Selecting safe psychotropics
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

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.
Post-MI patients

• 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.

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. 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.

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. Although earlier studies suggested that these drugs might cause depression, a recent systematic review rebuts that conclusion.

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. These agents—atorvastatin, fluv...
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. 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:

- Hypertension
- Arrhythmias
- Lipids and Liver enzymes
- Thrombosis risk.

The following section lists examples of medications that...
Post-MI patients 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.

**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

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**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.**

**HALT reminds us that all atypical antipsychotics carry some risk for the post-MI patient**
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.21 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