Cardiovascular medications may cause, exacerbate, or relieve neuropsychiatric symptoms. Historically, a host of medications with effects on the cardiovascular system have been associated with the development of depression, anxiety, psychosis, or delirium, while others have been thought to have antidepressant or antimanic effects. However, there are several factors that make it difficult to confirm whether a given cardiovascular medication causes a given neuropsychiatric symptom. First, neuropsychiatric symptoms are exceedingly common among patients with cardiovascular conditions. For example, approximately 15% of patients with recent myocardial infarction (MI), congestive heart failure (CHF), or recent coronary artery bypass graft (CABG) surgery suffer from major depressive disorder (MDD).1-3 Anxiety is also common among patients with coronary artery disease (CAD), especially among post-MI patients.2,4,5 Finally, delirium, which can present with psychotic symptoms, mood lability, and anxiety, is highly prevalent among hospitalized cardiac patients, especially among those undergoing surgery.6 Thus, it may appear that a particular cardiovascular medication frequently causes a particular neuropsychiatric syndrome, when in fact such a syndrome may occur commonly as part of the natural history of cardiac illness, and be unrelated to medication. In addition, the vast majority of studies that associate cardiovascular medications with neuropsychiatric consequences have been case reports and case series that may at best suggest a link between the taking of a medication and a clinical outcome. Such reports do not usually use standardized tools to evaluate the presence or severity of the reported neuropsychiatric symptoms; instead, they rely only on general reports of symptoms as observed by the authors. As we will discuss, well-controlled trials that examine the neuropsychiatric consequences of cardiovascular medications are relatively few and far between, and at times may contradict clinical reports.
Despite these cautions, many clinically important links exist between use of cardiovascular medications and neuropsychiatric syndromes. In this article, we will examine each class of cardiovascular medication and review the literature that describes the neuropsychiatric consequences of medications within that class. At the end of each section, we will synthesize the evidence into a “bottom-line” statement that summarizes the clinical relevance of the links between that particular class of cardiovascular medications and neuropsychiatric symptoms. Due to space limitations, we will not discuss drug interactions between cardiovascular agents and psychiatric medications in this review.

**β-Blockers**

A connection between the use of β-adrenergic blockers (β-blockers) and neuropsychiatric symptoms, especially fatigue and depression, has long been postulated. The lipophilic β-blockers (e.g., propranolol and metoprolol) cross the blood-brain barrier much more easily than do nonlipophilic β-blockers (e.g., atenolol), and the lipophilic β-blockers are thought to be associated with higher rates of neuropsychiatric consequences.

The association between the use of β-blockers and the development of depression has long been described; yet, it remains controversial. Many case reports and several small reviews have linked propranolol with depression, and a trial by Thiessen et al found that treatment with propranolol was associated with higher rates of antidepressant prescriptions than with other β-blockers (both lipophilic and hydrophilic). Similarly, Hallas found that new propranolol prescriptions were associated with high rates of new prescriptions for antidepressants, compared with prescription of diuretics. Further, a study that compared quality of life among patients taking capropril, enalapril, atenolol, and propranolol found that propranolol was associated with significantly lower scores on a global assessment of psychological functioning. In contrast, a randomized, controlled trial in 312 patients who received propranolol found no association between this agent and depression at 1 year. Furthermore, several of the trials listed above did not take into account confounding variables (e.g., benzodiazepine use and frequency of outpatient visits) that were found to account for the apparent relationship between use of β-blockers and the diagnosis of depression; in one study there was no association between use of β-blockers and depression after making this correction. Finally, a comprehensive review of more than 5800 patients prescribed propranolol found that this agent was rarely associated with depressive symptoms, and that such symptoms usually only arose after long-term use.

When trials have been expanded to include use of other β-blockers, the majority of studies and reviews have found no association between β-blockers (as a class of medication) and the presence of depression. Furthermore, there has been mixed evidence that lipophilic β-blockers are more strongly associated with depression than are nonlipophilic agents. The most extensive analysis of the association between β-blockers and depression, however, was a meta-analysis of 15 trials (more than 35 000 patients). Ko and colleagues found that β-blockers, as a class, were not associated with a significant increase in reports of depressive symptoms; furthermore, there were no differences between outcomes following use of lipophilic and nonlipophilic agents.

β-Blockers may be associated with adverse neuropsychiatric effects other than depression. Sedation, and to a somewhat lesser degree, fatigue, have been associated with use of β-blockers, both lipophilic and hydrophilic. For example, approximately 25% of patients who take atenolol report sedation—twice the number who report sedation on placebo—but no substantial differences in fatigue were observed between users of atenolol and placebo. In the large meta-analysis by Ko and colleagues noted above, the authors found a statistically significant, but small, increase in fatigue among patients taking β-blockers; there were 18 additional reports of fatigue per 1000 patients treated. Despite these reports of sedation and fatigue, β-blockers do not appear to cause cognitive dysfunction. Psychosis, usually in the context of delirium, has occurred rarely among patients taking propranolol, metoprolol, and atenolol. In addition to these adverse effects, there are also several therapeutic neuropsychiatric uses of β-blockers. β-Blockers, primarily propranolol, have been used to treat anxiety. These agents are often considered to be the
agents of choice for performance anxiety (eg, public speaking). In addition, β-blockers, especially the partial agonist, pindolol (which also blocks serotonin [5-HT]1A receptors) has been used adjunctively to enhance the benefits of selective serotonin reuptake inhibitors (SSRIs) in panic disorder and obsessive-compulsive disorder (OCD). Finally, two recent studies found that the administration of propranolol to patients immediately following trauma (within 6 hours) appears to reduce the risk of developing post-traumatic stress disorder (PTSD).

