

Consider PTSD subtypes in patient workup

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Posttraumatic stress disorder (PTSD) is a confusing diagnostic category because it includes victims of trauma as well as individuals exposed to trauma. Also, PTSD encompasses exposure to different types of trauma, which can have significant implications for symptom development and treatment.

Consider the treatment history of a male combat veteran who exhibits multiple PTSD symptoms, including nightmares, flashbacks, social isolation, anger, and guilt related to his war experiences. Several psychiatrists saw the patient, which resulted in multiple medication changes but little benefit. On further assessment, the practitioners noted that the veteran's war experiences were minimally problematic; the prominent nightmares, ruminations, flashbacks, and guilt were related to his witnessing a civilian female being sexually assaulted. The veteran's guilt about not intervening was the basis of his PTSD. This led to a change in treatment from pharmacotherapy to a focus on supportive therapy.

Conceptualizing subtypes of PTSD—similar to many DSM-IV-TR diagnoses such as phobias or delusional disorders—might help better define the diagnosis. Each subtype, as conceptualized below, might have its own prognosis and treatment. Our hope is that this strategy will benefit the patient by improving research and evidence-based practice.

PTSD subtypes

Victim-related trauma. Related to witnessing a criminal act or being a victim of a criminal act such as rape or assault. The patient is in a passive role.

Natural disasters, such as a tornado, earthquake, or hurricane.

Survivor guilt. The patient is not a perpetrator and might have been exposed to trauma, but symptoms are related to surviving while others close to the patient did not.

Perpetrator guilt. It is debatable whether this should be a PTSD subtype but our experience suggests that this pattern severely complicates PTSD diagnosis and treatment. It often is not initially disclosed by patients but surfaces when treatment is not working despite a strong therapeutic alliance.

PTSD not otherwise specified. This subtype is typical in patients who were not directly involved in a traumatic event but experienced symptoms related to it. Examples include picking up dead bodies, cleaning up a tornado site, or observing siblings being beaten. This category also may reflect an unclear picture if no primary subtype accounts for the majority of symptoms.

Qualifiers

Individuals who previously have been exposed to trauma are more vulnerable to subsequent trauma. Experiencing ongoing multiple traumatic events—such as in military combat—can have a cumulative effect. Thus, identifying episodes of trauma also should be part of the PTSD assessment.

Categorizing PTSD into subtypes might help better define the diagnosis and benefit patients by improving evidence-based medicine

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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-desmethylenlafaxine) 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. No adjustment in starting dosage is necessary for patients with hepatic impairment.

OVERDOSAGE: Human Experience with Overdosage- There is limited clinical experience with desvenlafaxine succinate overdose 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 overdose 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 overdose 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 overdose, 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 overdose 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).

This brief summary is based on Pristiq Prescribing Information W10529C004, revised February 2009.

Single event. The patient is exposed to a single traumatic episode, such as being the victim of a crime.

Multiple events/single episode. The patient is exposed to repeated, related traumatic events. Examples include ongoing military combat or child abuse.

Multiple events. The patient is exposed to ≥ 2 separate traumatic events. A combination such as this might include a serious motor vehicle accident followed by a natural disaster.

As the diagnosis of PTSD evolves, utilizing subtypes and qualifiers might clarify treatment strategies because some subtypes might be more amenable to certain psychopharmacologic or psychotherapeutic treatment regimens.

Diagnostic confusion

Some researchers question whether traumatic stress causes PTSD syndrome,¹ whereas others recommend “tightening” the diagnostic criteria.² Concerns regarding PTSD diagnosis are multiple and include:

- the importance of ruling out malingering³
- the effects of different diagnostic criteria resulting in disparate prevalence rates
- emphasizing the importance of dysfunction as a criterion for PTSD.⁴

Conceptual inconsistencies in DSM-IV-TR diagnostic criteria also can lead to confusion. Although there is a category of arousal symptoms, Criterion B4 (intense psychological distress) and Criterion B5 (physiological reactivity) are listed as re-experiencing symptoms rather than arousal symptoms. Finally, the criteria presented do not follow a logical progression. Research suggests that re-experiencing symptoms do not lead to avoidance but result in arousal symptoms, which in turn trigger avoidance.⁵

References

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