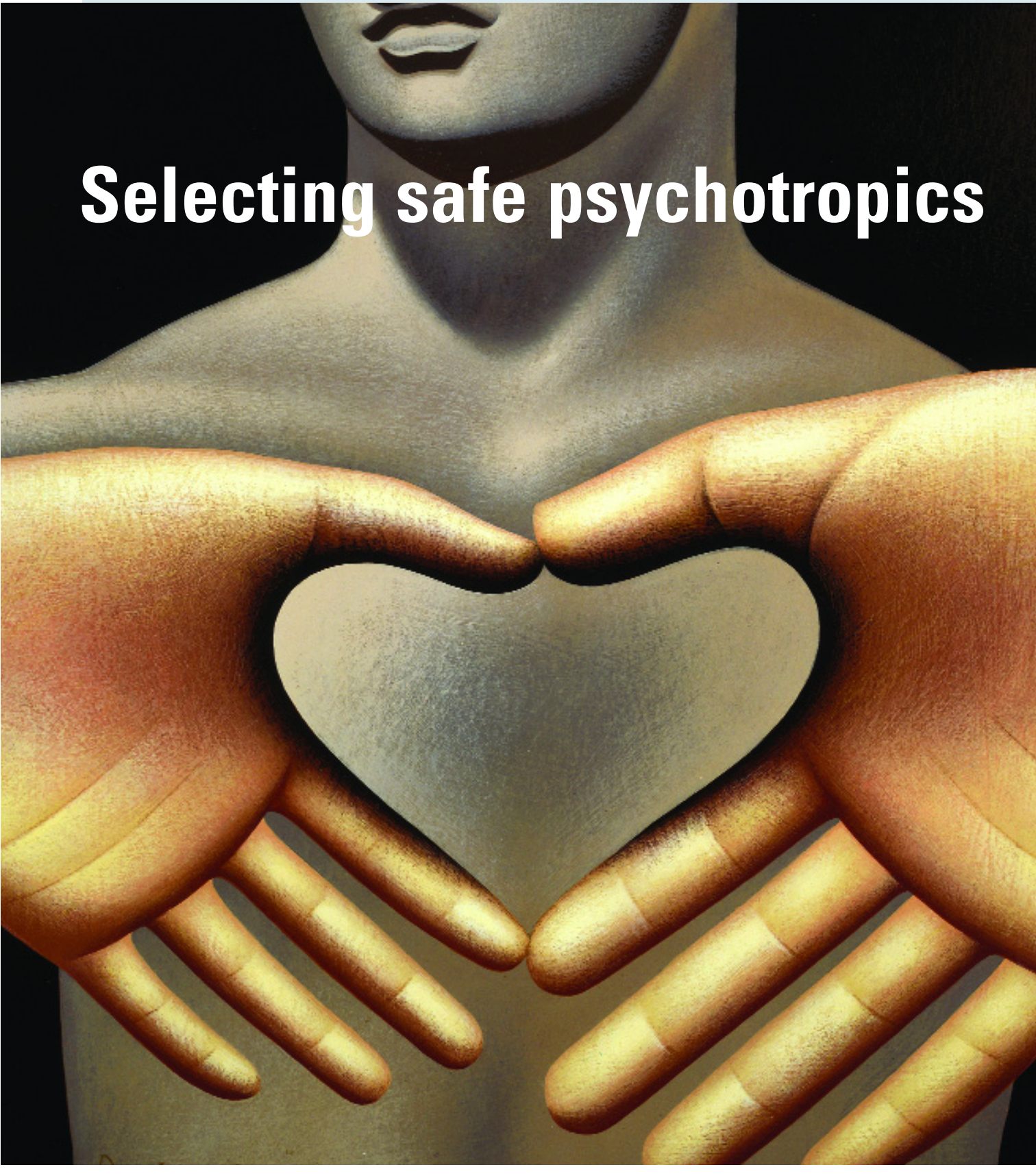
Selecting safe psychotropics



Current PSYCHIATRY

for post-MI patients

Prescribing for psychiatric patients with heart disease requires extra caution. These authors offer a heart-friendly decision tool for considering cardiac risk factors and potential drug-drug interactions.