β-Blockers have also been used to treat aggression among patients with a variety of illnesses. Overall, the evidence for any successful treatment of aggression with any agent, or class of agents, is limited; however, β-blockers appear to be the best-supported class of medications for the treatment of aggression related to traumatic brain injury. Furthermore, β-blockers appear to be effective in reducing aggression among patients with a variety of neuropsychiatric conditions (eg, schizophrenia and dementia, with a behavioral disturbance).

Propranolol is a first-line choice for the treatment of akathisia, an uncomfortable restless sensation that is induced by use of antipsychotics and other agents that affect dopamine neurotransmission (ie, are dopamine blockers). β-Blockers can also be used adjunctively to reduce the effects of autonomic hyperactivity among patients undergoing alcohol or benzodiazepine withdrawal. It is important to note that this treatment is only adjunctive, and has not been shown to prevent either delirium or seizures associated with alcohol withdrawal. Finally, pindolol, because of its effects on 5-HT1A autoreceptors, has been actively studied as a potential augmenting agent for patients with depression. A recent meta-analysis of nine randomized, controlled trials of pindolol in combination with SSRIs found that pindolol appears to speed up the response to SSRIs, although it does not appear to improve overall response rates.

Bottom line: β-Blockers as a class are not clearly associated with depression; there is the most evidence for a propranolol-depression link, but even this relationship is equivocal. In contrast, β-blockers are associated with increased rates of fatigue. Therapeutically, there is the most evidence for the use of β-blockers (especially propranolol) in the treatment of akathisia and performance anxiety, β-Blockers may help to prevent PTSD among those suffering trauma and may reduce aggression, but more data is needed.

Angiotensin-converting enzyme inhibitors

The neuropsychiatric consequences and therapeutic uses of angiotensin-converting enzyme (ACE) inhibitors are relatively limited. Captopril has been the ACE inhibitor most closely associated with mood effects, potentially due to its transport into the central nervous system (CNS) by a protein carrier. Several case reports and a small, open trial have found captopril to be efficacious in the treatment of major depression, although larger, randomized trials have not been performed. A randomized trial that compared the effects of captopril, propranolol, and methyldopa on quality of life, however, did find that captopril was superior on global quality-of-life measures than the other two antihypertensive medications. The possible mood-elevating effects of captopril are further supported by several reports of manic symptoms in association with use of captopril. There are fewer reports of mood effects of other ACE inhibitors, though lisinopril has been associated with the induction of mania in a single case report and has been used in the adjunctive treatment of depression in another report. Psychosis and delirium have been reported rarely with ACE inhibitors. ACE inhibitors do not appear to have profound cognitive effects, with small trials finding no cognitive dysfunction and perhaps even mild cognitive enhancement among patients taking captopril, but a double-blind trial of an ACE inhibitor, ceranapril, found that this agent did not improve cognition among patients with Alzheimer’s disease. ACE inhibitors also demonstrate low rates of fatigue and sedation.

Angiotensin-II blockers

Angiotensin-II blockers (including losartan, valsartan, and irbesartan) are relatively new agents, and as such, their neuropsychiatric consequences are as yet relatively undefined. For the most part, these agents do not appear to have clear associations with depression, mania, psychosis, delirium, cognitive impairment, or fatigue. One case report found that the combination of valsartan and hydrochlorothiazide was associated with the onset of depressive symptoms and a suicide attempt within 4 weeks of initiation of this medication, and that the symptoms of major depression then resolved within 10 days of its discontinuation, without other treatment. In addition, losartan was associated with the onset of psychosis and depression in an elderly patient; the symptoms resolved with
discontinuation, and then recurred with the reinstitution of losartan. Finally, with respect to the beneficial neuropsychiatric effects of angiotensin-II blockers, a promising study found that patients prescribed losartan had significant improvement in their cognitive function during such treatment, in contrast to those treated with hydrochlorothiazide. We are otherwise unaware of any reports or studies of neuropsychiatric effects of these medications; as clinical and research experience with these agents grows, further neuropsychiatric consequences of their use (beneficial or adverse) may become apparent. **Bottom line:** ACE inhibitors and angiotensin II receptor antagonists are associated with low rates of neuropsychiatric side effects, though mood symptoms, psychosis, and delirium have been reported. Therapeutically, there is little data, though there is some suggestion that captopril might improve depressive symptoms.

