Do beta blockers cause depression?

Andrew J. Muzyk, PharmD, and Jane P. Gagliardi, MD

Robert M. McCarron, DO
Series Editor

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Beyond their well-known role for treating cardiovascular disease, beta adrenergic receptor antagonists—beta blockers—are used for a variety of medical conditions, including coronary artery disease, hypertension, migraines, and tremor. Their usefulness makes them 1 of the most commonly prescribed medication classes. Unfortunately, their increased use comes with increased reports of depression. Being able to sort fact from fiction will help guide your care for patients taking beta blockers who report new or worsening depressive symptoms.

Does research support a link?

First reported in the 1960s, beta blocker-induced depression was thought to result from the drugs' antagonistic effect on norepinephrine at ß1 post-synaptic brain receptors. Prompted by case reports of a possible association between beta blockers and depression, 2 prescription database reviews found that patients taking beta blockers were more likely to receive a concurrent antidepressant prescription than patients prescribed other cardiovascular and diabetic medications.[1,2] However, these reviews had major limitations, such as inadequately defined methods for defining depression and lack of control for potential confounding factors.

Mechanistically, peripheral effects of beta blockers on the heart and kidneys lead to decreased chronotropy and inotropy as well as lower blood pressure. These cardiovascular and hemodynamic changes could cause fatigue, decreased energy, and sexual dysfunction that may be interpreted as symptoms of new-onset depression.

Researchers found that beta-blocker use was not associated with depression in a case-control study examining 4,302 New Jersey Medicaid records.[3] Also, because most patients in this study received propranolol, the authors were unable to confirm a long-held belief that highly lipophilic beta blockers (such as propranolol,

Practice Points

- Although patients with cardiovascular disease are at increased risk for developing depression, there is **no convincing evidence that adding beta blockers will further increase their risk.**
- **Initiating beta-blocker therapy at the lowest possible dose** and slowly titrating the dose over time could minimize adverse effects such as fatigue and sexual side effects.
- If a patient taking beta blockers develops **signs of major depression,** carefully evaluate and treat symptoms with appropriate psychotherapy, psychotropics, and monitoring.

Dr. Muzyk is a clinical pharmacist, Duke University Medical Center, and Dr. Galiardi is assistant professor of psychiatry and behavioral sciences and assistant clinical professor of medicine, Duke University School of Medicine, Durham, NC.

Table

Beta blockers and depression: Is there a link?

Study	Methods	Results
Bright et al, 1992[3]	Case-control study of 4,302 patients with new-onset depression	Beta-blocker use was not associated with depression after controlling for confounding factors, although depressed patients were more likely to receive beta blockers
van Melle et al, 2006[4]	A prospective study of post-myocardial infarction patients; 254 taking beta blockers, 127 controls	No significant differences in depressive symptoms or incidence of depressive disorder between beta-blocker users and nonusers
Gerstman et al, 1996[5]	New users of propranolol (n=704) other beta blockers (n=587), angiotensin-converting enzyme inhibitors (n=976), calcium channel blockers (n=742), and diuretics (n=773)	Depression occurred no more frequently among beta-blocker users than other subjects
Ko et al, 2002[6]	Quantitative review of randomized trials that tested beta blockers in myocardial infarction, heart failure, and hypertension	Beta-blocker therapy was not associated with a significant absolute annual increase in risk of depressive symptoms (6 per 1,000 patients; 95% confidence interval, -7 to 19)

metoprolol, and timolol) are more likely than hydrophilic beta blockers such as atenolol to produce depression.

A retrospective cohort study analyzed 381 patients from 2 myocardial infarction (MI) trials who had been assessed for depressive symptoms and severity.[4] Researchers matched 254 subjects taking beta blockers during hospitalization for MI with 127 subjects not taking beta blockers. Patients in the study were well balanced on multiple baseline characteristics, including demographics, history of depression, and left ventricular ejection fraction, although those who did not take beta blockers had a significantly higher incidence of chronic obstructive pulmonary disease, digoxin use, and pre-MI beta-blocker use. Researchers assessed depressive symptoms using the Beck Depression Inventory (BDI) at baseline and 3, 6, and 12 months post-MI and identified patients with depression using a Composite International Diagnostic Interview. They found no statistically significant difference in BDI scores between beta-blockers users and nonusers at discharge and at 3, 6, and 12 months post-MI after accounting for potential confounding factors, including:

- contraindications for beta-blocker use (other than history of depression)
- indicators and risk factors for cardiac disease
- baseline depressive symptoms
- benzodiazepine use.

