

The heart of depression: Treating patients who have cardiovascular disease

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Mrs. T, age 59, sustained an ST-elevation myocardial infarction (MI) 6 weeks ago. She has a history of hypertension, hyperlipidemia, and major depressive disorder (MDD). Before her MI, Mrs. T's MDD was well managed with cognitive-behavioral therapy (CBT). She states that her depressive symptoms have worsened since her MI, and clinicians determine that she is experiencing an acute depressive episode severe enough to require pharmacotherapy. Past medication trials for her depression include sertraline, up to 150 mg/d, and duloxetine, 60 mg/d, but her provider determined they were ineffective after an adequate trial duration. Her hypertension is well controlled on her current regimen, which includes lisinopril, 20 mg/d, metoprolol, 50 mg/d, simvastatin, 40 mg/d, and clopidogrel, 75 mg/d. Her father experienced sudden cardiac death and her mother and younger brother have a history of severe MDD.

Depression is more prevalent in patients with cardiovascular disease (CVD) than in the general population, with estimates as high as 23%.¹ Possible mechanisms to help explain the relationship between CVD and depression are summarized in *Table 1* (page 32).² Appropriate antidepressant selection and depression management strategies in patients with CVD, particularly after MI, may reduce the risk for additional cardiac events and reduce mortality.^{1,2}

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Antidepressant choices by class

Many older antidepressants, including tricyclic antidepressants (TCAs), are:

- contraindicated during acute recovery from MI
- cardiotoxic
- lethal in overdose
- not recommended for patients with CVD.^{1,3}

The FDA recently mandated additional labeling for desipramine to alert health care providers to the risk of using this agent in patients with CVD or a family history of sudden death, arrhythmias, or conduction abnormalities.³ Similar to TCAs, monoamine oxidase inhibitors (MAOIs) general-



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Practice Points

- Selective serotonin reuptake inhibitors, particularly **citalopram and sertraline, are generally well tolerated, effective, and safe** to use in patients with cardiovascular disease (CVD), although clinicians must be aware of the risk of drug-drug interactions with these agents.
- **Tricyclic antidepressants and monoamine oxidase inhibitors** are contraindicated in patients with CVD.
- **The FDA warns against using desipramine** in patients with cardiovascular disease; fluoxetine and other CYP2C19 inhibitors may reduce the efficacy of clopidogrel.
- Whether **pharmacologic or nonpharmacologic treatment of depression improves long-term cardiac outcomes** needs to be clarified with sufficiently powered studies.

Table 1

The link between depression and cardiovascular disease

Depressed patients with CVD often exhibit:

- Dysregulation of the autonomic nervous system, including decreased heart rate variability and increased heart rate
- Increase in inflammatory markers, including CRP, TNF- α , and interleukin-6
- Increase in platelet activity and coagulation
- Accelerated atherogenesis via endothelial dysfunction

Other factors that impact cardiovascular risk in patients with depression include:

- Lifestyle, including activity level and tobacco use
- Medication adherence

CRP: C-reactive protein; CVD: cardiovascular disease; TNF: tumor necrosis factor

Source: Reference 2

Clinical Point

In depressed post-MI patients, treatment with mirtazapine or citalopram does not increase the incidence of cardiac events

ly are not recommended for use in this population because of the risk of hypertensive crisis, orthostatic hypotension, tachycardia, and increased QTc interval.² Trazodone, which might help relieve insomnia, is as-

sociated with orthostasis and tachycardia. These effects may occur more frequently in patients with cardiac disease.⁴

Selective serotonin reuptake inhibitors (SSRIs) are effective antidepressants post-MI, have antiplatelet activity, and may improve surrogate markers of cardiac risk, although further research is needed.^{5,6} Individual SSRIs vary in their effects on the cytochrome P450 (CYP450) system, and therefore carry different risks of drug-drug interactions (see *Related Resources*, page 34).

The cardiovascular impact of serotonin-norepinephrine reuptake inhibitors is unknown. These agents may be associated with hypertension and tachycardia.⁷ Additional research on the use of bupropion and mirtazapine in patients with CVD also is warranted. However, bupropion has been used to help patients with CVD stop smoking and likely is safe, although it may be associated with an increase in blood pressure.^{2,7} Bupropion and mirtazapine also can affect appetite and weight, which require monitoring in CVD patients. The Myocardial Infarction and Depression-Intervention

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Table 2

SSRIs and cardiovascular disease: Results from RCTs

Study	Design	Results
SADHART ¹⁴	Randomized, double-blind trial of sertraline vs placebo for 24 weeks for depression following MI or unstable angina (N=369)	Sertraline was more effective than placebo as measured by CGI-I, but not HAM-D in the total sample; both measures demonstrated statistical significance in patients with a history of MDD and those with HAM-D score >18 with 2 past episodes of MDD; incidence of severe cardiovascular events was 14.5% with sertraline and 22.4% with placebo (<i>P</i> = NS)
ENRICH ¹⁸	Randomized, double-blind, controlled trial of early CBT supplemented with SSRI (usually sertraline) if necessary vs usual care for depression and low perceived social support after MI (N=2,481)	Intervention had a modest effect on depressive symptoms; antidepressant use reduced the risk of death or nonfatal MI
CREATE ¹⁵	Randomized, controlled, 12-week, parallel-group trial of 284 depressed patients with coronary artery disease first randomized to weekly interpersonal psychotherapy for 12 weeks plus clinical management or clinical management only, then randomized to citalopram or placebo for 12 weeks	Although the effect size was small, citalopram was more effective for depression than placebo and did not differ in effect on cardiac parameters, such as blood pressure, heart rate, or ECG change (<i>P</i> = .005)