**Calcium channel blockers**

Calcium channel blockers (CCBs) are associated with relatively low rates of adverse neuropsychiatric consequences. Fatigue (and associated sedation) occurs at rates greater than placebo, but it is an uncommon side effect that rarely limits therapy. Although CCBs theoretically have cognitive benefits, these agents have on occasion been associated with delirium; verapamil and diltiazem have been named in single case reports, and nicardipine has been associated with confusion among patients undergoing opiate withdrawal. However, CCBs may have several beneficial neuropsychiatric effects. For example, these agents have been reported to have favorable effects in patients with mood disorders. There have been multiple reports that described the use of verapamil for the treatment of acute mania. Several early case reports suggested that verapamil was effective in the treatment of mania, and small trials have suggested that verapamil may be as effective as lithium in the treatment of mania. For example, in a trial comparing verapamil and lithium in the treatment of 20 patients with mania, Garza-Trevino and colleagues found that both treatments were effective, with no significant differences between lithium and verapamil. More recent trials have found lithium to be more effective than verapamil (in a single-blind trial) and no more effective than placebo (in a small, double-blind trial), and interest in its use in acute mania has generally waned. However, given the relative safety of verapamil in pregnancy and the encouraging initial results with its use, a recent study of the use of verapamil in the treatment of both pregnant and non-pregnant women with bipolar disorder was conducted. The authors found that verapamil was effective in the treatment of acute mixed and manic states. In contrast to the studies of verapamil, there has been little study of other CCBs for acute mania; diltiazem was associated with the development of mania in one case report. Verapamil and other CCBs have also been used as maintenance treatment for patients with bipolar disorder. A crossover trial of verapamil and lithium in the maintenance treatment of bipolar disorder found that these agents were equally effective, although there is some suggestion that this agent is ineffective in patients with refractory illness. There have been three reports of nimodipine’s efficacy in bipolar illness, including a small but well-designed on-off-on trial; however, the largest trial showed relatively modest results in monotherapy of patients with refractory bipolar affective illness. Finally, a retrospective study found that diltiazem was effective in the maintenance treatment of bipolar illness. Despite this somewhat encouraging data in both acute mania and maintenance treatment of bipolar illness, there have been no comprehensive trials of CCBs (combining adequate numbers of patients with a prospective, double-blind design) that would lead practitioners to use these agents as front-line treatment for patients with bipolar disorder at this juncture. CCBs have been studied in the treatment of depressive symptoms, with somewhat less encouraging results. Verapamil was found to be less effective than amitriptyline (a tricyclic antidepressant [TCA]) in a double-blind trial for depression, and ineffective for depression among patients refractory to TCAs. One trial found that, in patients receiving electroconvulsive therapy (ECT) there was greater mood improvement among those taking nicardipine compared with placebo (the study was originally designed to determine whether nicardipine improved ECT-associated cognitive impairment; it did not). Furthermore, because CCBs may be effective in the treatment of cerebrovascular disease, nimodipine has been used to augment antidepressant treatment of patients suffering from vascular depression—ie, new-onset depression in older adults associated with vascular lesions—in a pair of double-blind, placebo-controlled studies. Both studies found that nimodipine was superior to placebo in reducing the symptoms and lowering the rates of recurrence.
There have been limited trials regarding the use of CCBs in the treatment of anxiety disorders. A double-blind trial revealed modest anxiolytic effects of verapamil among patients with panic disorder, and open trials of diltiazem and nimodipine for panic disorder also had positive results; a trial of nifedipine for free-floating anxiety and phobia had a negative result. Bottom line: CCBs may be associated with fatigue in some patients, but otherwise cause few neuropsychiatric symptoms. Therapeutically, verapamil has been the most-studied agent in several trials of mania and bipolar disorder, and has had mixed but generally positive results; this agent may prove to be a viable option for patients with bipolar disorder who are pregnant or fail first-line therapies, though larger studies are needed.

**Diuretics**

Diuretics are generally associated with low rates of neuropsychiatric adverse events. Thiazide diuretics, which minimally cross the blood-brain barrier, can more indirectly result in neuropsychiatric complications due to their effects on electrolytes (primarily sodium and calcium) and their effects on lithium excretion (effectively doubling serum lithium levels when the two are coadministered). One case series of eight patients has reported a link between use of thiazide diuretics and depression, although other evidence for this association is lacking. Hyponatremia and hypercalcemia associated with the use of thiazide diuretics have been reported to lead to delirium and psychosis. Thiazides may also exacerbate hyponatremia (and associated neuropsychiatric symptoms) caused by SSRIs via the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Induction of lithium toxicity by thiazides can result in multiple neurologic and psychiatric symptoms (including confusion, anterograde amnesia, and severe tremor); one report has noted mania-like symptoms. Overall, thiazide diuretics are not frequently associated with fatigue, sedation, cognitive impairment, or other neuropsychiatric symptoms, and have not been used therapeutically for neuropsychiatric conditions.

