significant ECG changes. Importantly, there was a moderate level of medical comorbidity in this study's participants, with about half having pre-existing controlled hypertension.

Neither ketamine nor esketamine has been studied in patients with CVD and depression. Ketamine does appear to cause transient hypertension in the subanesthetic doses used for depression treatment. Furthermore, there have been no studies assessing the long-term cardiovascular effects of ketamine or esketamine in any vulnerable population. It is unclear at this point if repeated administration with ketamine, and thus repeated transient increases in blood pressure, could have negative long-term cardiovascular consequences. Thus, it may be inappropriate for patients with uncontrolled hypertension, or patients at risk for cardiovascular events. While ketamine and esketamine are promising novel antidepressants, their cardiovascular effects need further study, especially in high-risk populations.

4 Summary and Conclusions

Typically, SSRIs are the first-line treatment choice in older adults or in patients with CVD because of their ease of use, safety, and tolerability. However, the newer drugs described here are often used in the case of inadequate response or intolerance to SSRIs. The paucity of data in the use of these newer antidepressants in older adults and other groups vulnerable to cardiovascular side effects is concerning. In fact, there were no relevant studies found for vilazodone and levomilnacipran. It is apparent from this review that further research is urgently needed to address the evidence gaps regarding safety and efficacy in these patients. In the meantime, a clinician will be faced with uncertainty.

Nevertheless, we conclude that, with careful attention to the potential adverse events and contraindications that have been associated with each of these drugs as discussed in this review, second-line antidepressants may provide safe effective alternatives for older adults and patients with CVD who do not respond to SSRIs.

When any of these drugs are used, starting at a low dose for 1–2 weeks before titrating may improve tolerability, although this strategy has the risk that a patient may remain on a sub-therapeutic dose. Care to avoid drug–drug interactions (e.g., bupropion plus paroxetine, which inhibits the metabolism of both bupropion and paroxetine) is essential, especially as elderly patients and those with CVD often have multiple medical comorbidities and concurrently receive many medications. We recognize that most clinicians will be unfamiliar with the pharmacokinetic properties of these drugs and potential drug–drug interactions, but it is important to obtain this information before administering these drugs.

We do not recommend routinely administering an ECG before or after initiating these medications, as one would do for a TCA. There is no evidence this is needed. However, safety may be improved by checking resting and orthostatic blood pressure before and 1 week after initiating certain drugs (e.g., venlafaxine, duloxetine), or following a dose increase when needed. We especially want to emphasize the importance of following the guidelines for blood pressure monitoring during esketamine administration and ketamine infusion.

While we do not recommend avoiding the use of these drugs, we also do not recommend overuse of these or any antidepressant. These drugs should be reserved for clear-cut cases of major depression, minor depression coupled with suicidal thoughts, or other indicated diagnoses such as certain anxiety disorders. The mere presence of depressive symptoms, particularly in the context of comorbid medical illness, should not be sufficient.

Again, we acknowledge that the evidence summarized in this review carries uncertainty, given the paucity of high-quality research. We strongly urge that more research be conducted to clarify the proper use, safety, and efficacy of these antidepressants in patients vulnerable to cardiovascular complications.

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