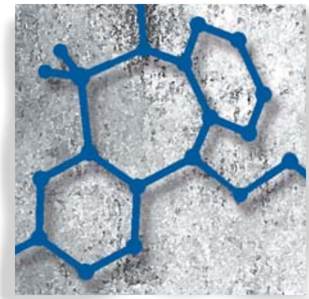
Neuropsychiatric consequences of cardiovascular medications

Jeff C. Huffman, MD; Theodore A. Stern, MD



The use of cardiovascular medications can have a variety of neuropsychiatric consequences. Many cardiovascular agents cause higher rates of fatigue and sedation than placebo, and case reports of medication-induced mood syndromes, psychosis, and cognitive disturbances exist for many cardiovascular drugs. Depression has been associated with β-blockers, methyldopa, and reserpine, but more recent syntheses of the data have suggested that these associations are much weaker than originally believed. Though low cholesterol levels have been associated with depression and suicide, lipid-lowering agents have not been associated with these adverse effects. Finally, cardiovascular medications may have beneficial neuropsychiatric consequences; for example, the use of clonidine in patients with attention deficit-hyperactivity disorder, the use of prazosin for patients with post-traumatic stress disorder, and the use of propranolol for performance anxiety and akathisia.

 Dialogues Clin Neurosci. 2007;9:29-45.

Keywords: *cardiovascular agent; adverse effect; neurologic manifestation; mood disorder; psychotic disorder; delirium; fatigue*

Author affiliations: Department of Psychiatry, Massachusetts General Hospital, Boston, Mass, USA; Harvard Medical School, Boston, Mass, USA

Address for correspondence: Jeff C. Huffman, MD, Massachusetts General Hospital, 55 Fruit Street/Warren 1220C, Boston, MA 02114, USA
(e-mail: jhuffman@partners.org)

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.

Selected abbreviations and acronyms

ACE	*angiotensin-converting enzyme*
ADHD	*attention deficit-hyperactivity disorder*
CCB	*calcium channel blocker*
HMG CoA	*3-hydroxy-3-methylglutaryl coenzyme A*
PTSD	*post-traumatic stress disorder*
SSRI	*selective serotonin reuptake inhibitor*

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 (eg, propranolol and metoprolol) cross the blood-brain barrier much more easily than do nonlipophilic β-blockers (eg, 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,[7-11] and a trial by Thiessen et al[12] found that treatment with propranolol was associated with higher rates of antidepressant prescriptions than with other β-blockers (both lipophilic and hydrophilic). Similarly, Hallas[13] 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.[14] In contrast, a randomized, controlled trial in 312 patients who received propranolol found no association between this agent and depression at 1 year.[15] Furthermore, several of the trials listed above did not take into account confounding variables (eg, 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.[16] 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.[17]

When trials have been expanded to include use of other β-blockers,[18-20] 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.[20] 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).[21] 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.[22,23] 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.[24] In the large meta-analysis by Ko and colleagues[21] 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.[25,26] Psychosis, usually in the context of delirium, has occurred rarely among patients taking propranolol,[27-29] metoprolol,[30] and atenolol.[31]

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).[32] In addition, β-blockers, especially the partial agonist, pindolol (which also blocks serotonin $[5\text{-HT}]_{1A}$ receptors) has been used adjunctively to enhance the benefits of selective serotonin reuptake inhibitors (SSRIs) in panic disorder[33,34] and obsessive-compulsive disorder (OCD).[35] 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).[36,37]

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.[38] 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).[39-41]

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).[42] β-Blockers can also be used adjunctively to reduce the effects of autonomic hyperactivity among patients undergoing alcohol or benzodiazepine withdrawal.[43,44] 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-HT_{1A} 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.[45]

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.[46,47] Several case reports and a small, open trial have found captopril to be efficacious in the treatment of major depression,[48-50] 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.[51] The possible mood-elevating effects of captopril are further supported by several reports of manic symptoms in association with use of captopril.[52-54] 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[55] and has been used in the adjunctive treatment of depression in another report.[56] Psychosis and delirium have been reported rarely with ACE inhibitors.[57-59] ACE inhibitors do not appear to have profound cognitive effects, with small trials finding no cognitive dysfunction[60] and perhaps even mild cognitive enhancement[61] among patients taking captopril, but a double-blind trial of an ACE inhibitor, ceranapril,[62] found that this agent did not improve cognition among patients with Alzheimer's disease. ACE inhibitors also demonstrate low rates of fatigue and sedation.[63,64]

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.[65-67] 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.[68] 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.[69] 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.[70] 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.[71-73] 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 nicarpidine has been associated with confusion among patients undergoing opiate withdrawal.[74-76]

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,[77,78] and small trials have suggested that verapamil may be as effective as lithium in the treatment of mania,[79-82] For example, in a trial comparing verapamil and lithium in the treatment of 20 patients with mania, Garza-Trevino and colleagues[79] 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)[83] and no more effective than placebo (in a small, double-blind trial),[84] 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 nonpregnant women with bipolar disorder was conducted.[85] 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.[86]

Verapamil and other CCBs have also been used as maintenance treatment for patients with bipolar disorder.[87,88] A crossover trial of verapamil and lithium in the maintenance treatment of bipolar disorder found that these agents were equally effective,[88] although there is some suggestion that this agent is ineffective in patients with refractory illness.[89] There have been three reports of nimodipine's efficacy in bipolar illness,[90-92] including a small but well-designed on-off-on trial[90]; 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.[93] 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,[81] and ineffective for depression among patients refractory to TCAs.[94] 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 nicarpidine improved ECT-associated cognitive impairment; it did not).[95] 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.[96,97] 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,[98] 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.[99]

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,[47,100] can more indirectly result in neuropsychiatric complications due to their effects on electrolytes (primarily sodium and calcium)[101-105] 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.[106] Hyponatremia and hypercalcemia associated with the use of thiazide diuretics have been reported to lead to delirium and psychosis.[102,103] Thiazides may also exacerbate hyponatremia (and associated neuropsychiatric symptoms) caused by SSRIs via the syndrome of inappropriate antidiuretic hormone secretion (SIADH).[104,105] 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.[107] Overall, thiazide diuretics are not frequently associated with fatigue, sedation, cognitive impairment,[108] 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.[109] Thiamine deficiency can lead to Wernicke's encephalopathy (characterized by confusion, opthalmoplegia, and ataxia), and indeed, use of loop diuretics was associated with this syndrome in one case report.[110]

The carbonic anhydrase inhibitor acetazolamide can be associated with fatigue and sedation, especially early in treatment.[111] Epstein and Grant[112] found that nearly half of carbonic anhydrase inhibitor-treated patients had a mild syndrome of fatigue, malaise, anorexia, and depression, and that such symptoms were associated with acidosis; there have been no further reports of depressive syndromes with this agent. Delirium can occur rarely with acetazolamide use; acetazolamide toxicity, which is especially common in patients with renal failure, is characterized by fatigue, lethargy, and confusion.[113-115] Acetazolamide may also have therapeutic neuropsychiatric consequences, especially among patients with apnea. It stimulates central respiratory drive and may therefore provide benefits in both central and obstructive sleep apnea.[116,117] In addition, there has been a single case report of its use in acute mania[118] and a small study found that acetazolamide, particularly when combined with an anticonvulsant, might prove beneficial to patients with refractory symptoms in bipolar disorder.[119] Finally, Inoue and colleagues[120] used acetazolamide to treat patients with a variety of atypical psychoses, and found that approximately 70% of patients improved.

Bottom line: Diuretics most often cause neuropsychiatric symptoms indirectly, through electrolyte abnormalities (thiazides) or vitamin deficiencies (loop diuretics). Acetazolamide is associated with fatigue and with delirium in renal failure. Small studies suggest that acetazolamide may provide benefits in sleep apnea or bipolar disorder.