Other diuretics similarly have relatively few neuropsychiatric effects. Loop diuretics (such as furosemide and ethacrynic acid) are not associated with mood syndromes, psychosis, or impaired cognition. However, long-term use of furosemide is associated with thiamine deficiency—one study found that over 90% of patients taking 80 mg per day (and more than half of patients taking 40 mg per day) for CHF had a substantial deficiency of thiamine. Thiamine deficiency can lead to Wernicke’s encephalopathy (characterized by confusion, ophthalmoplegia, and ataxia), and indeed, use of loop diuretics was associated with this syndrome in one case report. The carbonic anhydrase inhibitor acetazolamide can also be associated with fatigue and sedation, especially early in treatment.

In addition, there has been a single case report of its use in acute mania and a small study found that acetazolamide, particularly when combined with an anticonvulsant, might prove beneficial to patients with refractory symptoms in bipolar disorder. Finally, Inoue and colleagues used acetazolamide to treat patients with a variety of atypical psychoses, and found that approximately 70% of patients improved.

**Centrally acting agents**

**Clonidine**

Clonidine, a central α-adrenergic agonist, is associated with a number of neuropsychiatric effects. Fatigue and sedation are the most common effects, with sedation occurring in one third or more of patients. Mood disturbance has been infrequently described with clonidine; pooled information suggests that depression occurs in approximately 1% to 2% of patients taking clonidine,
and there are no case reports of clonidine-induced depression or mania, though there has been one report of hypomania in a patient with pre-existing depression.\textsuperscript{121,122} Hallucinations can occur with clonidine, though rarely; one case report describes a man with two episodes of hallucinations associated with clonidine that resolved with discontinuation in both instances.\textsuperscript{126} Finally, clonidine may also affect cognition in certain patients. It has been associated with cognitive slowing,\textsuperscript{123,125} and there have been at least seven case reports of delirium associated with the use of clonidine.\textsuperscript{128} However, the neuropsychiatric consequences of clonidine are most often those associated with its therapeutic uses. Clonidine has been used to treat a variety of neuropsychiatric illnesses. Clonidine is frequently used (as second-line monotherapy or as an adjunctive agent) to treat attention deficit-hyperactivity disorder (ADHD), particularly among patients with comorbid tics or prominent hyperactivity, impulsivity, or aggression.\textsuperscript{127-129} Clonidine is generally less effective than are psychostimulants in the treatment of ADHD, but a recent meta-analysis found that clonidine is moderately efficacious as monotherapy for symptoms of ADHD.\textsuperscript{125} Another large study found that clonidine was efficacious both as monotherapy and as an adjunctive agent for patients with ADHD and comorbid tics.\textsuperscript{128}

In addition, clonidine is frequently used to reduce symptoms of opiate withdrawal; clonidine decreases norepinephrine release during opiate withdrawal by binding presynaptically to the \( \alpha_2 \) receptors.\textsuperscript{47} A comprehensive review\textsuperscript{130} of clonidine use for opiate withdrawal found that withdrawal symptoms were generally reduced similarly by clonidine and by a tapering schedule of long-acting opiates (e.g., methadone). Rates of completion of withdrawal protocols were similar with use of clonidine and an opiate taper. However, subjects had more side effects with clonidine and stayed in treatment longer when opiates were used. Similarly, clonidine appears to be marginally less effective than buprenorphine (a mixed opiate agonist/antagonist) for opiate withdrawal.\textsuperscript{131}

Other therapeutic uses for clonidine have included its use in the treatment of alcohol withdrawal, for which it appears to reduce many of the adrenergic symptoms associated with such withdrawal\textsuperscript{132,133}; however, as with \( \beta \)-blockers, clonidine is best used—if at all—as an adjunctive agent, as there is no evidence that this agent in effective in reducing rates of seizure, psychosis, or delirium associated with alcohol withdrawal.\textsuperscript{134-136} Clonidine has been used in the treatment of Tourette’s syndrome (TS). It is moderately effective in reducing tics and other symptoms of this disorder.\textsuperscript{137,138} Finally, use of clonidine has also been reported in a variety of other conditions, including Korsakoff’s syndrome (a neuropsychiatric syndrome caused by thiamine deficiency),\textsuperscript{141,142} bipolar mania,\textsuperscript{143} and conduct disorder,\textsuperscript{144} though there is insufficient evidence to adequately assess the benefits of clonidine in these conditions.

**Bottom line:** Clonidine is consistently associated with fatigue and sedation; delirium is infrequently associated with its use. Clonidine also has several therapeutic uses for neuropsychiatric disorders, serving as a first- or second-line treatment for ADHD and Tourette’s syndrome; it is also commonly used to reduce symptoms of opiate withdrawal.

