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How to treat PTSD in patients with comorbid mood disorders

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Antidepressants may trigger hypomania in patients with bipolar spectrum disorders

Major depressive disorder (MDD) and bipolar spectrum disorders are associated with some symptoms of—and fully defined—posttraumatic stress disorder (PTSD). Many traumatic experiences can lead to this comorbidity, the most common being exposure to or witnessing combat for men and rape and sexual molestation for women.[1]

Trauma has major prognostic and treatment implications for affectively ill patients, including those whose symptoms do not meet PTSD's full diagnostic criteria. This article aims to help clinicians by:

- presenting evidence characterizing the overlap between affective disorders and PTSD
- reviewing evidence that the bipolar spectrum may be broader than generally thought, an insight that affects PTSD treatment
- making a case for routine PTSD screening for all patients with affective illnesses
- recommending PTSD treatments tailored to the patient's comorbid affective disorder.

Overlap of trauma and affective illness

PTSD is remarkably comorbid with mood disorders. Americans with MDD and bipolar disorder (BPD) are 7 and 9.4 times, respectively, more likely to meet criteria for PTSD than persons in the general population, according to odds ratios Kessler et al[2] calculated from the National Comorbidity Survey database.

I have never seen a patient with PTSD who did not also meet criteria for an affective disorder. The

Table 1

Evidence of bipolar spectrum features in major depressive episodes

Study	Design	Conclusion
Akiskal and Mallya, 1987[4]	200 community mental health clinic patients diagnosed as having MDD	50% could be classified as having a bipolar disorder
Benazzi, 1997[5]	203 consecutively presenting patients with depression	45% met criteria for bipolar II disorder
Akiskal and Benazzi, 2005[6]	563 consecutive patients presenting with a DSM-IV-diagnosed MDE	58% showed features of bipolar II disorder
Akiskal et al, 2006[7]	493 patients in a French national study presenting with MDE	65% were determined to fall along the 'bipolar spectrum'
Rabakowski et al, 2005[8]	880 Polish outpatients presenting with MDE	40% met criteria for bipolar disorder

MDD: major depressive disorder; MDE: major depressive episode

concurrence of PTSD and MDD is not the product of overlapping diagnostic criteria. Rather, evidence indicates these are distinct diagnostic entities.[3] A review of diagnostic criteria for PTSD and hypomania/mania leads to the same conclusion.

Bipolar spectrum disorders

DSM-IV-TR assumes that mood disorders fall neatly into boxes. Other data (***Table 1***)[4-8] indicate that these disorders fall along a continuum or—more conservatively—that the scope of bipolarity is much wider than DSM-IV-TR recognizes. This is a controversial topic, and the individual clinician's position could impact how one manages PTSD patients.

In this article, I include bipolar I disorder, bipolar II disorder, and mixed depression within the "bipolar spectrum disorders." If one accepts this—and I do—it follows that 50% to 70% of all major depressive episodes (MDEs) are bipolar in nature.[4-9] Depending on your practice setting, you may see a higher or lower base rate of bipolar spectrum disorders.

Mixed depression is not recognized in DSM-IV-TR, and the purpose of this article is not to defend its inclusion as a bipolar spectrum phenomenon. A proposed definition of mixed depression[9] requires the presence of an MDE contaminated by ≥3 features of hypomania or mania, without euphoria or inflated self-esteem/grandiosity (***Table 2, page 50***).[10]

Some experts believe episodes of hypomania and mania frequently occur in the illness course of persons with mixed depression; indeed, mixed depression is a predictor of a bipolar course. It is observed in outpatient[9] and inpatient settings.[11] Common forms of mixed depression feature combinations of irritability, psychomotor agitation (mild to severe), increased talkativeness (which may fall short of frank pressured speech), racing or "crowded" thoughts (or "mental overactivity"), and distractibility. Other than increased self-esteem/grandiosity, any symptoms within DSM-IV-TR criterion B for a hypomanic or manic episode may be seen in mixed depression. Psychosis is an exclusion criterion for mixed depression.