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How do you safely treat a psychiatrically ill patient who is taking seven to nine potent cardiovascular medications? Our approach is to organize the effects of psychiatric drugs into a systematic, easy-to-use framework, which we remember by the mnemonic HALT. It reminds us to consider any drug's effect on hypertension, arrhythmias, lipids and liver enzymes, and risk of thrombosis. Using HALT as a decision tool can help you avoid drug-drug interactions when selecting psychotropics for patients with a history of myocardial infarction (MI).

The multi-medication challenge

In psychiatry, medication guidelines and algorithms encourage us to start with monotherapy before we try more complex regimens.[1-3] Cardiologists, however, jump directly to a multi-medication, cardio-protective approach for today's post-MI patient.[4-5] The cardiac standard of care includes angiotensin-converting enzyme (ACE) inhibitors, cardioselective beta-blockers, lipid-lowering agents, and platelet and clotting inhibitors.

Adding even one psychotropic to such a complex daily regimen could risk an adverse reaction. But, unfortunately, no guidelines exist for the medical management of psychiatrically ill post-MI patients, and research is very limited:

- only one randomized, controlled trial has examined drug treatment of their depression

continued

Table

THREE TYPES OF ACUTE CORONARY SYNDROMES

Type	Diagnostic features
ST elevation MI	ST elevation in two contiguous ECG leads or new left bundle-branch block
Non-ST elevation MI	Positive CPK-MB or positive troponin levels and ST depression on ECG
Unstable angina	ST depression or T-wave inversion with no enzyme release

MI: myocardial infarction
CPK-MB: creatine phosphokinase of muscle band (an enzyme released by ischemic heart muscle)

- no randomized, controlled trials have addressed bipolar mania or psychosis drug treatment.

Pathophysiology of acute coronary syndromes

Acute coronary syndromes present as three broad types: ST elevation MI, non-ST elevation MI, and unstable angina (*Table*). ST elevation MI, non-ST elevation MI and—to a lesser extent—unstable angina result from plaque rupture within the coronary intima, with sudden occlusion of one or more coronary arteries or branches and ischemia to the affected myocardium. Multiple pathologic processes—such as hypertension, dyslipidemia, or inflammatory disease—may weaken or injure the vascular lumen, and the development of a thrombus at the plaque rupture site involves many steps and triggers.

Ischemic myocardial injury increases an acute MI survivor's risk of arrhythmias, heart failure, and sudden death. Tachycardia related to psychological stress can trigger these cardiac events in patients with heart disease. The goal of post-MI medical therapy is to protect the heart from further hypertensive injuries, arrhythmias, dyslipidemias, and thrombus formation.

The goal of post-MI medical therapy is to protect the heart from further ischemic injury

Typical post-MI medications

ACE inhibitors. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to angiotensin II. Angiotensin II—a vasoconstrictor—increases blood pressure, restricts blood flow to the kidney, and stimulates aldosterone secretion by the adrenal cortex. ACE inhibition results in lower plasma levels of angiotensin II, with decreased blood pressure, vasopressor activity, and aldosterone secretion; this last effect may increase serum potassium.

Two ACE inhibitors—lisinopril and ramipril—have been shown in clinical trials to protect against recurrent cardiac events.[6,7] ACE inhibitors may have variable effects among different ethnic groups. For example, ACE inhibitors have shown a less robust blood pressure-lowering effect in black patients than in non-blacks in some clinical trials.[8]

Beta blockers. Beta-adrenergic receptor blocking agents compete with beta-adrenergic agonists for available receptor sites in the heart and lungs. Cardioselective or beta-1 adrenergic agents such as metoprolol affect primarily the receptors in the heart and can slow the sinus rate and decrease AV nodal conduction. Metoprolol reduces heart rate, cardiac output, and systolic blood pressure, and inhibits reflex and drug-induced tachycardia. These pharmacologic actions lower oxygen demand, thus reducing the risk of ischemia and arrhythmias.

Beta blockers are a mainstay in regimens prescribed for post-MI outpatient treatment.[9] Although earlier studies suggested that these drugs might cause depression, a recent systematic review rebuts that conclusion.[10]

Lipid-lowering agents. First-line treatments of hyperlipidemia include HMG-CoA reductase inhibitors (or "statins") and niacin (also known as nicotinic acid). These drugs have been shown to lower lipids (cholesterol and triglycerides), reduce low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) levels, and increase high-density lipoproteins (HDL).