**Methyldopa**

Methyldopa is infrequently used in clinical practice, except in patients with pregnancy-induced hypertension. It may reduce blood pressure via central \( \alpha_2 \) agonism, and may also act as a false (norepinephrine) neurotransmitter.\textsuperscript{47,123} As with many cardiovascular agents, the most common neuropsychiatric consequences of methyldopa use are sedation and fatigue; a comprehensive review by Paykel and colleagues\textsuperscript{123} found that sedation occurs in approximately one third of methyldopa-treated patients, with high rates of associated fatigue. For example, Levine and colleagues found that patients treated with methyldopa had lower self-reported quality of life and vitality than did those taking captopril in a 24-week trial.\textsuperscript{145} and a similar trial found that patients on methyldopa showed more fatigue than did those on captopril.\textsuperscript{146} Impaired concentration and decreased performance on measures of neuropsychological functioning have been reported with methyldopa,\textsuperscript{147,148} though a more recent trial found no cognitive impairment with methyldopa compared with five other antihypertensives;\textsuperscript{149} such cognitive effects may be due to sedation. However, perhaps the best-known neuropsychological consequence of methyldopa use is depression. It appears that depressive symptoms may occur more frequently with methyldopa than with most other antihypertensive agents, and it is thought that this effect may be related to reduced norepinephrine levels. An early study of methyldopa found increased rates of depression with this agent, especially in those with a history of depression,\textsuperscript{150} and a study of elderly patients found methyldopa to be more
strongly associated with depressive symptoms than were β-blockers; overall, it appears that reported depressive reactions to methyldopa often occur in patients with prior depressive episodes. In contrast, a critical review of the literature by Long and Kathol found no clear evidence that methyldopa was associated with the development of depressive symptoms, in contrast to reserpine. Similarly, a review of 80 patients found no significant association between methyldopa and depression. Overall, the association between methyldopa and depression is similar to that with β-blockers: suggestion of a connection in early case reports and small trials, with larger reviews unsupportive of a definitive association. Methyldopa, among its other actions, is a dopa decarboxylase inhibitor, and was reported to work synergistically with levodopa in patients with Parkinson’s disease in several early reports in the 1970s. However, there have been no recent reports to our knowledge, and it is not used in clinical practice for this indication, having been replaced by the dopa decarboxylase inhibitor, carbidopa. Finally, methyldopa has been associated with the onset of psychotic symptoms and acute confusional states, although these effects are rare. Bottom line: Methyldopa is clearly associated with fatigue and sedation. In contrast to early studies linking methyldopa with depression, later reviews and studies have found this association to be relatively weak. Other neuropsychiatric symptoms are uncommon.

Reserpine

Reserpine, an older antihypertensive medication that is now rarely used, can have a variety of neuropsychiatric effects. This agent acts by inhibiting the uptake of monoamine neurotransmitters into storage granules, resulting in the metabolism of these neurotransmitters by monoamine oxidase. This depletion of catecholamine neurotransmitters results in its antihypertensive effects and likely contributes to its association with depression and fatigue. Reserpine has long been associated with the onset of depressive symptoms, with a bevy of reports in the 1950s that linked reserpine use with depression, and a later review by members of our group citing an incidence of up to 15%. However, other (generally more recent) reports call this association into question. First, the depressive symptoms associated with use of reserpine appear to include sedation, malaise, and fatigue, but may not meet formal criteria for major depression; those who meet the full criteria tend to receive higher doses and to have a history of depression. Furthermore, two relatively large studies, one examining the onset of depressive symptoms among patients taking diuretics, β-blockers, and reserpine in over 4000 patients, and a large study of hypertension in the elderly that used low doses of reserpine, found very low rates of depression with reserpine use. In summary, reserpine is unquestionably associated with fatigue and sedation in a substantial subset of patients, and may be associated with the development of depressive symptoms, though this latter association is not as strong or as clear as once thought. Reserpine may also affect cognition in the elderly, most likely due to its sedative properties, though one study of five antihypertensive agents found no effect of reserpine on cognition in the elderly. Psychosis has been associated with reserpine withdrawal—presumably due to rebound increases in dopamine levels after discontinuation. Finally, reserpine has been used for treatment purposes. It has been used in cases of refractory mania with good effect, and it was, along with chlorpromazine, one of the first agents used to treat psychosis. Its antipsychotic effects and tolerability appear inferior to those of current antipsychotic medications, but this agent is still used, though rarely, in combination with atypical antipsychotics in refractory cases or to treat psychosis associated with phencyclidine. At one time, reserpine, especially via intravenous administration, was thought to have potential as a rapid-acting antidepressant, but its effects appear to be transitory and overall less effective than standard treatments.

Bottom line: Reserpine is associated with both sedation and daytime fatigue. Incidence of depression may be elevated among patients taking reserpine. However, other (generally more recent) reports question this association. It may provide benefit to patients with mania or psychosis, but is not first-line therapy for either condition.