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.[121-123] 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.[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.[124] Finally, clonidine may also affect cognition in certain patients. It has been associated with cognitive slowing,[123,125] and there have been at least seven case reports of delirium associated with the use of clonidine.[126]

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.[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.[127] Another large study found that clonidine was efficacious both as monotherapy and as an adjunctive agent for patients with ADHD and comorbid tics.[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 α_2 receptors.[47] A comprehensive review[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 (eg, 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.[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[132,133]; however, as with β-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.[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.[137-140] 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),[141,142] bipolar mania,[143] and conduct disorder,[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 α_2 agonism, and may also act as a false (norepinephrine) neurotransmitter.[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[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,[145] and a similar trial found that patients on methyldopa showed more fatigue than did those on captopril.[146] Impaired concentration and decreased performance on measures of neuropsychological functioning have been reported with methyldopa,[147,148] though a more recent trial found no cognitive impairment with methyldopa compared with five other antihypertensives;[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,[150] and a study of elderly patients found methyldopa to be more strongly associated with depressive symptoms than were β-blockers;[148] overall, it appears that reported depressive reactions to methyldopa often occur in patients with prior depressive episodes.[151,152] In contrast, a critical review of the literature by Long and Kathol[153] 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.[154] 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.[155-157] 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 decarboxlyase inhibitor, carbidopa. Finally, methyldopa has been associated with the onset of psychotic symptoms and acute confusional states, although these effects are rare.[158,159]

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.[47]

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,[160-163] and a later review by members of our group citing an incidence of up to 15%.[164] 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[47,162]; 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,[165] and a large study of hypertension in the elderly that used low doses of reserpine,[166] 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,[167,168] and may be associated with the development of depressive symptoms, though this latter association is not as strong or as clear as once thought.[169]

Reserpine may also affect cognition in the elderly,[170] most likely due to its sedative properties, though one study of five antihypertensive agents found no effect of reserpine on cognition in the elderly.[171] Psychosis has been associated with reserpine withdrawal—presumably due to rebound increases in dopamine levels after discontinuation.[172,173]

Finally, reserpine has been used for treatment purposes. It has been used in cases of refractory mania with good effect,[174-176] 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,[47] but this agent is still used, though rarely, in combination with atypical antipsychotics in refractory cases or to treat psychosis associated with phencyclidine.[176-180] 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.[181]

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 α_1-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 α_1 antagonists.[182-184] This effect is relatively infrequent (presenting in approximately 5% to 15% of patients),[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.[185] Sleep disturbance and anxiety can occur with these agents, though such symptoms are usually mild[186,187]; there has been a single case report of psychosis associated with doxazosin.[188] Finally, aside from a small case series describing encephalopathy in three patients with end-stage renal disease,[189] α_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.[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,[191-195] 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.[191,196]

Bottom line: Fatigue is the most common neuropsychiatric side effect associated with α-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,[197] mild anxiety,[198] psychosis,[199] and delirium (due to withdrawal of hydralazine that has led to acute hypertension in a patient receiving hydralazine for afterload reduction).[200] Furthermore, hydralazine does not appear to adversely affect cognition (with longer-term use) in the elderly.[201]

One neuropsychiatric consequence of hydralazine use is systemic lupus erythematosus; in fact, hydralazine is perhaps the most common cause of drug-induced lupus.[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.[203]

Nitrates (nitroglycerin, isosorbide dinitrate, and nitroprusside)

Nitrates, 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.[204] A single case report has also described hallucinations and suicidal ideation in a patient taking isosorbide dinitrate,[205] but mood symptoms or psychotic symptoms have not otherwise been associated with nitrate medications.

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.[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 [209,210] by reducing the risk of recurrent vascular events, although a recent systematic review of aspirin for vascular dementia found no such evidence.[211] Nilsson and colleagues[212] also found that high-dose aspirin (325 mg/day) use was associated with reduced rates of development of Alzheimer's disease—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.[213] 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,[214] and there have been case reports of disopyramide-associated psychosis.[215,216] 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.[217,218]

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.[219-223] 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.[224] Mania has also been reported in association with this agent.[225] Finally, like hydralazine, procainamide is a leading cause of drug-induced lupus; this usually occurs after long-term exposure, and neuropsychiatric manifestations are uncommon.[226] 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[227,228]; psychosis has also occurred in the context of quinidine use.[229,230] More chronic cognitive syndromes have also been reported rarely with use of quinidine.[231-233] 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,[234] 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.[235]

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,[236] hallucinations, and dysarthria.[237] Delusions, hallucinations, and depressed mood[238] have also described in a report of three cases.

Bottom line: Most class I antiarrthymic 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 antiarrythmics, amiodarone has been increasingly used in recent years, especially for patients with atrial fibrillation (AF). Amiodarone is listed as a class III antiarrthymic 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[239]; 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),[240] while hyperthyroidism can be associated with sleep disturbance, anxiety, apprehension, and, at times, depressive or maniform symptoms, with or without psychosis.[241] In addition, amiodarone has been directly associated with delirium,[242-245] depressive symptoms,[246,247] and fatigue[251]; 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,[47] 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).[249] 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."[250] Digoxin-associated delusions and other psychotic symptoms often occur in the context of delirium, although rarely digoxin toxicity may present with isolated psychotic symptoms.[251-254] 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.[255-257] Depression linked with use of digoxin—as with many mood syndromes associated with cardiovascular medications—presents with prominent fatigue, low appetite, and impaired sleep.[47] Despite these reports, however, larger prospective trials have not supported a strong link between digoxin and the development of depression.[258,259]

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.[260-263] 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.[264,265] 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.[266] 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.[267-269] 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,[270-272] and a large longitudinal study found that patients in the lowest one third of cholesterol levels had elevated rates of suicide.[273] A review of additional studies similarly found a low cholesterol-suicide link,[272] even with correction for confounding factors; such low levels of cholesterol appears associated with depressive symptoms as well as frank suicidality.[274] The mechanism of this association is unclear, but is thought by some to be mediated by serotonergic neurotransmission.[275]

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.[276-279] Overall, there have been only a handful of reports of depressive symptoms associated with statin use,[280-282] and prospective studies of statins' effects on mood and cognition have found that these agents do not consistently cause depressed mood or impair cognition.[276,277,283,284]

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.[285] At this stage, several studies both supporting and refuting the utility of statins in the prevention and treatment 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,[286] and a large case-control study found that patients taking statins had a reduced incidence of Alzheimer's dementia.[287] In contrast, other well-designed studies have found no such benefit,[288,289] and further research is needed.

Otherwise, the statins appear to have few neuropsychiatric consequences, with occasional reports of anxiety, sleep disturbance (especially with lovastatin), and fatigue, but no other substantial neuropsychiatric effects.[267-269,290]

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.

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, clinicians will be better able to make fully-informed prescribing decisions for their patients. ❑

The authors would like to thank Sara Nadelman for editorial assistance.

Consecuencias neuropsiquiátricas de los medicamentos cardiovasculares

El empleo de medicamentos cardiovasculares puede tener una variedad de consecuencias neuropsiquiátricas. Muchos fármacos cardiovasculares provocan con mayor frecuencia fatiga y sedación respecto del placebo y también existen muchos reportes de casos de síntomas afectivos, psicosis y trastornos cognitivos inducidos por varios de estos medicamentos. Se ha asociado la depresión con beta-bloqueadores, metildopa y reserpina, pero análisis recientes de estos datos han sugerido que estas asociaciones son mucho más débiles que lo que originalmente se pensaba. Aunque los niveles reducidos de colesterol se han asociado con depresión y suicidio, los fármacos reductores de lípidos no se han asociado con estos efectos adversos. Por último, los fármacos cardiovasculares pueden tener efectos neuropsiquiátricos útiles; por ejemplo, el empleo de clonidina en pacientes con trastorno por déficit atencional con hiperactividad, el uso de prazosin en pacientes con trastorno por estrés postraumático y la indicación de propranolol en la ansiedad de rendimiento y en la acatisia.

Conséquences neuropsychiatriques des traitements cardiovasculaires

Les traitements cardiovasculaires peuvent avoir des conséquences neuropsychiatriques variées. De nombreux produits cardiovasculaires induisent une fatigue et une sédation plus importantes que le placebo. Des troubles cognitifs, de l'humeur et psychotiques ont été considérés comme provoqués par un grand nombre de ces traitements cardiotropes. La dépression a parfois été associée aux β-bloquants, à la méthyldopa et à la réserpine, mais des données plus récentes laissent penser que ces associations sont beaucoup moins importantes qu'initialement pressenties. Bien que des cholestérolémies basses aient été associées à la dépression et au suicide, les hypolipémiants n'ont pas été incriminés dans de tels effets indésirables. Les traitements cardiovasculaires peuvent finalement avoir des conséquences neuropsychiatriques bénéfiques : par exemple, l'utilisation de la clonidine chez les patients atteints d'un déficit de l'attention/hyperactivité, l'utilisation de la prazosine pour ceux souffrant d'un syndrome de stress post-traumatique, et l'utilisation du propranolol pour l'anxiété de performance (trac) et l'akathisie.