HMG-CoA reductase inhibitors have been shown in large international trials to reduce mortality from cardiac events in post-MI patients.[11] These agents—atorvastatin, flu-

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vastatin, lovastatin, pravastatin, and simvastatin—are associated with some side effect risks, including hepatotoxicity and rhabdomyolysis. Most are metabolized by cytochrome P450 3A4; the exception is fluvastatin, which is metabolized by CYP 2C9.

Niacin has been shown to decrease serum levels of apolipoprotein B-100—the major protein component of VLDL and LDL fractions—and of lipoprotein (a), an LDL variant independently associated with coronary risk.[12] Niaspan—a long-acting formulation of niacin—is indicated to reduce recurrent nonfatal MI risk in patients with a history of MI and hypercholesterolemia. Niacin's side effects include flushing, increased serum transaminase levels, slightly reduced platelet count, and (rarely) rhabdomyolysis.

Box

HALT: A DECISION TOOL FOR PRESCRIBING TO THE POST-MI PATIENT

- **H** Can this agent cause or worsen **hypertension?**
- **A** Can this agent increase the risk of **arrhythmia?**
- **L** Can this agent adversely affect **lipids**? Can it affect medication serum levels due to **liver** enzyme inhibition or liver injury?
- **T** Can this agent increase the risk of **thrombosis** or bleeding?

Clotting and platelet inhibitors. Anticoagulants such as warfarin sodium and platelet inhibitors such as clopidogrel are major components of drug therapy to prevent blood clots in post-MI patients.

Warfarin is indicated to reduce the risk of death, recurrent MI, and thromboembolic events such as stroke or systemic embolization after MI. It acts by inhibiting the synthesis of vitamin K-dependent clotting factors II, VII, IX, and X and anticoagulant proteins C and S.

Most newer-generation antidepressants are safe for patients with heart disease

Warfarin is metabolized by numerous CYP isoenzymes—principally 2C9, but also 2C19, 2C8, 2C18, 1A2, and 3A4—and interacts with many drugs that are metabolized by the same enzyme systems.[12] Although some cardio-protective drugs and NSAIDs may lead to drug interactions due to CYP2C9, most common psychotropics do not inhibit this isoenzyme.

The protein-binding properties of some psychotropics—such as fluoxetine, sertraline, paroxetine, and risperidone—may increase warfarin levels in some patients. Thus, closer monitoring of warfarin levels is warranted when using these agents. Divalproex—because of its protein binding and potential for thrombocytopenia and liver injury—should be used with caution in patients receiving warfarin.

Clopidogrel is indicated for reducing the risk of MI, stroke, and vascular death in patients with atherosclerosis documented by recent stroke, recent MI, or established peripheral arterial disease.[13] This drug selectively inhibits adenosine diphosphate (ADP) from binding to its platelet receptor and activates the ADP-mediated glycoprotein GPIIb/IIIa complex, which inhibits platelet aggregation. Clopidogrel can inhibit the CYP 2C9 isoenzyme. Thrombotic thrombocytopenic purpura has been reported rarely following use of clopidogrel, sometimes after brief exposure (< 2 weeks). The medical team must watch for GI bleeding, a potential side effect.

HALT: A decision framework

A decision tool based on the mnemonic HALT can help psychiatrists systematically and safely add antidepressants, antipsychotics, and mood-stabilizing agents to the complicated regimens of post-MI patients (*Box*). As HALT suggests, any selection strategy must address the agent's impact on:

- **H**ypertension
- **A**rrhythmias
- **L**ipids and **L**iver enzymes
- **T**hrombosis risk.

The following section lists examples of medications that

fit the HALT framework well and others that do not. The psychiatrist, cardiologist, and primary care physician should all be aware of the different agents the post-MI patient is taking and monitor for adherence and drug interactions.

Selecting an antidepressant

Most newer-generation antidepressants are safe and effective for patients with heart disease.

Venlafaxine increases heart rate and blood pressure minimally. Fluoxetine, paroxetine, and bupropion tend to interact to some degree with drugs metabolized by CYP2D6, including beta blockers. Mirtazapine may increase appetite and cause weight gain, which can exacerbate hypertension and alter lipid levels. Even so, minimal drug interactions and end-organ effects should not preclude the use of any of these antidepressants when the drug is best suited for managing a patient's depressive disorder.