α-Adrenergic agents

The α1-adrenergic antagonists prazosin, doxazosin, and alfuzosin are used as antihypertensive agents and to treat symptoms of benign prostatic hypertrophy. In general, there are few adverse neuropsychiatric consequences associated with these medications. Fatigue is the most common neuropsychiatric effect, occurring in
association with all $\alpha_1$ antagonists.\textsuperscript{182-184} This effect is relatively infrequent (presenting in approximately 5\% to 15\% of patients),\textsuperscript{182,183} but it does occur more often than with placebo, and can lead to its discontinuation. Depression is not consistently associated with this class of agents, although there have been rare occurrences reported in association with prazosin use.\textsuperscript{185} Sleep disturbance and anxiety can occur with these agents, though such symptoms are usually mild\textsuperscript{186,187}; there has been a single case report of psychosis associated with doxazosin.\textsuperscript{188} Finally, aside from a small case series describing encephalopathy in three patients with end-stage renal disease,\textsuperscript{190} $\alpha_1$ antagonists have not been frequently implicated in the development of delirium, and a study of nonelderly patients found that prazosin-treated patients performed slightly better on cognitive testing than did patients given hydrochlorothiazide (HCTZ) or propranolol.\textsuperscript{190} With respect to therapeutic uses, prazosin has been increasingly studied in the treatment of PTSD; it is thought to reduce the abnormal hyperadrenergic activity seen in patients with this illness. Multiple studies have found that prazosin reduces nightmares and sleep disturbances among patients with PTSD,\textsuperscript{191-197} and there has been more recent evidence that prazosin may have broader therapeutic effects in this disorder, reducing daytime symptoms and the overall burden of PTSD symptoms.\textsuperscript{191,196} 

\textit{Bottom line:} Fatigue is the most common neuropsychiatric side effect associated with $\alpha$-adrenergic antagonists; other neuropsychiatric side effects are infrequent. Prazosin appears to improve sleep-related symptoms of PTSD and may reduce the overall burden of symptoms in this disorder.

**Vasodilators**

**Hydralazine**

Hydralazine, a systemic vasodilator, the use of which is usually reserved for patients with severe hypertension, occasionally has neuropsychiatric side effects. Fatigue or asthenia occur slightly more often with hydralazine than with placebo, although this effect is not prominent. Hydralazine has been associated on rare occasions with the direct onset of depression,\textsuperscript{197} mild anxiety,\textsuperscript{198} psychosis,\textsuperscript{199} and delirium (due to withdrawal of hydralazine that has led to acute hypertension in a patient receiving hydralazine for afterload reduction).\textsuperscript{200} Furthermore, hydralazine does not appear to adversely affect cognition (with longer-term use) in the elderly.\textsuperscript{201} One neuropsychiatric consequence of hydralazine use is systemic lupus erythematosus; in fact, hydralazine is perhaps the most common cause of drug-induced lupus.\textsuperscript{202} However, drug-induced lupus affects the CNS less commonly than does idiopathic lupus, and though mood symptoms and fatigue may occur with hydralazine-induced lupus, more serious neuropsychiatric reactions have not been clearly described.\textsuperscript{203} 

**Nitrites (nitroglycerin, isosorbide dinitrate, and nitroprusside)**

Nitrites, most commonly used to treat angina, have minimal neuropsychiatric side effects. The rapid reduction in blood pressure caused by these agents can theoretically lead to an acute confusional state, and, indeed, nitroprusside-induced delirium has occurred in at least one patient.\textsuperscript{204} A single case report has also described hallucinations and suicidal ideation in a patient taking isosorbide dinitrate,\textsuperscript{205} but mood symptoms or psychotic symptoms have not otherwise been associated with nitrate medications. 

\textit{Bottom line:} Vasodilators are generally associated with low rates of neuropsychiatric consequences. Hydralazine is a leading cause of drug-induced lupus, but this syndrome affects the central nervous system much less commonly than the idiopathic form of the disorder.

**Antiplatelet and anticoagulant agents**

Aspirin (salicylic acid) has few neuropsychiatric consequences. It has not been consistently associated with mood symptoms, fatigue, sedation, anxiety, psychosis, or delirium when used at therapeutic doses. However, salicylate intoxication can lead to psychosis and delirium, possibly as a result of acidosis.\textsuperscript{206-208} Therapeutically, aspirin may have beneficial effects in patients with dementia. There has been some suggestion that aspirin may reduce the rate of cognitive decline in the elderly, particularly among patients with vascular dementia,\textsuperscript{209,210} by reducing the risk of recurrent vascular events, although a recent systematic review of aspirin for vascular dementia found no such evidence.\textsuperscript{211} Nilsson and colleagues\textsuperscript{212} also found that high-dose aspirin (325 mg/day) use was associated with reduced rates of development of Alzheimer’s dis-
ease—presumably as a result of its anti-inflammatory effects—but more comprehensive study is needed. Finally, the anti-inflammatory effects of aspirin have been postulated to have potential benefit in depression, given recent suggestions that inflammation may contribute to the pathophysiology of this disease. There has been a single, small, open trial in 24 depressed patients who had not responded to a 4-week trial of SSRIs; the authors found that the addition of aspirin to the SSRI led to rapid and sustained response in approximately one half of patients. However, much more research is required to determine whether the addition of aspirin to an antidepressant regimen for depression is indicated.

The antiplatelet agent, clopidogrel, has not been associated with significant neuropsychiatric consequences; as experience with this agent increases, adverse neuropsychiatric effects or therapeutic uses for neuropsychiatric disorders may become apparent. Similarly, the anti-coagulant medications, heparin and warfarin, are not commonly associated with neuropsychiatric effects.

Bottom line: Use of antiplatelet and anticoagulant medications has not been consistently associated with substantial neuropsychiatric consequences. Aspirin may cause delirium in toxicity.