CBT: cognitive-behavioral therapy; CGI-I: Clinical Global Impressions-Improvement scale; CREATE: Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy; ENRICH: Enhancing Recovery in Coronary Heart Disease Patients; HAM-D: Hamilton Depression Rating Scale; MDD: major depressive disorder; MI: myocardial infarction; NS: nonsignificant; RCT: randomized controlled trial; SADHART: Sertraline Antidepressant Heart Attack Randomized Trial; SSRI: selective serotonin reuptake inhibitor

Trial (MIND-IT) reveals that antidepressant treatment with mirtazapine or citalopram does not increase the incidence of cardiac events and does not improve long-term depression status compared with treatment as usual in depressed post-MI patients.⁸ Orthostatic hypotension is a possible adverse effect of mirtazapine,⁷ and this antidepressant may reduce the antihypertensive effect of clonidine.

Monitor for interactions

Drug interaction databases—including Micromedex, Lexi-Comp, or Facts and Comparisons—can differ with regard to identifying and classifying drug interactions. Therefore, individual clinicians often carry the burden of recognizing potential drug-drug interactions. Preskorn and Flockhart⁹ suggest developing a “personal formulary” of the medications clinicians regularly prescribe to minimize drug-drug interactions. This formulary includes knowledge of a drug’s:

- enzymes responsible for elimination
- half-life
- relevant clinical trials
- receptor affinities
- common adverse effects.

Following these recommendations reveals several considerations when selecting an antidepressant for Mrs. T:

- Studies of SSRIs have shown them to be safe and well tolerated in post-MI patients. Because Mrs. T failed only 1 previous SSRI trial (sertraline), it would be reasonable to select an alternate agent within this class.

- An FDA alert highlights the risk of using clopidogrel in combination with drugs such as omeprazole, ketoconazole, fluoxetine, and fluvoxamine.¹⁰ These medications are CYP2C19 inhibitors, which can reduce clopidogrel’s effect by inhibiting conversion of the parent drug to its active metabolite.

- Adding a strong CYP2D6 inhibitor, such as fluoxetine or paroxetine, could increase the effects of metoprolol, which is a CYP2D6 substrate.¹¹

Clinical Point

It is unknown whether pharmacologic management of depression can reduce the risk of future cardiac events

continued

Related Resources

- Summers KM, Martin KE, Watson K. Impact and clinical management of depression in patients with coronary artery disease. *Pharmacotherapy*. 2010;30:304-322.
- Indiana University School of Medicine. P450 drug interaction table. Indiana University School of Medicine. <http://medicine.iupui.edu/clinpharm/ddis/table.asp>.

Drug Brand Names

Bupropion • Wellbutrin, Zyban	Lisinopril • Prinivil, Zestril Metoprolol • Lopressor, Toprol
Citalopram • Celexa	Mirtazapine • Remeron
Clopidogrel • Plavix	Omeprazole • Prilosec
Desipramine • Norpramin	Paroxetine • Paxil
Duloxetine • Cymbalta	Sertraline • Zoloft
Fluoxetine • Prozac	Simvastatin • Zocor
Fluvoxamine • Luvox	Trazodone • Desyrel
Ketoconazole • Nizoral	

Disclosure

Dr. Bostwick reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Cardiac outcomes

Evidence is insufficient to ascertain whether pharmacologic management of depression can reduce the risk of future cardiac events. Data evaluating SSRIs' effects on cardiac outcomes are equivocal^{5,12,13} and limited by inadequate power.^{14,15} Preliminary evidence suggests patients who respond to antidepressant treatment may have improved cardiovascular outcomes.^{16,17} Evidence obtained from the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), the Enhancing Recovery in Coronary Heart Disease Patients (ENRICH) trial, and the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial suggest the SSRIs sertraline and citalopram can be used safely, with minimal bleeding risk, to treat depression in CVD patients (*Table 2, page 33*).^{14,15,18} When treating depressed patients who have CVD, remember to include nonpharmacologic options, such as psychotherapy, in the treatment plan, although studies have not yet shown improved cardiovascular mortality rates in patients receiving CBT.^{8,17,18}

Although other SSRIs may be helpful for Mrs. T, citalopram is one of the best-studied agents post-MI, with the CREATE study supporting its efficacy and tolerability in this population. Citalopram has negligible drug interactions, although it is

a weak inhibitor of CYP2D6 and the possibility of increasing metoprolol's effects should be monitored. All SSRIs are associated with an increased risk of bleeding in patients receiving antiplatelet therapy; however, in Mrs. T's case the risks are minimal, which makes citalopram a reasonable option. CBT also could be resumed to optimize Mrs. T's treatment.

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