REFERENCES

1. Connerney I, Shapiro PA, McLaughlin JS, Bagiella E, Sloan RP. Relation between depression after coronary artery bypass surgery and 12-month outcome: a prospective study. *Lancet*. 2001;358:1766-1771.
2. Konstam V, Moser DK, De Jong MJ. Depression and anxiety in heart failure. *J Card Fail*. 2005;11:455-463.
3. van Melle JP, de Jonge P, Spijkerman TA, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med*. 2004;66:814-822.
4. Moser DK, Dracup K. Is anxiety early after myocardial infarction associated with subsequent ischemic and arrhythmic events? *Psychosom Med*. 1996;58:395-401.
5. Frasure-Smith N, Lesperance F, Talajic M. The impact of negative emotions on prognosis following myocardial infarction: is it more than depression? *Health Psychol*. 1995;14:388-398.
6. Sockalingam S, Parekh N, Bogoch II, et al. Delirium in the postoperative cardiac patient: a review. *J Card Surg*. 2005;20:560-567.
7. Patten SB. Propranolol and depression: evidence from the antihypertensive trials. *Can J Psychiatry*. 1990;35:257-259.
8. Oppenheim G. Propranolol-induced depression: mechanism and management. *Aust N Z J Psychiatry*. 1983;17:400-402.
9. McNeil GN, Shaw PK, Dock DS. Substitution of atenolol for propranolol in a case of propranolol-related depression. *Am J Psychiatry*. 1982;139:1187-1188.
10. Pollack MH, Rosenbaum JF, Cassem NH. Propranolol and depression revisited: three cases and a review. *J Nerv Ment Dis*. 1985;173:118-119.
11. Fitzgerald JD. Propanolol-induced depression. *BMJ*. 1967;2:372-373.
12. Thiessen BQ, Wallace SM, Blackburn JL, Wilson TW, Bergman U. Increased prescribing of antidepressants subsequent to beta-blocker therapy. *Arch Intern Med*. 1990;150:2286-2290.
13. Hallas J. Evidence of depression provoked by cardiovascular medication: a prescription sequence symmetry analysis. *Epidemiology*. 1996;7:478-484.

14. Steiner SS, Friedhoff AJ, Wilson BL, Wecker JR, Santo JP. Antihypertensive therapy and quality of life: a comparison of atenolol, captopril, enalapril and propranolol. *J Hum Hypertens*. 1990;4:217-225.
15. Perez-Stable EJ, Halliday R, Gardiner PS, et al. The effects of propranolol on cognitive function and quality of life: a randomized trial among patients with diastolic hypertension (no increase in depression at 12 months, 312 patients). *Am J Med*. 2000;108:359-365.
16. Bright RA, Everitt DE. Beta-blockers and depression. Evidence against an association. *JAMA*. 1992;267:1783-1787.
17. Stoudemire A, Brown JT, Harris RT, et al. Propranolol and depression: a reevaluation based on a pilot clinical trial. *Psychiatr Med*. 1984;2:211-218.
18. Carney RM, Rich MW, teVelde A, Saini J, Clark K, Freedland KE. Prevalence of major depressive disorder in patients receiving beta-blocker therapy versus other medications. *Am J Med*. 1987;83:223-226.
19. Ried LD, McFarland BH, Johnson RE, Brody KK. Beta-blockers and depression: the more the murkier? *Ann Pharmacother*. 1998;32:699-708.
20. Gerstman BB, Jolson HM, Bauer M, Cho P, Livingston JM, Platt R. The incidence of depression in new users of beta-blockers and selected antihypertensives. *J Clin Epidemiol*. 1996;49:809-815.
21. Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM. Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA*. 2002;288:351-357.
22. Dimsdale JE, Newton RP, Joist T. Neuropsychological side effects of beta-blockers. *Arch Intern Med*. 1989;149:514-525.
23. Paykel ES, Fleminger R, Watson JP. Psychiatric side effects of antihypertensive drugs other than reserpine. *J Clin Psychopharmacol*. 1982;2:14-39.
24. Tenormin (atenolol) prescribing information. Wilmington, Del: AstraZeneca; 2005.
25. Dimsdale JE, Newton RP. Cognitive effects of beta-blockers. *J Psychosom Res*. 1992;36:229-236.
26. Dimsdale JE, Newton RP, Joist T. Neuropsychological side effects of beta-blockers. *Arch Intern Med*. 1989;149:514-525.
27. Love JN, Handler JA. Toxic psychosis: an unusual presentation of propranolol intoxication. *Am J Emerg Med*. 1995;13:536-537.
28. McGahan DJ, Wojslaw A, Prasad V, Blankenship S. Propranolol-induced psychosis. *Drug Intell Clin Pharm*. 1984;18:601-603.
29. Parker WA. Propranolol-induced depression and psychosis. *Clin Pharmacol*. 1985;4:214-218.
30. Viadero JJ, Wong SH, White WB. Acute psychotic behavior associated with atenolol. *Am J Psychiatry*. 1983;140:1382.
31. Fisher AA, Davis M, Jeffery I. Acute delirium induced by metoprolol. *Cardiovasc Drugs Ther.* 2002;16:161-165.
32. Schneier FR. Clinical practice. Social anxiety disorder. *N Engl J Med*. 2006;355:1029-1036.
33. Zamorski MA, Albucher RC. What to do when SSRIs fail: eight strategies for optimizing treatment of panic disorder. *Am Fam Physician*. 2002;66:1477-1484.
34. Hirschmann S, Dannon PN, Iancu I, Dolberg OT, Zohar J, Grunhaus L. Pindolol augmentation in patients with treatment-resistant panic disorder: A double-blind, placebo-controlled trial. *J Clin Psychopharmacol*. 2000;20:556-559.
35. Dannon PN, Sasson Y, Hirschmann S, Iancu I, Grunhaus LJ, Zohar J. Pindolol augmentation in treatment-resistant obsessive compulsive disorder: a double-blind placebo controlled trial. *Eur Neuropsychopharmacol*. 2000;10:165-169.