HALT reminds us that all atypical antipsychotics carry some risk for the post-MI patient

Sertraline. Excellent articles and systematic reviews have addressed the importance of treating depression in patients with heart disease.[14-16] However, only one recent randomized, double-blind, controlled trial has addressed antidepressant therapy for major depressive disorder in patients with acute MI or unstable angina.[17] The trial included 369 patients (64% male; mean age 57) with MDD who received the selective serotonin reuptake inhibitor (SSRI) sertraline, 50 to 200 mg/d, or placebo for 24 weeks.

Compared with placebo, sertraline did not significantly affect left ventricular ejection fraction, ventricular premature complexes, QTc interval, or other cardiac measures. Depressive symptoms improved more with sertraline than with placebo in patients who had a history of at least one episode of major depressive disorder (MDD) or severe MDD (defined as a Hamilton Depression Scale score ≥ 18 and two or more prior episodes of MDD). The authors concluded that sertraline is safe and effective for recurrent depression in patients with recent MI or unstable angina and without other life-threatening medical conditions.

Using the HALT framework, sertraline does not exacerbate hypertension or increase heart rate, which can trigger arrhythmias. It does not cause weight gain or affect lipid levels and is a weak inhibitor of liver enzymes. Like other SSRIs, it may make platelets "less sticky" and reduce the risk of thrombogenesis.

Selecting an antipsychotic

Using the HALT framework reminds us that all atypical antipsychotics carry some cardiovascular risks in the post-MI population. Although none are known to directly increase heart rate, ziprasidone can increase the QT interval and pose a significant risk for arrhythmia. It therefore should be avoided in post-MI patients.[18]

Olanzapine has greater potential for causing weight gain than risperidone or quetiapine and may increase the risk of excessive weight gain and hyperlipidemia in patients who are not on a well-controlled diet. Quetiapine causes some significant orthostatic hypotension, no significant QT prolongation, and some weight gain. Risperidone is metabolized by the CYP2D6 isoenzyme and can cause orthostatic hypotension, some weight gain, and slight QT prolongation; it—like other atypical antipsychotics—is not known to alter thrombocyte function or thrombus formation.

The recently approved antipsychotic aripiprazole causes some orthostatic hypotension, no significant QT prolongation, and slight weight gain. It is metabolized by CYP3A4 and 2D6 and does not inhibit those enzymes. It is highly bound to albumin and does not interfere with warfarin.[19]

Bottom Line

Most post-MI patients take multiple cardio-protective drugs that can interact with psychotropics. HALT reminds clinicians to consider how any drug for depression, psychosis, or bipolar disorder may increase the patient's risk of hypertension, arrhythmias, elevated lipids and liver enzymes, and thrombus formation.

Related resources

- American College of Cardiology www.acc.org
- *Physicians' Desk Reference* (56th ed). Montvale, NJ: Medical Economics, 2002.

DRUG BRAND NAMES

Aripiprazole • Abilify
Atorvastatin • Lipitor
Bupropion • Wellbutrin
Clopidogrel bisulfate • Plavix
Divalproex • Depakote
Fluoxetine • Prozac
Fluvastatin • Lescol
Lisinopril • Prinivil
Lovastatin • Mevacor
Metoprolol • Toprol-XL
Mirtazapine • Remeron
Niacin • Niaspan
Paroxetine • Paxil
Pravastatin • Pravachol
Olanzapine • Zyprexa
Ramipril • Altace
Sertraline • Zoloft
Simvastatin • Zocor
Venlafaxine • Effexor-XR
Warfarin • Coumadin
Ziprasidone • Geodon

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Selecting a mood stabilizer

Bipolar disorder presents numerous dilemmas when treating the post-MI patient. The three agents approved for treating bipolar mania—lithium, divalproex, and olanzapine—all require close therapeutic monitoring.