Mixed depression responds poorly to antidepressant monotherapy. Validation studies suggest that mixed depression is a bipolar variant, as determined by its capacity to predict a bipolar course and its association with a family history of bipolar disorder and age of onset.[9]

PTSD risk in affective illness

An adolescent sample. A preliminary cross-sectional study conducted by our group indicates that adolescents with affective disorders may have a much higher risk of developing PTSD than psychiatric comparison subjects.[12] We used modules from the Structured Clinical Interview for DSM-IV (SCID) to screen for intra-episode psychopathology (as opposed to lifetime

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Validation studies suggest that mixed depression is a bipolar variant

Table 2

Diagnostic characteristics of a hypomanic episode, DSM-IV-TR criteria A and B

A. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual nondepressed mood.

B. During the period of mood disturbance, 3 or more of the following symptoms have persisted (4 if the mood is only irritable) and have been present to a significant degree:

1) inflated self-esteem or grandiosity
2) decreased need for sleep (eg, feels rested after only 3 hours of sleep)
3) more talkative than usual or pressure to keep talking
4) flight of ideas or subjective experience that thoughts are racing
5) distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli)
6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
7) excessive involvement in pleasurable activities that have a high potential for painful consequences (eg, the person engages in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

Source: Diagnostic and statistical manual of mental disorders, 4th ed, text rev. Washington, DC: American Psychiatric Association; 2000

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In our study, an adult patient with bipolar disorder was 5 times more likely to have PTSD than one with MDD

prevalence of disorders) in 79 adolescents with MDD, 34 with BPD as defined in the DSM-IV-TR, and 26 with neither affective disorder (psychiatric controls). We found:

- 38.2% of subjects with BPD met criteria for PTSD, compared with 13.9% of those with MDD (OR 4.9; $P = .001$)
- 3.8% of adolescents without a mood disorder met criteria for PTSD.

We also found that comorbid PTSD was associated with a 4.5-fold higher risk of a suicide attempt, even after we controlled for BPD diagnosis. When we controlled for the presence of other concurrent anxiety disorders, the likelihood of an adolescent with PTSD having attempted suicide remained significant (OR 3.4; $P = .023$). This finding suggests that PTSD is an independent risk factor for a suicide attempt.

An adult sample. We then focused on adults meeting criteria for MDD or BPD. In a study of 187 consecutively presenting affectively ill patients, we used the SCID to screen for multiple anxiety disorders including PTSD.[13] Lifetime—as opposed to intra-episode—PTSD prevalence was 23.8% among the 118 patients with MDD and 62.3% among the 69 patients with BPD. A patient with BPD was 5 times more likely to have PTSD than a patient with MDD (OR 5.3; $P < .0001$). The most common cause of trauma leading to PTSD was sexual molestation or rape as a child or adolescent in this predominantly female Latino population.

Populations at risk for PTSD

The prevalence of PTSD in clinical samples varies, depending on the population studied. For instance, women are at much higher risk for developing PTSD than men, even in comparisons where men are exposed to a greater number of traumatic events and analyses control for differences in the prevalence of sexual abuse. The gender difference is greater if the trauma occurs during childhood.[14] Essentially all patients in our adolescent and adult studies developed PTSD in response to childhood or adolescent sexual trauma.[12,13]

A population exposed to a high rate of violent crime would be expected to show a higher PTSD prevalence than one exposed to substantially less violence. The base rate of PTSD also is much higher in affectively ill patients than in the general population.

An analysis by Otto et al[15] found a 16% lifetime prevalence of concomitant PTSD in 1,214 persons with BPD (not the manifold forms within the bipolar spectrum). Oquendo et al[16] reported a 25.7% lifetime prevalence of PTSD in 230 patients with a history of MDD. Other epidemiologic[2] and clinical

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Checklist

DSM-IV-TR diagnostic criteria for posttraumatic stress disorder

	Criterion A. The person has been exposed to a traumatic event in which both of the following have been present:
☐	1. The person has experienced, witnessed, or been confronted with an event or events that involve actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others
☐	2. The person's response involved intense fear, helplessness, or horror
	Criterion B. The traumatic event is persistently re-experienced in at least 1 of the following ways:
☐	1. Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions
☐	2. Recurrent distressing dreams of the event
☐	3. Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur upon awakening or when intoxicated)
☐	4. Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
☐	5. Physiologic reactivity upon exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
	Criterion C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by at least 3 of the following:
☐	1. Efforts to avoid thoughts, feelings, or conversations associated with the trauma
☐	2. Efforts to avoid activities, places, or people that arouse recollections of the trauma
☐	3. Inability to recall an important aspect of the trauma
☐	4. Markedly diminished interest or participation in significant activities
☐	5. Feeling of detachment or estrangement from others
☐	6. Restricted range of affect
☐	7. Sense of foreshortened future
	Criterion D. Persistent symptoms of increasing arousal (not present before the trauma), indicated by at least 2 of the following:
☐	1. Difficulty falling or staying asleep
☐	2. Irritability or outbursts of anger
☐	3. Difficulty concentrating
☐	4. Hypervigilance
☐	5. Exaggerated startle response
☐	**Criterion E.** Duration of disturbance (symptoms in B, C, and D) is >1 month
☐	**Criterion F.** Disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