36. Vaiva G, Ducrocq F, Jezequel K, et al. Immediate treatment with propranolol decreases posttraumatic stress disorder two months after trauma. *Biol Psychiatry*. 2003;54:947-949. Erratum in: *Biol Psychiatry*. 2003;54:1471.
37. Pitman RK, Sanders KM, Zusman RM, et al. Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. *Biol Psychiatry*. 2002;51:189-192.
38. Fleminger S, Greenwood RJ, Oliver DL. Pharmacological management for agitation and aggression in people with acquired brain injury. *Cochrane Database Syst Rev*. 2003;1:CD003299.
39. Haspel T. Beta-blockers and the treatment of aggression. *Harv Rev Psychiatry*. 1995;2:274-281.
40. Fava M. Psychopharmacologic treatment of pathologic aggression. *Psychiatr Clin North Am*. 1997;20:427-451.
41. Peskind ER, Tsuang DW, Bonner LT, et al. Propranolol for disruptive behaviors in nursing home residents with probable or possible Alzheimer disease: a placebo-controlled study. *Alzheimer Dis Assoc Disord*. 2005;19:23-28.
42. Sachdev PS. Neuroleptic-induced movement disorders: an overview. *Psychiatr Clin North Am*. 2005;28:255-274.
43. Horwitz RI, Gottlieb LD, Kraus ML. The efficacy of atenolol in the outpatient management of the alcohol withdrawal syndrome. Results of a randomized clinical trial. *Arch Intern Med*. 1989;149:1089-1093.
44. Kraus ML, Gottlieb LD, Horwitz RI, Anscher M. Randomized clinical trial of atenolol in patients with alcohol withdrawal. *N Engl J Med*. 1985;313:905-909.
45. Ballesteros J, Callado LF. Effectiveness of pindolol plus serotonin uptake inhibitors in depression: a meta-analysis of early and late outcomes from randomised controlled trials. *J Affect Disord*. 2004;79:137-147.
46. Cushman DW, Wang FL, Fung WC, Harvey CM, DeForrest JM. Differentiation of angiotensin-converting enzyme (ACE) inhibitors by their selective inhibition of ACE in physiologically important target organs. *Am J Hypertens*. 1989;2:294-306.
47. Keller S, Frishman WH. Neuropsychiatric effects of cardiovascular drug therapy. *Cardiol Rev*. 2003;11:73-93.
48. Hertzman M, Adler LW, Arling B, Kern M. Lisinopril may augment antidepressant response. *J Clin Psychopharmacol*. 2005;25:618-620.
49. Germain L, Chouinard G. Captopril treatment of major depression with serial measurements of blood cortisol concentrations. *Biol Psychiatry*. 1989;25:489-493.
50. Germain L, Chouinard G. Treatment of recurrent unipolar major depression with captopril. *Biol Psychiatry*. 1988;23:637-641.
51. Croog SH, Levine S, Testa MA, et al. The effects of antihypertensive therapy on the quality of life. *N Engl J Med*. 1986;314:1657-1664.
52. Gajula RP, Berlin RM. Captopril-induced mania. *Am J Psychiatry*. 1993;150:1429-1430.
53. Patten SB, Brager N, Sanders S. Manic symptoms associated with the use of captopril. *Can J Psychiatry*. 1991;36:314-315.
54. McMahon T. Bipolar affective symptoms associated with use of captopril and abrupt withdrawal of pargyline and propranolol. *Am J Psychiatry*. 1985;142:759-760.
55. Skop BP, Masterson BJ. Mania secondary to lisinopril therapy. *Psychosomatics*. 1995;36:508-509.
56. Vuckovic A, Cohen BM, Zubenko GS. The use of captopril in treatment-resistant depression: an open trial. *J Clin Psychopharmacol*. 1991;11:395-396.
57. Tarlow MM, Sakaris A, Scoyni R, Wolf-Klein G. Quinapril-associated acute psychosis in an older woman. *J Am Geriatr Soc*. 2000;48:1533.
58. Ahmad S. Enalapril-induced acute psychosis. *DICP*. 1991;25:558-559.
59. Gillman MA, Sandyk R. Reversal of captopril-induced psychosis with naloxone. *Am J Psychiatry*. 1985;142:270.
60. Ebert U, Kirch W. Effects of captopril and enalapril on electroencephalogram and cognitive performance in healthy volunteers. *Eur J Clin Pharmacol.* 1999;55:255-257.
61. Currie D, Lewis RV, McDevitt DG, Nicholson AN, Wright NA. Central effects of the angiotensin-converting enzyme inhibitor, captopril. I. Performance and subjective assessments of mood. *Br J Clin Pharmacol*. 1990;30:527-536.
62. Sudilovsky A, Cutler NR, Sramek JJ, et al. A pilot clinical trial of the angiotensin-converting enzyme inhibitor ceranapril in Alzheimer disease. *Alzheimer Dis Assoc Disord*. 1993;7:105-111.
63. Capoten (captopril) prescribing information. Princeton, NJ: Brisol-Myers Squibb; 1996.
64. Zestril (lisinopril) prescribing information. Wilmington, Del; McNeil Consumer & Specialty Pharmaceuticals; 2002.
65. Markham A, Goa KL. Valsartan. A review of its pharmacology and therapeutic use in essential hypertension. *Drugs*. 1997;54:299-311. Review.
66. Weber M. Clinical safety and tolerability of losartan. *Clin Ther.* 1997;19:604-616.
67. Croom KF, Curran MP, Goa KL, Perry CM. Irbesartan: a review of its use in hypertension and in the management of diabetic nephropathy. *Drugs*. 2004;64:999-1028.
68. Ullrich H, Passenberg P, Agelink MW. Episodes of depression with attempted suicide after taking valsartan with hydrochlorothiazide [in German]. *Dtsch Med Wochenschr*. 2003;128:2534-2536.