Lithium, olanzapine, and divalproex are the standard first-choice therapies for patients with acute mania, whereas olanzapine and divalproex are known to be more effective than lithium in patients with mixed states.[1] Using the HALT framework, none of these mood stabilizers directly aggravates hypertension. However, lithium can cause significant electrolyte aberrations, and its combination with ACE inhibitors could increase the risk of sudden death from arrhythmia.[20]

Divalproex is known to elevate liver enzymes, and its combination with lipid-lowering agents carries the risk of significant liver injury.[12] Divalproex also is known to result in some thrombocytopenia and could increase patients' risk for bleeding complications when combined with clopidogrel, aspirin, warfarin, or niacin.

Divalproex has a black-box warning of increased risk of hemorrhagic pancreatitis. Patients who take divalproex with other agents known to affect platelet and clotting function should be watched closely.

Olanzapine, as discussed above, carries a risk of weight gain and requires careful dietary control in post-MI patients. Alternate atypical antipsychotics may need to be considered as mood-stabilizing therapy if the risk/benefit ratio of electrolyte imbalance (lithium), liver enzyme elevation and thrombocytopenia (divalproex), or weight gain (olanzapine) is not favorable.

References

1. Dennehy EB, Suppes T. Medication algorithms in bipolar disorder. *J Pract Psychiatry Behav Health* 1999;5:142-52.
2. Crismon ML, Trivedi, M, Pigott TA, et al. The Texas Medication Algorithm Project: report of the Texas Consensus Conference Panel on Medication Treatment of Major Depressive Disorder. *J Clin Psychiatry* 1999;60(3):142-56.
3. Chiles JA, Miller AL, Crismon ML, et al. The Texas Medication Algorithm Project: Development and implementation of the schizophrenic algorithm. *Psychiatric Services* 1999;50(1):69-74.
4. Ryan TJ, Antman EM, Brooks NH, et al. 1999 Update: ACC/AHA guidelines for the management of patients with acute myocardial infarction. Executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction.) *J Am Coll Cardiol* 1999;34(3):890-911.
5. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (committee on Management of Patients With Unstable Angina). *J Am Coll Cardiol* 2000;36:970-1062.
6. Zuanetti G, Latini R, Maggioni AP, et al. Effect of the ACE inhibitor lisinopril on mortality in diabetic patients with acute myocardial infarction: data from the GISSI-3 study. *Circulation* 1997;96(12):4239-45.
7. Dagenais GR, Yusuf S, Bourassa MG, et al. Effects of ramipril on coronary events in high-risk persons: results of the Heart Outcomes Prevention Evaluation Study. *Circulation* 2001;104(5):522-6.
8. The ALLHAT officers and coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288(23):2981-97.
9. Andersen K, Ehlers D, Wiedemann HC, et al. Beta blockers: evidence versus wishful thinking. *Am J Cardiol* 1999;83(5B):64D-67D.
10. Ko DT, Hebert PR, Coffey CS, Sedrakayan A, Jeptha CP, Krumholz HM. B-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA* 2002;288(3):351-7.
11. Newby L, Kristinsson A, Bhapkar M, et al. Early statin initiation and outcomes in patients with acute coronary syndromes. *JAMA* 2002;287(23):3087-95.
12. *Physicians' Desk Reference* (56th ed). Montvale, NJ: Medical Economics, 2002.
13. Yusuf S, Zhoa F, Mehta SR, et al, for the Clopidogrel in Unstable Angina to Prevent Recurrent Events trial investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502.
14. Glassman AH, Roose SP, Bigger JT, Jr. The safety of tricyclic antidepressants in cardiac patients: risk-benefit reconsidered. *JAMA* 1993;269:2673-5.
15. Glassman AH, Shapiro PA. Depression and the course of coronary artery disease. *Am J Psychiatry* 1998;155:4-11.
16. Rugulies R. Depression as a predictor for coronary heart disease: a review and meta-analysis. *Am J Prev Med* 2002;23(1):1-11.
17. Glassman AH, O'Connor C, Califf R, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA* 2002;288(6):701-9.
18. Glassman AH. Clinical management of cardiovascular risks during treatment with psychotropic drugs. *J Clin Psychiatry* 2002;63(suppl 9):9-17.
19. Bristol-Myers Squibb Co. Aripiprazole (Abilify): prescribing information. www.abilify.com.
20. Chandragiri SS, Pasol E, Gallagher RM. Lithium, ACE inhibitors, NSAIDs, and verapamil: a possible fatal combination. *Psychosomatics* 1998;39(3):281-2.