In fact, after controlling for baseline depression, researchers found that beta-blocker users demonstrated significantly lower BDI scores 3 months post-MI than nonusers. Based on these results, the authors concluded that clinicians should not be deterred from prescribing beta blockers because the drugs' benefit in reducing morbidity and mortality in cardiovascular disease greatly outweighs the risk—if any—of new-onset depression associated with beta-blocker use.

Two additional studies reported no significant difference in the incidence of depression between patients who received beta blockers and those who received other antihypertensives or placebo.[5,6] Future studies assessing depression among subjects randomized to beta blockers vs placebo would be helpful, though withholding beta blockers in some cardiac conditions is not justifiable, and such studies may not be feasible.

Clinical Point

Studies show no significant difference in incidence of depression between patients who received beta blockers and those who did not

Treatment for psychiatric patients

Evidence supports beta-blocker use in coronary artery disease and congestive heart failure. Although patients with these

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voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: *Skin and subcutaneous tissue disorders* – Angioedema. **DRUG INTERACTIONS: Central Nervous System (CNS)-Active Agents-**The risk of using Pristiq in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when Pristiq is taken in combination with other CNS-active drugs [*see Warnings and Precautions (5.13)*]. **Monoamine Oxidase Inhibitors (MAOIs)-** Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on antidepressants with pharmacological properties similar to Pristiq (SNRIs or SSRIs), or who have recently had SNRI or SSRI therapy discontinued prior to initiation of an MAOI [*see Contraindications (4.2)*]. **Serotonergic Drugs-** Based on the mechanism of action of Pristiq and the potential for serotonin syndrome, caution is advised when Pristiq is coadministered with other drugs that may affect the serotonergic neurotransmitter systems [*see Warnings and Precautions (5.2)*]. **Drugs that Interfere with Hemostasis (eg, NSAIDs, Aspirin, and Warfarin)-** Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Pristiq is initiated or discontinued. **Ethanol-** A clinical study has shown that desvenlafaxine does not increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking Pristiq. **Potential for Other Drugs to Affect Desvenlafaxine-**Inhibitors of CYP3A4 (ketoconazole)- CYP3A4 is a minor pathway for the metabolism of Pristiq. Concomitant use of Pristiq with potent inhibitors of CYP3A4 may result in higher concentrations of Pristiq. Inhibitors of other CYP enzymes- Based on *in vitro* data, drugs that inhibit CYP isozymes 1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of Pristiq. **Potential for Desvenlafaxine to Affect Other Drugs-** Drugs metabolized by CYP2D6 (desipramine)- *In vitro* studies showed minimal inhibitory effect of desvenlafaxine on CYP2D6. Clinical studies have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6 metabolism at the dose of 100 mg daily. Concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 can result in higher concentrations of that drug. Drugs metabolized by CYP3A4 (midazolam)- *In vitro*, desvenlafaxine does not inhibit or induce the CYP3A4 isozyme. Concomitant use of Pristiq with a drug metabolized by CYP3A4 can result in lower exposures to that drug. Drugs metabolized by CYP1A2, 2A6, 2C8, 2C9 and 2C19- *In vitro*, desvenlafaxine does not inhibit CYP1A2, 2A6, 2C8, 2C9, and 2C19 isozymes and would not be expected to affect the pharmacokinetics of drugs that are metabolized by these CYP isozymes. **P-glycoprotein Transporter-** *In vitro*, desvenlafaxine is not a substrate or an inhibitor for the P-glycoprotein transporter. The pharmacokinetics of Pristiq are unlikely to be affected by drugs that inhibit the P-glycoprotein transporter, and desvenlafaxine is not likely to affect the pharmacokinetics of drugs that are substrates of the P-glycoprotein transporter. **Electroconvulsive Therapy-** There are no clinical data establishing the risks and/or benefits of electroconvulsive therapy combined with Pristiq treatment. **USE IN SPECIFIC POPULATIONS: Pregnancy-** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Teratogenic effects– Pregnancy Category C- There are no adequate and well-controlled studies of Pristiq in pregnant women. Therefore, Pristiq should be used during pregnancy only if the potential benefits justify the potential risks. Non-teratogenic effects- Neonates exposed to SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [*see Warnings and Precautions (5.2)*]. When treating a pregnant woman with Pristiq during the third trimester, the physician should carefully consider the potential risks and benefits of treatment [*see Dosage and Administration (2.2)*]. **Labor and Delivery-** The effect of Pristiq on labor and delivery in humans is unknown. Pristiq should be used during labor and delivery only if the potential benefits justify the potential risks. **Nursing Mothers-** Desvenlafaxine (O-desmethylvenlafaxine) is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Pristiq, a decision should be made whether or not to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Only administer Pristiq to breastfeeding women if the expected benefits outweigh any possible risk. **Pediatric Use-** Safety and effectiveness in the pediatric population have not been established [*see Box Warning and Warnings and Precautions (5.1)*]. Anyone considering the use of Pristiq in a child or adolescent must balance the potential risks with the clinical need. **Geriatric Use-** Of the 3,292 patients in clinical studies with Pristiq, 5% were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients; however, in the short-term, placebo-controlled studies, there was a higher incidence of systolic orthostatic hypotension in patients ≥65 years of age compared to patients <65 years of age treated with Pristiq [*see Adverse Reactions (6)*]. For elderly patients, possible reduced renal clearance of desvenlafaxine should be considered when determining dose [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.6)*]. If Pristiq is poorly tolerated, every other day dosing can be considered. SSRIs and SNRIs, including Pristiq, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [*see Warnings and Precautions (5.12)*]. Greater sensitivity of some older individuals cannot be ruled out. **Renal Impairment-** In subjects with renal impairment the clearance of Pristiq was decreased. In subjects with severe renal impairment (24-hr CrCl < 30 mL/min) and end-stage renal disease, elimination half-lives were significantly prolonged, increasing exposures to Pristiq; therefore, dosage adjustment is recommended in these patients [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.6) in the full prescribing information*]. **Hepatic Impairment-** The mean $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively. The recommended dose in patients with hepatic impairment is 50 mg/day. Dose escalation above 100 mg/day is not recommended [*see Clinical Pharmacology (12.6)*].