69. Ahmad S. Losartan and reversible psychosis. *Cardiology*. 1996;87:569-570.
70. Tedesco MA, Ratti G, Mennella S, et al. Comparison of losartan and hydrochlorothiazide on cognitive function and quality of life in hypertensive patients. *Am J Hypertens*. 1999;12:1130-1134.
71. Talbert RL, Bussey HI. Update on calcium-channel blocking agents. *Clin Pharm*. 1983;2:403-416.
72. Norvasc (amlodipine) prescribing information. New York, NY: Pfizer Labs; 2003.
73. Calan (verapamil) prescribing information. Chicago, Ill: GD Searle LLC, a subsidiary of Pharmacia Corporation, 2003.
74. Jacobsen FM, Sack DA, James SP. Delirium induced by verapamil. *Am J Psychiatry*. 1987;144:248.
75. Busche CJ. Organic psychosis caused by diltiazem. *J R Soc Med*. 1988;81:296-297.
76. Silverstone PH, Attenburrow MJ, Robson P. The calcium channel antagonist nifedipine causes confusion when used to treat opiate withdrawal in morphine-dependent patients. *Int Clin Psychopharmacol*. 1992;7:87-90.
77. Dubovsky SL, Franks RD, Lifschitz M, Coen P. Effectiveness of verapamil in the treatment of a manic patient. *Am J Psychiatry*. 1982;139:502-504.
78. Dubovsky SL, Franks RD, Schrier D. Phenelzine-induced hypomania: effect of verapamil. *Biol Psychiatry*. 1985;20:1009-1014.
79. Garza-Trevino E, Overall JE, Hollister LE. Verapamil versus lithium in acute mania. *Am J Psychiatry*. 1992;149:121–122.
80. Giannini AJ, Houser WL, Loiselle RH, Giannini MC, Price WA. Antimanic effects of verapamil. *Am J Psychiatry*. 1984;141:1602–1603.
81. Hoschl C, Kozeny J. Verapamil in affective disorders: a controlled, double-blind study. *Biol Psychiatry*. 1989;25:128-140.
82. Dubovsky SL, Franks RD, Allen S, Murphy J. Calcium antagonists in mania: a double-blind study of verapamil. *Psychiatry Res*. 1986;18:309–320.
83. Walton SA, Berk M, Brook S. Superiority of lithium over verapamil in mania: a randomized, controlled, single-blind trial. *J Clin Psychiatry*. 1996;57:543-546.
84. Janicak PG, Sharma RP, Pandey G, Davis JM. Verapamil for the treatment of acute mania: a double-blind, placebo-controlled trial. *Am J Psychiatry*. 1998;155:972-973.
85. Wisner KL, Peindl KS, Perel JM, Hanusa BH, Piontek CM, Baab S. Verapamil treatment for women with bipolar disorder. *Biol Psychiatry*. 2002;51:745-752.
86. Palat GK, Movahed A. Secondary mania associated with diltiazem. *Clin Cardiol*. 1985;8:251.
87. Giannini AJ, Loiselle RH. Verapamil maintenance therapy in bipolar patients. *J Clin Psychiatry*. 1996;57:136.
88. Gitlin MJ, Weiss J. Verapamil as maintenance treatment in bipolar illness: a case report. *J Clin Psychopharmacol*. 1984;4:341-343.
89. Kennedy S, Ozersky S, Robillard M. Refractory bipolar illness may not respond to verapamil. *J Clin Psychopharmacol*. 1986;6:316-317.
90. Pazzaglia PJ, Post RM, Ketter TA, George MS, Marangell LB. Preliminary controlled trial of nimodipine in ultra-rapid cycling affective dysregulation. *J Clin Psychopharmacol*. 1987;7:101-103.
91. Giannini AJ, Verapamil and lithium in maintenance therapy of manic patients. *J Clin Pharmacol*. 1987;27:980-982.
92. Yingling DR, Utter G, Vengalil S, Mason B. Calcium channel blocker, nimodipine, for the treatment of bipolar disorder during pregnancy. *Am J Obstet Gynecol*. 2002;187:1711-1712.
93. Pazzaglia PJ, Post RM, Ketter TA, et al. Nimodipine monotherapy and carbamazepine augmentation in patients with refractory recurrent affective illness. *J Clin Psychopharmacol*. 1998;18:404-413.
94. Adlersberg S, Toren P, Mester R, Rehavi M, Skolnick P, Weizman A. Verapamil is not an antidepressant in patients resistant to tricyclic antidepressants. *Clin Neuropharmacol*. 1994;17:294-297.
95. Dubovsky SL, Buzan R, Thomas M, Kassner C, Cullum CM. Nicardipine improves the antidepressant action of ECT but does not improve cognition. *J ECT*. 2001;17:3-10.
96. Taragano FE, Allegri R, Vicario A, Bagnatti P, Lyketsos CG. A double blind, randomized clinical trial assessing the efficacy and safety of augmenting standard antidepressant therapy with nimodipine in the treatment of 'vascular depression'. *Int J Geriatr Psychiatry*. 2001;16:254-260.
97. Taragano FE, Bagnatti P, Allegri RF. A double-blind, randomized clinical trial to assess the augmentation with nimodipine of antidepressant therapy in the treatment of "vascular depression". *Int Psychogeriatr*. 2005;17:487-498.
98. Klein E, Uhde TW. Controlled study of verapamil for treatment of panic disorder. *Am J Psychiatry.1988;145:431-434*.
99. Balon R, Ramesh C. Calcium channel blockers for anxiety disorders? *Ann Clin Psychiatry*. 1996;8:215-220.
100. Seno S, Shaw SM, Christian JE. Distribution and urinary excretion of furosemide in the rat. *J Pharm Sci*. 1969;58:935-938.
101. Gammon GD, Docherty JP. Thiazide-induced hypercalcemia in a manic-depressive patient. *Am J Psychiatry*. 1980;137:1453-1455.
102. Chow KM, Kwan BC, Szeto CC. Clinical studies of thiazide-induced hyponatremia. *J Natl Med Assoc*. 2004;96:1305-1308.
103. Haensch CA, Hennen G, Jorg J. Reversible exogenous psychosis in thiazide-induced hyponatremia of 97 mmol/l [in German]. *Nervenarzt*. 1996;67:319-322.
104. Rosner MH. Severe hyponatremia associated with the combined use of thiazide diuretics and selective serotonin reuptake inhibitors. *Am J Med Sci*. 2004;327:109-111.
105. Kirby D, Ames D. Hyponatraemia in elderly psychiatric patients treated with Selective Serotonin Reuptake Inhibitors and venlafaxine: a retrospective controlled study in an inpatient unit. *Int J Geriatr Psychiatry*. 2002;17:231-237.
106. Okada F, Kirby D, Harrigan S, Ames D. Depression after treatment with thiazide diuretics for hypertension. *Am J Psychiatry*. 1985;142:1101-1102.
107. Nurnberger JI Jr. Diuretic-induced lithium toxicity presenting as mania. *J Nerv Ment Dis*. 1985;173:316-318.
108. Gray SL, Lai KV, Larson EB. Drug-induced cognition disorders in the elderly: incidence, prevention and management. *Drug Saf*. 1999;21:101-122.
109. Zenuk C, Healey J, Donnelly J, Vaillancourt R, Almalki Y, Smith S. Thiamine deficiency in congestive heart failure patients receiving long term furosemide therapy. *Can J Clin Pharmacol*. 2003;10:184-188.
110. McLean J, Manchip S. Wernicke's encephalopathy induced by magnesium depletion. *Lancet*. 1999;353:1768.
111. Acetazolamide prescribing information. Hawthorne, NY: Taro Pharmaceuticals; 1997.
112. Epstein DL, Grant WM. Carbonic anhydrase inhibitor side effects. Serum chemical analysis. *Arch Opthalmol*. 1977;95:1378-1382.
113. Rowe TO. Acetazolamide delirium. *Am J Psychiatry*. 1977;134:587-588.
114. Schwenk MH, St Peter WL, Meese MG, Singhal PC. Acetazolamide toxicity and pharmacokinetics in patients receiving hemodialysis. *Pharmacotherapy*. 1995;15:522-527.
115. Miguel E, Guell R, Anton A, Montiel JA, Mayos M. Acute confusional syndrome associated with obstructive sleep apnea aggravated by acidosis secondary to oral acetazolamide treatment [in Spanish]. *Arch Bronconeumol*. 2004;40:283-286.
116. Tojima H, Kunitomo F, Kimura H, Tatsumi K, Kuriyama T, Honda Y. Effects of acetazolamide in patients with the sleep apnoea syndrome. *Thorax*. 1988;43:113-119.
117. Javaheri S. Acetazolamide improves central sleep apnea in heart failure: a double-blind, prospective study. *Am J Respir Crit Care Med*. 2006;173:234-237.
118. Brandt C, Grunze H, Normann C, Walden J. Acetazolamide in the treatment of acute mania. A case report. *Neuropsychobiology*. 1998;38:202-203.
119. Hayes SG. Acetazolamide in bipolar affective disorders. *Ann Clin Psychiatry*. 1994;6:91-98.
120. Inoue H, Hazama H, Hamazoe K, et al. Antipsychotic and prophylactic effects of acetazolamide (Diamox) on atypical psychosis. *Folia Psychiatr Neurol Jpn*. 1984;38:425-436.
121. Catapres-TTS (clonidine) prescribing information. Indianapolis, Ind: Boeringer-Mannheim; 2006.
122. Keller S, Frishman WH. Neuropsychiatric effects of cardiovascular drug therapy. *Cardiol Rev*. 2003;11:73-93.
123. Paykel ES, Fleminger R, Watson JP. Psychiatric side effects of antihypertensive drugs other than reserpine. *J Clin Psychopharmacol*. 1982;2:14-39.
124. Enoch MD, Hammad GE. Acute hallucinosis due to clonidine. *Curr Med Res Opin*. 1977;4:670-671.
125. Callaway E, Halliday R, Naylor H, Brandeis D. Clonidine and scopolamine: differences and similarities in how they change human information processing. *Prog Neuropsychopharmacol Biol Psychiatry*. 1991;15:497-502.