Selected antiarrhythmic medications

Class I agents

These agents, which exert their therapeutic effects by blocking sodium channels, were commonly prescribed for many years, especially among acutely ill patients in intensive care settings. Their popularity has waned recently, though they remain in use.

Disopyramide (Class Ia)

The majority of neuropsychiatric consequences of disopyramide use result from the anticholinergic properties of this medication. Delirium can result from such anticholinergic effects, and there have been case reports of disopyramide-associated psychosis. Other neuropsychiatric consequences of use are uncommon. Therapeutically, disopyramide has been studied in the treatment of neurally mediated hypotension among patients who suffer from chronic fatigue; small studies suggest that it may provide benefit to persons whose fatigue is related to such hypotension.

Procainamide (Class Ia)

Although procainamide is generally associated with low rates of neuropsychiatric side effects, procainamide-induced psychosis has been reported in a variety of case reports involving seven patients. The mechanism of this association is ill-defined, and it is not clear whether some of these psychotic symptoms occurred in the broader context of delirium, as disorientation has also been reported as an uncommon side effect of this medication. Mania has also been reported in association with this agent. Finally, like hydralazine, procainamide is a leading cause of drug-induced lupus; this usually occurs after long-term exposure, and neuropsychiatric manifestations are uncommon. Among its more common side effects, fatigue can occur, but it is generally mild.

Quinidine (Class Ia)

Quinidine, a derivative of the cinchona plant, has been associated with neuropsychiatric events, most famously the constellation of symptoms known as cinchonism. Cinchonism may result in delirium along with a variety of effects on hearing and vision, with gastrointestinal side effects, and with cardiovascular events; psychosis has also occurred in the context of quinidine use. More chronic cognitive syndromes have also been reported rarely with use of quinidine. Quinidine does not appear to be associated with mood changes, and fatigue and sedation may occur but are not prominent.

Lidocaine (Class Ib)

Systemic use of lidocaine has been associated with a variety of neuropsychiatric effects. Lloyd and colleagues in a review of the neuropsychiatric effects of antiarrhythmics, report that delirium, psychotic symptoms, and anxiety may be consequences of lidocaine use. Furthermore, a specific review of 15 cases of adverse neuropsychiatric effects of lidocaine found that mood symptoms and apprehension/anxiety were the most common such effects; confusion and psychotic symptoms (hallucinations and delusions) were also common in this cohort.

Flecainide (Class Ic)

Flecainide is now rarely used; as with other class I agents, the literature on the neuropsychiatric consequences of its
use has been limited to case reports. Flecainide has been associated with psychosis, especially in toxicity, with new-onset paranoia, hallucinations, and dysarthria. Delusions, hallucinations, and depressed mood have also described in a report of three cases. **Bottom line:** Most class I antiarrhythmic agents have been associated with psychosis and delirium in case reports. The syndrome of cinchonism associated with quinidine may include sensory changes along with delirium, and procainamide is a cause of drug-induced lupus.

**Class III agents**

**Amiodarone**

In contrast to the above antiarrhythmics, amiodarone has been increasingly used in recent years, especially for patients with atrial fibrillation (AF). Amiodarone is listed as a class III antiarrhythmic agent that is thought to act via sodium, potassium, and calcium channel blockade. The structure of amiodarone is similar to that of thyroid hormone, and thyroid abnormalities occur in approximately 15% of patients taking amiodarone due to its high iodine content and its direct toxic effects on the thyroid; both hypothyroidism (more common) and hyperthyroidism may occur. Through this indirect mechanism, neuropsychiatric effects of amiodarone may occur, as hypothyroidism is commonly associated with fatigue and depressive symptoms (and occasionally psychosis), while hyperthyroidism can be associated with sleep disturbance, anxiety, apprehension, and, at times, depressive or manic symptoms, with or without psychosis. In addition, amiodarone has been directly associated with delirium, depressive symptoms, and fatigue; these effects have not been studied comprehensively but do not appear to be frequent complications of amiodarone use. **Bottom line:** Amiodarone is associated with thyroid abnormalities in 15% of patients, and untreated thyroid dysregulation can lead to a variety of mood, cognitive, and psychotic symptoms. In contrast, direct neuropsychiatric effects of amiodarone are uncommon.

**Digoxin**

Derived from the foxglove plant, *Digitalis lanata*, digoxin is used in the treatment of congestive heart failure and as a rate control agent for atrial fibrillation and atrial flutter. Digoxin has been associated with a wide variety of neuropsychiatric side effects, both in toxicity and at therapeutic levels. Keller and Fishman, in their excellent review of the neuropsychiatric effects of cardiovascular medications, described the range of neuropsychiatric symptoms associated with digoxin. Such effects include fatigue, depression, psychosis, and delirium, and the prescribing information for digoxin reports “mental disturbance” in 5% of patients taking digoxin (vs 1% with placebo). It appears that cognitive effects, such as delirium, may be the most common neuropsychiatric consequences of digoxin use, as over 80% of digoxin-associated adverse psychiatric effects reported to a Canadian national registry were classified as “encephalopathy.” Digoxin-associated delusions and other psychotic symptoms often occur in the context of delirium, although rarely digoxin toxicity may present with isolated psychotic symptoms. In addition, visual changes (such as blurred or yellow vision) and hallucinations are relatively common side effects of digoxin use. Depressive symptoms have been associated with digoxin in small trials and case reports, and digoxin toxicity can sometimes masquerade as depression. Depression linked with use of digoxin—as with many mood syndromes associated with cardiovascular medications—presents with prominent fatigue, low appetite, and impaired sleep. Despite these reports, however, larger prospective trials have not supported a strong link between digoxin and the development of depression. **Bottom line:** Digoxin is associated with delirium and other cognitive effects, especially in toxicity. Visual changes and hallucinations may also occur with digoxin use, even at normal serum levels.