OVERDOSAGE: Human Experience with Overdosage- There is limited clinical experience with desvenlafaxine succinate overdosage in humans. In premarketing clinical studies, no cases of fatal acute overdose of desvenlafaxine were reported. The adverse reactions reported within 5 days of an overdose > 600 mg that were possibly related to Pristiq included headache, vomiting, agitation, dizziness, nausea, constipation, diarrhea, dry mouth, paresthesia, and tachycardia. Desvenlafaxine (Pristiq) is the major active metabolite of venlafaxine. Overdose experience reported with venlafaxine (the parent drug of Pristiq) is presented below; the identical information can be found in the *Overdosage* section of the venlafaxine package insert. In postmarketing experience, overdose with venlafaxine (the parent drug of Pristiq) has occurred predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (eg, prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported. Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage, as opposed to some characteristic(s) of venlafaxine-treated patients, is not clear. Prescriptions for Pristiq should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Management of Overdosage-** Treatment should consist of those general measures employed in the management of overdosage with any SSRI/SNRI. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Induction of emesis is not recommended. Because of the moderate volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for desvenlafaxine are known. In managing an overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians Desk Reference (PDR®).

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Related Resources

- Rivelli S, Jiang W. Depression and ischemic heart disease: what have we learned from clinical trials? Curr Opin Cardiol. 2007;22(4):286-291.
- National guideline clearinghouse. Secondary prevention of coronary artery disease. www.guideline.gov/summary/summary.aspx?docid=14585.

Drug Brand Names

Atenolol • Tenormin
Digoxin • Lanoxin
Metoprolol • Lopressor, Toprol-XL
Propranolol • Inderal
Timolol • Blocadren

Disclosure

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conditions are at increased risk for developing depression,[7] there is little evidence that their risk will be further increased by adding beta blockers (***Table, page 51***).[3-6] Although patients taking beta blockers report a higher incidence of fatigue and sexual side effects—which could be interpreted as related to depression—studies do not support an association between these medications and depression. As with any medication, initiate beta-blocker therapy with the lowest possible dose and titrate slowly to minimize side effects. Any patient who develops signs and symptoms of major depression should be thoroughly evaluated and treated with appropriate psychotherapy, psychotropics, and careful monitoring.

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