126. Delaney J, Spevack D, Doddamani S, Ostfeld R. Clonidine-induced delirium. *Int J Cardiol*. 2006;113:276-278.
127. Conner D, Fletcher K, Swanson J. A meta-analysis of clonidine for symptoms of attention deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 1999;58:1551–1559.
128. Kurlan R. Treatment of ADHD in children with tics: a randomized controlled trial. *Neurology*. 2002;58:527–536.
129. Wolraich ML, Wibbelsman CJ, Brown TE, et al. Attention-deficit/hyperactivity disorder among adolescents: a review of the diagnosis, treatment, and clinical implications. *Pediatrics*. 2005;115:1734-1746.
130. Gowing L, Farrell M, Ali R, White J. Alpha2 adrenergic agonists for the management of opioid withdrawal. *Cochrane Database Syst Rev*. 2003;2:CD002024.
131. Collins ED, Kleber HD, Whittington RA, Heitler NE. Anesthesia-assisted vs buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: a randomized trial. *JAMA*. 2005;294:903-913.
132. Wilkins AJ, Jenkins WJ, Steiner JA. Efficacy of clonidine in treatment of alcohol withdrawal state. *Psychopharmacology (Berl).* 1983;81:78-80.
133. Baumgartner GR, Rowen RC. Clonidine vs chlordiazepoxide in the management of acute alcohol withdrawal syndrome. *Arch Intern Med*. 1987;147:1223-1226.
134. Cushman P Jr. Clonidine and alcohol withdrawal. *Adv Alcohol Subst Abuse*. 1987;7:17-28. Review.
135. Robinson BJ, Robinson GM, Maling TJ, Johnson RH. Is clonidine useful in the treatment of alcohol withdrawal? *Alcohol Clin Exp Res*. 1989;13:95-98.
136. Ozdemir V, Bremner KE, Naranjo CA. Treatment of alcohol withdrawal syndrome. *Ann Med*. 1994;26:101-105. Review.
137. Jimenez-Jimenez FJ, Garcia-Ruiz PJ. Pharmacological options for the treatment of Tourette's disorder. *Drugs*. 2001;61:2207-2220. Review.
138. Robertson MM, Stern JS. Gilles de la Tourette syndrome: symptomatic treatment based on evidence. *Eur Child Adolesc Psychiatry*. 2000;9 Suppl 1:I60-7I5. Review.
139. Leckman JF, Hardin MT, Riddle MA, Stevenson J, Ort SI, Cohen DJ. Clonidine treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry.* 1991;48:324-328.
140. Gaffney GR, Perry PJ, Lund BC, Bever-Stille KA, Arndt S, Kuperman S. Risperidone versus clonidine in the treatment of children and adolescents with Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry*. 2002;41:330-336.
141. Leckman JF, Cohen DJ, Detlor J, Young JG, Harcherik D, Shaywitz BA. Clonidine in the treatment of Tourette syndrome: a review of data. *Adv Neurol*. 1982;35:391-401.
142. McEntee WJ, Mair RG. Memory enhancement in Korsakoff's psychosis by clonidine: further evidence for a noradrenergic deficit. *Ann Neurol*. 1980;7:466-470.
143. Tudorache B, Diacicov S. The effect of clonidine in the treatment of acute mania. *Rom J Neurol Psychiatry*. 1991;29:209-213.
144. Fava M. Psychopharmacologic treatment of pathologic aggression. *Psychiatr Clin North Am*. 1997;20:427-51.
145. Levine S, Croog SH, Sudilovsky A, Testa MA. Effects of antihypertensive medications on vitality and well-being. *J Fam Pract*. 1987;25:357-363.
146. Schoenberger JA, Croog SH, Sudilovsky A, Levine S, Baume RM. Self-reported side effects from antihypertensive drugs. A clinical trial. Quality of Life Research Group. *Am J Hypertens.*1990;3:123-132.
147. Adler S. Methyldopa-induced decrease in mental activity. *JAMA*. 1974;230:1428-1429.
148. Wurzelmann J, Frishman WH, Aronson M, Masur D, Ooi WL. Neuropsychological effects of antihypertensive drugs. *Cardiol Clin*. 1987;5:689-701.
149. Muldoon MF, Waldstein SR, Ryan CM, et al. Effects of six anti-hypertensive medications on cognitive performance. *J Hypertens*. 2002;20:1643-1652.
150. Bant WP. Antihypertensive drugs and depression: a reappraisal. *Psychol Med*. 1978;8:275-283.
151. Pottash AL, Black HR, Gold MS. Psychiatric complications of antihypertensive medications. *J Nerv Ment Dis*. 1981;169:430-438.
152. McKinney WT Jr, Kane FJ Jr. Depression with the use of alpha-methyldopa. *Am J Psychiatry*. 1967;124:80-81.
153. Long TD, Kathol RG. Critical review of data supporting affective disorder caused by nonpsychotropic medication. *Ann Clin Psychiatry*. 1993;5:259-270.
154. DeMuth GW, Ackerman SH. Alpha-methyldopa and depression: a clinical study and review of the literature. *Am J Psychiatry*. 1983;140:534-538.
155. Kofman OS. A therapeutic paradox? Combined treatment of Parkinson's disease with levodopa and methyldopa. *Arch Neurol*. 1973;29:120-121.
156. Sweet RD, Lee JE, McDowell FH. Methyldopa as an adjunct to levodopa treatment of Parkinson's disease. *Clin Pharmacol Ther*. 1972;13:23-27.
157. Sweet RD, Lee JE, McDowell F. Alpha-methyldopa as an adjunct to levodopa treatment of Parkinson's disease. *Trans Am Neurol Assoc*. 1971;96:59-65.
158. Endo M, Hirai K, Ohara M. Paranoid-hallucinatory state induced in a depressive patient by methyldopa: a case report. *Psychoneuroendocrinology*. 1978;3:211-215.
159. Hawkins DJ. Acute organic brain syndrome psychosis with methyldopa therapy: case report. *Mo Med*. 1976;73:476, 481.
160. Quetsch RM, Achor RW, Litin EM, Faucett RL. Depressive reactions in hypertensive patients; a comparison of those treated with Rauwolfia and those receiving no specific antihypertensive treatment. *Circulation*. 1959;19:366-375.
161. Kass I, Brown EC. Treatment of hypertensive patients with Rauwolfia compounds and reserpine; depressive and psychotic changes. *JAMA*. 1955;159:1513-1516.
162. Ayd FJ Jr. Drug-induced depression; fact or fallacy. *N Y State J Med*. 1958;58:354-356.
163. Fries ED. Mental depression in hypertensive patients treated for long periods with large doses of reserpine. *N Engl J Med*. 1954;251:1006-1008.
164. Rauch SL, Stern TA, Zusman RM. Neuropsychiatric considerations in the treatment of hypertension. *Int J Psychiatry Med*. 1991;21:291-308.
165. Applegate WB, Pressel S, Wittes J, et al. Impact of the treatment of isolated systolic hypertension on behavioral variables. Results from the systolic hypertension in the elderly program. *Arch Intern Med*. 1994;154:2154-2160.
166. Goldstein G, Materson BJ, Cushman WC, et al. Treatment of hypertension in the elderly: II. Cognitive and behavioral function. Results of a Department of Veterans Affairs Cooperative Study. *Hypertension*. 1990;15:361-369.
167. Webster J, Koch HF. Aspects of tolerability of centrally acting antihypertensive drugs. *J Cardiovasc Pharmacol*. 1996;27(suppl 3):S49-S54.
168. Rosen RC, Kostis JB. Biobehavioral sequellae associated with adrenergic-inhibiting antihypertensive agents: a critical review. *Health Psychol*. 1985;4:579-604.
169. Aumeister AA, Hawkins MF, Uzelac SM. The myth of reserpine-induced depression: role in the historical development of the monoamine hypothesis. *J Hist Neurosci*. 2003;12:207-220.
170. Gray SL, Lai KV, Larson EB. Drug-induced cognition disorders in the elderly: incidence, prevention and management. *Drug Saf*. 1999;21:101-122.
171. Prisant LM, Spruill WJ, Fincham JE, Wade WE, Carr AA, Adams MA. Depression associated with antihypertensive drugs. *J Fam Pract*. 1991;33:481-485.
172. Kent TA, Wilber RD. Reserpine withdrawal psychosis: the possible role of denervation supersensitivity of receptors. *J Nerv Ment Dis*. 1982;170:502-504.
173. Samuels AH, Taylor AJ. Reserpine withdrawal psychosis. *Aust N Z J Psychiatry*. 1989;23:129-130.
174. Telner JI, Lapierre YD, Horn E, Browne M. Rapid reduction of mania by means of reserpine therapy. *Am J Psychiatry*. 1986;143:1058.
175. Bacher NM, Lewis HA. Lithium plus reserpine in refractory manic patients. *Am J Psychiatry*. 1979;136:811-814.
176. Watt DC. The effect of reserpine on the duration of manic attacks. *J Neurol Neurosurg Psychiatry*. 1958;21:297-300.
177. Healy DJ, Dalack GW, Meador-Woodruff JH. Clozapine-reserpine combination for refractory psychosis. *Schizophr Res*. 1997;25:259-260.
178. Solon EN. Risperidone-reserpine combination in refractory psychosis. *Schizophr Res*. 1996;22:265-266.
179. Berlant JL. Reserpine and phencyclidine-associated psychosis: three case reports. *J Clin Psychiatry*. 1985;46:542-544.