**Lipid-lowering agents**

**Gemfibrozil, niacin, and bile acid sequestrants**

The lipid-lowering agent gemfibrozil is not associated with significant neuropsychiatric consequences; there are no clear associations with mood or psychotic symptoms, delirium or dementia are uncommon, and fatigue appears to occur at rates similar to placebo. Niacin was once thought to have beneficial neuropsychiatric effects—with small, but suggestive, reports in the 1950s and 1960s that nicotinic acid was effective in the treatment of depression and schizophrenia. However (as with many apparent associations we have discussed), once systematic reviews were performed, there appeared
to be no evidence for an association between nicotinic acid and antidepressant or antipsychotic effects. Adverse neuropsychiatric effects of niacin are uncommon. Bile acid sequestrants (such as cholestyramine) also have low rates of associated neuropsychiatric effects; there has been a report of cholestyramine-induced metabolic acidosis leading to delirium. However, the most frequently-used lipid-lowering agents are the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors ("statins"), and because of their widespread use these agents require further discussion.

**HMG-CoA reductase inhibitors**

The HMG-CoA reductase inhibitors are in widespread use. Overall, these agents have been associated with few neuropsychiatric effects. Lovastatin and pravastatin are more lipophilic than the other agents (such as atorvastatin and pravastatin), and therefore they can more easily cross the blood-brain barrier and potentially cause more neuropsychiatric effects; however, clinical experience has not found great differences between these agents in this regard.

One important area of interest concerns cholesterol levels and the risk of mood symptoms and aggressive acts. Low cholesterol levels have been correlated with depression, aggression, and suicide in several longitudinal studies. Several early studies found a correlation between low cholesterol and deaths from suicide, and a large longitudinal study found that patients in the lowest one third of cholesterol levels had elevated rates of suicide. A review of additional studies similarly found a low cholesterol-suicide link, even with correction for confounding factors; such low levels of cholesterol appears associated with depressive symptoms as well as frank suicidality. The mechanism of this association is unclear, but is thought by some to be mediated by serotonergic neurotransmission. Despite these findings, lowering serum cholesterol with statins has not been associated with increased rates of depression, noncardiac deaths, or suicide in several large prospective studies and a meta-analysis. Overall, there have been only a handful of reports of depressive symptoms associated with statin use, and prospective studies of statins’ effects on mood and cognition have found that these agents do not consistently cause depressed mood or impair cognition. The second area of interest with respect to these medications is their potential ability to prevent or treat Alzheimer’s dementia. Some authors have postulated that statins’ apparent ability to decrease Aβ peptides (thought to be part of an inflammatory pathway in Alzheimer’s disease) may lead to the therapeutic use of statins for patients with Alzheimer’s dementia. At this stage, several studies both supporting and refuting the utility of statins in the prevention and treatment of Alzheimer’s disease have been published. For example, a small study of atorvastatin found that this agent provides clinical benefit in patients with mild-to-moderate Alzheimer’s, and a large case-control study found that patients taking statins had a reduced incidence of Alzheimer’s dementia. In contrast, other well-designed studies have found no such benefit, and further research is needed.

**Conclusion**

In summary, the vast majority of neuropsychiatric consequences of cardiovascular medications are documented by case reports or open trials that are unable to definitively answer questions about causality. Indeed, a number of assumed associations (eg, between β-blockers and depression) appear weak or nonexistent when more comprehensive prospective trials are performed. Despite this, numerous cardiovascular medications can have neuropsychiatric side effects, ranging from mood symptoms to cognitive effects to psychosis, and though a given agent may not consistently cause neuropsychiatric symptoms in the general population, idiosyncratic reactions are possible. Cardiovascular medications can also have beneficial neuropsychiatric effects (eg, the use of clonidine in ADHD and tic disorders and prazosin for sleep disturbance in PTSD). With more formal study of the associations between cardiac medications and their neuropsychiatric effects, additional research may shed light on the underlying mechanisms and potential therapeutic strategies.

**Bottom line:** Lipid-lowering agents are associated with low rates of neuropsychiatric effects. Low absolute cholesterol levels have been correlated with depression and suicide, but several large trials of HMG-CoA reductase inhibitors have not found increased rates of depression and suicide associated with these drugs. Statins may have therapeutic effects in the prevention or treatment of Alzheimer’s dementia; studies thus far have had mixed results and further research is needed.
chiatric effects, clinicians will be better able to make fully-informed prescribing decisions for their patients.

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