180. Berlant JL. Neuroleptics and reserpine in refractory psychoses. *J Clin Psychopharmacol*. 1986;6:180-184.
181. Price LH, Charney DS, Heninger GR. Reserpine augmentation of desipramine in refractory depression: clinical and neurobiological effects. *Psychopharmacology (Berl).* 1987;92:431-437.
182. Carruthers SG. Adverse effects of alpha 1-adrenergic blocking drugs. *Drug Saf*. 1994;11:12-20.
183. MacDonald R, Wilt TJ, Howe RW. Doxazosin for treating lower urinary tract symptoms compatible with benign prostatic obstruction: a systematic review of efficacy and adverse effects. *BJU Int.* 2004;94:1263-1270.
184. Guay DR. Extended-release alfuzosin hydrochloride: a new alpha-adrenergic receptor antagonist for symptomatic benign prostatic hyperplasia. *Am J Geriatr Pharmacother*. 2004;2:14-23.
185. Beers MH, Passman LJ. Antihypertensive medications and depression. *Drugs*. 1990;40:792-799.
186. Pessina AC, Ciccariello L, Perrone F, et al. Clinical efficacy and tolerability of alpha-blocker doxazosin as add-on therapy in patients with hypertension and impaired glucose metabolism. *Nutr Metab Cardiovasc Dis*. 2006;16:137-147.
187. Benson D, Peterson LG, Bartay J. Neuropsychiatric manifestations of antihypertensive medications. *Psychiatr Med*. 1983;1:205-214.
188. Evans M, Perera PW, Donoghue J. Drug induced psychosis with doxazosin. *BMJ*. 1997;314:1869.
189. Chin DKF Cho Ak, Tse CY. Neuropsychiatric complications related to use of prazosin in patients with renal failure. *BMJ*. 1986; 293:1347.
190. Lasser NL, Nash J, Lasser VI, Hamill SJ, Batey DM. Effects of antihypertensive therapy on blood pressure control, cognition, and reactivity. A placebo-controlled comparison of prazosin, propranolol, and hydrochlorothiazide. *Am J Med*. 1989;86:98-103.
191. Raskind MA, Peskind ER, Kanter ED, et al. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. *Am J Psychiatry*. 2003;160:371-373.
192. Taylor F, Raskind MA. The alpha1-adrenergic antagonist prazosin improves sleep and nightmares in civilian trauma posttraumatic stress disorder. *J Clin Psychopharmacol*. 2002;22:82-85.
193. Peskind ER, Bonner LT, Hoff DJ, Raskind MA. Prazosin reduces trauma-related nightmares in older men with chronic posttraumatic stress disorder. *J Geriatr Psychiatry Neurol*. 2003;16:165-671.
194. Raskind MA, Thompson C, Petrie EC, et al. Prazosin reduces nightmares in combat veterans with posttraumatic stress disorder. *J Clin Psychiatry*. 2002;63:565-568.
195. Maher MJ, Rego SA, Asnis GM. Sleep disturbances in patients with post-traumatic stress disorder: epidemiology, impact and approaches to management. *CNS Drugs*. 2006;20:567-590.
196. Taylor FB, Lowe K, Thompson C, et al. Daytime prazosin reduces psychological distress to trauma specific cues in civilian trauma posttraumatic stress disorder. *Biol Psychiatry*. 2006;59:577-581.
197. Shrivastava S, Kochar MS. The dual risks of depression and hypertension: treatment of coexisting disorders requires vigilance. *Postgrad Med* [online]. Available at: http://www.postgradmed.com/issues/2002/06_02/shrivastava.htm. Accessed December 2006.
198. Stevens JD, Binstok G, Mullane JF, et al. Propranolol-hydralazine combination in essential hypertension. *Clin Ther*. 1983;5:525-539.
199. Moser M, Syner J, Malitz S, Mattingly TW. Acute psychosis as a complication of hydralazine therapy in essential hypertension. *JAMA*. 1953;152:1329-1331.
200. Black JR, Mehta J. Precipitation of heart failure following sudden withdrawal of hydralazine. *Chest*. 1979;75:724-725.
201. Goldstein G, Materson BJ, Cushman WC, et al. Treatment of hypertension in the elderly: II. Cognitive and behavioral function. Results of a Department of Veterans Affairs Cooperative Study. *Hypertension*. 1990;15:361-369.
202. Sarzi-Puttini P, Atzeni F, Capsoni F, Lubrano E, Doria A. Drug-induced lupus erythematosus. *Autoimmunity*. 2005;38:507-518.
203. Alarcon-Segovia D, Wakim KG, Worthington JW, Ward LE. Clinical and experimental studies on the hydralazine syndrome and its relationship to systemic lupus erythematosus. *Medicine (Baltimore).* 1967;46:1-33.
204. Harmon C, Wohlreich MM. Sodium nitroprusside-induced delirium. *Psychosomatics*. 1995;36:83-85.
205. Rosenthal R. Visual hallucinations and suicidal ideation attributed to isosorbide dinitrate. *Psychosomatics*. 1987;28:555-556.
206. Good AE, Welch MH. Hospital-acquired salicylate intoxication. report of a case with psychosis, acidosis, and coma. *J Rheumatol*. 1975;2:52-60.
207. Sawrer-Foner GJ, Morrison GH. Acute toxic psychosis due to acetyl-salicylic acid. *Can Serv Med J*. 1955;11:599-606.
208. Durnas C, Cusack BJ. Salicylate intoxication in the elderly. Recognition and recommendations on how to prevent it. *Drugs Aging*. 1992;2:20-34.
209. Nelson M, Reid C, Beilin L, et al. Rationale for a trial of low-dose aspirin for the primary prevention of major adverse cardiovascular events and vascular dementia in the elderly: Aspirin in Reducing Events in the Elderly (ASPREE). *Drugs Aging*. 2003;20:897-903.
210. Roman G. Perspectives in the treatment of vascular dementia. *Drugs Today (Barc).* 2000;36:641-653.
211. Williams PS, Rands G, Orrel M, Spector A. Aspirin for vascular dementia. *Cochrane Database Syst Rev*. 2000;4:CD001296.
212. Nilsson SE, Johansson B, Takkinen S, et al. Does aspirin protect against Alzheimer's dementia? A study in a Swedish population-based sample aged > or =80 years. *Eur J Clin Pharmacol*. 2003;59:313-319.
213. Mendlewicz J, Kriwin P, Oswald P, Souery D, Alboni S, Brunello N. Shortened onset of action of antidepressants in major depression using acetylsalicylic acid augmentation: a pilot open-label study. *Int Clin Psychopharmacol*. 2006;21:227-231.
214. Nies AS, Gal J, Gerber JG. Complications of disopyramide therapy. *Lancet*. 1979;1:330-331.
215. Padfield PL, Smith DA, Fitzsimons EJ, McCruden DC. Disopyramide and acute psychosis. *Lancet*. 1977;1:1152.
216. Ahmad S, Sheikh AI, Meeran MK. Disopyramide-induced acute psychosis. *Chest*. 1979;76:712.
217. Bou-Holaigah I, Rowe PC, Kan J, Calkins H. The relationship between neurally mediated hypotension and the chronic fatigue syndrome. *JAMA*. 1995;274:961-967.
218. Rowe PC, Bou-Holaigah I, Kan JS, Calkins H. Is neurally mediated hypotension an unrecognised cause of chronic fatigue? *Lancet*. 1995;345:623-624.
219. Bizjak ED, Nolan PE Jr, Brody EA, Galloway JM. Procainamide-induced psychosis: a case report and review of the literature. *Ann Pharmacother*. 1999;33:948-951.
220. Harrington L. Procainamide-induced psychosis. *Crit Care Nurse*. 1993;13:70-72. Review.
221. Schubert DS, Gabinet L, Hershey LA. Psychosis induced by sustained-release procainamide. *Can Med Assoc J*. 1984;131:1188-1190.
222. Menken M. Procainamide-induced psychosis. *JAMA*. 1979;241:1107-1108.
223. McCrum ID, Guidry JR. Procainamide-induced psychosis. *JAMA*. 1978;240:1265-1266.
224. Flanagan AD. Pharmacokinetics of a sustained release procainamide preparation. *Angiology*. 1982;33:71-77.
225. Rice H, Haltzman S, Tucek C. Mania associated with procainamide. *Am J Psychiatry*. 1988;145:129-130.
226. Rubin RL. Drug-induced lupus. *Toxicology*. 2005;209:135-147.
227. Cohen IS, Jick H, Cohen SI. Adverse reactions to quinidine in hospitalized patients: findings based on data from the Boston Collaborative Drug Surveillance Program. *Prog Cardiovasc Dis*. 1977;20:151-163.
228. Wolf LR, Otten EJ, Spadafora MP. Cinchonism: two case reports and review of acute quinine toxicity and treatment. *J Emerg Med*. 1992;10:295-301.
229. Deleu D, Schmedding E. Acute psychosis as idiosyncratic reaction to quinidine: report of two cases. *BMJ (Clin Res Ed).* 1987;294:1001-1002.
230. Johnson AG, Day RO, Seldon WA. A functional psychosis precipitated by quinidine. *Med J Aust*. 1990;153:47-49.
231. Gilbert GJ. Quinidine dementia. *Am J Cardiol*. 1978;41:791.
232. Gilbert GJ. Quinidine dementia. *JAMA*. 1977;237:2093-2094.
233. Billig N, Buongiorno P. Quinidine-induced organic mental disorders. *J Am Geriatr Soc*. 1985;33:504-506.
234. Lloyd BL, Greenblatt DJ. Neuropsychiatric sequelae of pharmacotherapy of cardiac arrhythmias and hypertension. *J Clin Psychopharmacol*. 1981;1:394-398.

235. Saravay SM, Marke J, Steinberg MD, Rabiner CJ. "Doom anxiety" and delirium in lidocaine toxicity. *Am J Psychiatry*. 1987;144:159-163.
236. Bennett MI. Paranoid psychosis due to flecainide toxicity in malignant neuropathic pain. *Pain*. 1997;70:93-94.
237. Ramhamadany E, Mackenzie S, Ramsdale DR. Dysarthria and visual hallucinations due to flecainide toxicity. *Postgrad Med J*. 1986;62:61-62.
238. Drerup U. Central nervous system side effects due to anti-arrhythmia therapy. Psychotic depression due to flecainide [in German]. *Dtsch Med Wochenschr*. 1988;113:386-388.
239. Martino E, Bartalena L, Bogazzi F, Braverman LE. The effects of amiodarone on the thyroid. *Endocr Rev*. 2001;22:240-254.
240. Jackson IM. The thyroid axis and depression. *Thyroid*. 1998;8:951-956.
241. Brownlie BE, Rae AM, Walshe JW, Wells JE. Psychoses associated with thyrotoxicosis - "thyrotoxic psychosis." A report of 18 cases, with statistical analysis of incidence. *Eur J Endocrinol*. 2000;142:438-444.
242. Athwal H, Murphy G Jr, Chun S. Amiodarone-induced delirium. *Am J Geriatr Psychiatry.* 2003;11:696-697.
243. Barry JJ, Franklin K. Amiodarone-induced delirium. *Am J Psychiatry*. 1999;156:1119.
244. Trohman RG, Castellanos D, Castellanos A, Kessler KM. Amiodarone-induced delirium. *Ann Intern Med*. 1988;108:68-69.
245. Anastasiou-Nana MI, Anderson JL, Nanas JN, et al. High incidence of clinical and subclinical toxicity associated with amiodarone treatment of refractory tachyarrhythmias. *Can J Cardiol*. 1986;2:138-145.
246. Odelola AT. More on amiodarone-induced depression. *Br J Psychiatry*. 1999;175:590-591.
247. Ambrose A, Salib E. Amiodarone-induced depression. *Br J Psychiatry*. 1999;174:366-367.
248. Hilleman D, Miller MA, Parker R, Doering P, Pieper JA. Optimal management of amiodarone therapy: efficacy and side effects. *Pharmacotherapy*. 1998;18:138S-145S.
249. Patten SB, Love EJ. Neuropsychiatric adverse drug reactions: passive reports to Health and Welfare Canada's adverse drug reaction database (1965-present). *Int J Psychiatry Med*. 1994;24:45-62.
250. Lanoxin (digoxin) prescribing information. Research Triangle Park, NC: GlaxoSmithKline; 2005.
251. Durakovic Z, Vucelic B, Plavsic F. Acute psychoses caused by digitalis poisoning [in Croatian]. *Lijec Vjesn*. 1991;113:417-419.
252. Carney MW, Rapp S, Pearce K. Digoxin toxicity presenting with psychosis in a patient with chronic phobic anxiety. *Clin Neuropharmacol*. 1985;8:193-195.
253. Singh RB, Singh VP, Somani PN. Psychosis: a rare manifestation of digoxin intoxication. *J Indian Med Assoc*. 1977;69:62-63.
254. Gupta OP, Singh S, Gupta HM. Psychosis - a feature of digitalis intoxication. *Indian Heart J*. 1975;27:69-70.
255. Wamboldt FS, Jefferson JW, Wamboldt MZ. Digitalis intoxication misdiagnosed as depression by primary care physicians. *Am J Psychiatry*. 1986;143:219-221.
256. Song YH, Terao T, Shiraishi Y, Nakamura J. Digitalis intoxication misdiagnosed as depression-revisited. *Psychosomatics*. 2001;42:369-370.
257. el-Mallakh RS, Hedges S, Casey D. Digoxin encephalopathy presenting as mood disturbance. *J Clin Psychopharmacol*. 1995;15:82-83.
258. Patten SB, Lavorato DH. Medication use and major depressive syndrome in a community population. *Compr Psychiatry*. 2001;42:124-131.
259. Patten SB, Williams JV, Love EJ. Case-control studies of cardiovascular medications as risk factors for clinically diagnosed depressive disorders in a hospitalized population. *Can J Psychiatry*. 1996;41:469-476.
260. Thompson LJ, Proctor RC. Depressive and anxiety reactions treated with nicotinic acid and phenobarbital. *N C Med J*. 1953;14:420-426.
261. Tonge WL. Nicotinic acid in the treatment of depression. *Ann Intern Med.* 1953;38:551-553.
262. Osmond H, Hoffer A. Massive niacin treatment in schizophrenia. Review of a nine-year study. *Lancet*. 1962;1:316-319.
263. Hoffer A. Nicotinic acid: an adjunct in the treatment of schizophrenia. *Am J Psychiatry*. 1963;120:171-173.
264. Kleijnen J, Knipschild P. Niacin and vitamin B6 in mental functioning: a review of controlled trials in humans. *Biol Psychiatry*. 1991;29:931-941.
265. Ban TA. Negative findings with nicotinic acid in the treatment of schizophrenias. *Int Pharmacopsychiatry.1974;9:172-187*.
266. Eaves ER, Korman MG. Cholestyramine induced hyperchloremic metabolic acidosis. *Aust N Z J Med*. 1984;14:670-672.
267. Davidson MH, Stein EA, Hunninghake DB, et al. Worldwide Expanded Dose Simvastatin Study Group. Lipid-altering efficacy and safety of simvastatin 80 mg/day: worldwide long-term experience in patients with hypercholesterolemia. *Nutr Metab Cardiovasc Dis*. 2000;10:253-2562.
268. Chung N, Cho SY, Choi DH, et al. STATT: a titrate-to-goal study of simvastatin in Asian patients with coronary heart disease. Simvastatin Treats Asians to Target. *Clin Ther*. 2001;23:858-870.
269. Buajordet I, Madsen S, Olsen H. Statins--the pattern of adverse effects with empahsis on mental reactions. Data from a national and an international database [in Norwegian]. *Tidsskr Nor Laegeforen* .1997;117:3210-3213.
270. Brunner J, Parhofer KG, Schwandt P, Bronisch T. Cholesterol, essential fatty acids, and suicide. *Pharmacopsychiatry*. 2002;35:1-5.
271. Golier JA, Marzuk PM, Leon AC, Weiner C, Tardiff K. Low serum cholesterol level and attempted suicide. *Am J Psychiatry*. 1995;152:419-423.
272. Sullivan PF, Joyce PR, Bulik CM, Mulder RT, Oakley-Browne M. Total cholesterol and suicidality in depression. *Biol Psychiatry*. 1994;36:472-477.
273. Neaton JD, Blackburn H, Jacobs D, et al. Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. *Arch Intern Med*. 1992;152:1490-1500.
274. Steegmans PH, Hoes AW, Bak AA, van der Does E, Grobbee. Higher prevalence of depressive symptoms in middle-aged men with low serum cholesterol levels. *Psychosom Med*. 2000;62:205-211.
275. Vevera J, Fisar Z, Kvasnicka T, et al. Cholesterol-lowering therapy evokes time-limited changes in serotonergic transmission. *Psychiatry Res.* 2005;133:197-203.
276. Yang CC, Jick SS, Jick H. Lipid-lowering drugs and the risk of depression and suicidal behavior. *Arch Intern Med*. 2003;163:1926-1932.
277. Young-Xu Y, Chan KA, Liao JK, Ravid S, Blatt CM. Long-term statin use and psychological well-being. *J Am Coll Cardiol*. 2003;42:690-697.
278. Stewart RA, Sharples KJ, North FM, Menkes DB, Baker J, Simes J. Long-term assessment of psychological well-being in a randomized placebo-controlled trial of cholesterol reduction with pravastatin. The LIPID Study Investigators. *Arch Intern Med*. 2000;160:3144-3152.
279. Law MR, Thompson SG, Wald NJ. Assessing possible hazards of reducing serum cholesterol. *BMJ*. 1994;308:373-379.
280. Kassler-Taub K, Woodward T, Markowitz JS. Depressive symptoms and pravastatin. *Lancet*. 1993;341:371-372.
281. Lechleitner M, Hoppichler F, Konwalinka G, Patsch JR, Braunsteiner H. Depressive symptoms in hypercholesterolaemic patients treated with pravastatin. *Lancet.*1992;340:910.
282. Duits N, Bos FM. Depressive symptoms and cholesterol-lowering drugs. *Lancet*. 1993;341:114.
283. Muldoon MF, Barger SD, Ryan CM, et al. Effects of lovastatin on cognitive function and psychological well-being. *Am J Med*. 2000;108:538-546.
284. Kostis JB, Rosen RC, Wilson AC. Central nervous system effects of HMG CoA reductase inhibitors: lovastatin and pravastatin on sleep and cognitive performance in patients with hypercholesterolemia. *J Clin Pharmacol*. 1994;34:989-996.
285. Paris D, Townsend KP, Humphrey J, Obregon DF, Yokota K, Mullan M. Statins inhibit A beta-neurotoxicity in vitro and A beta-induced vasoconstriction and inflammation in rat aortae. *Atherosclerosis*. 2002;161:293-239.
286. Sparks DL, Sabbagh MN, Connor DJ, et al. Atorvastatin for the treatment of mild to moderate Alzheimer disease: preliminary results. *Arch Neurol.* 2005;62:753-757.
287. Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA . Statins and the risk of dementia. *Lancet*. 2000;356:1627-1631.
288. Rea TD, Breitner JC, Psaty BM, et al. Statin use and the risk of incident dementia: the Cardiovascular Health Study. *Arch Neurol*. 2005;62:1047-1051.
289. Zandi PP, Sparks DL, Khachaturian AS, et al. Do statins reduce risk of incident dementia and Alzheimer disease? The Cache County Study. *Arch Gen Psychiatry*. 2005;62:217-224.
290. Shaefer EJ. HMG-CoA reductase inhibitors for hypercholesterolemia. *N Engl J Med*. 1988;319:1222-1223.