Source: Adapted from Diagnostic and statistical manual of mental disorders, 4th ed, text rev. Washington, DC: American Psychiatric Association; 2000

studies[12,13] suggest a considerably higher base rate of PTSD among persons with bipolar disorders than those with MDD.

The method of ascertaining the presence of this disorder may be another variable affecting the reported PTSD prevalence. Persistent avoidance—including "efforts to avoid thoughts, feelings, or conversations associated with the trauma"—is a diagnostic feature of PTSD.[10] Researchers and clinicians who do not intentionally screen patients for PTSD are not likely to detect it. Determining the true prevalence of PTSD requires empathic inquiry about exposure to traumatic events.

PTSD screening

Humans are remarkably resilient, and most persons exposed to major trauma are thought not to develop PTSD. However, in my experience, because PTSD appears to be common among persons with affective illness, determining whether such patients have been traumatized is important for prognosis and treatment selection.

continued

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Effective screening for PTSD requires empathic inquiry about patients' exposure to traumatic events

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To get started, you could create a 1-page form to record traumatic events and identify features of PTSD according to DSM-IV-TR criteria (***Checklist, page 51***).[10] PTSD screening without a form can become second nature with practice; an experienced clinician can screen a traumatized patient for the disorder within 3 to 5 minutes.

When screening for a history of trauma, ask patients in a straightforward manner if they have:

- been victims of violent crimes
- witnessed violent crimes
- been exposed to events in which people could have suffered grave injury
- experienced emotional, physical, or sexual abuse.

A person who has experienced emotional abuse but not physical or sexual abuse cannot meet DSM-IV-TR criterion A and therefore does not meet full criteria for PTSD. Many emotionally abused persons meet criteria B through F, however, and they are most reasonably managed similarly to persons who also meet criterion A. When formulating a treatment plan, I recommend using clinical judgment rather than rigid adherence to DSM-IV-TR.

Treating PTSD in depression

Pharmacotherapy and psychotherapeutic interventions are important to PTSD patients' recovery. Limited resources often prevent these patients from receiving expert psychotherapeutic intervention, however, leaving pharmacotherapy as the mainstay of treatment. This is unfortunate, because psychological interventions may be sufficient and preferred in some instances (***Box***).[17-20]

Pharmacotherapy for comorbid MDD. Selective serotonin reuptake inhibitors (SSRIs) and venlafaxine are first-line interventions for PTSD in depressed patients who do not meet criteria for a bipolar spectrum disorder. Placebo-controlled studies suggest that sertraline,[21,22] fluoxetine,[23] and paroxetine,[24] are effective; doses higher than those used to treat depression may be required. Extended-release venlafaxine[25] in dosages similar to those needed for depressive disorders also can be effective.

Bupropion does not appear to be beneficial in treating PTSD.

The monoamine oxidase inhibitor phenelzine was long used successfully in treating PTSD but for the most part has been replaced by SSRIs. Because of its associated dietary restrictions, risk of hypertensive crises, and other side effects, phenelzine probably is best reserved for patients who do not respond to treatment with SSRIs or venlafaxine.

Pharmacotherapy for comorbid bipolar spectrum. If one accepts that most patients meeting criteria for MDE have a bipolar spectrum disorder, then most affectively ill patients with PTSD would need to be treated as if they have bipolar disorder. Oddly enough, this creates difficulties for the use of not only antidepressants and benzodiazepines, but also mood stabilizers:

- Patients with BPD and comorbid anxiety disorders, including PTSD, may be resistant to mood stabilizers.[26,27]
- Antidepressants can precipitate hypomanic or manic switches or onset of mixed hypomania, a mixed state, or rapid cycling in patients with a bipolar spectrum disorder.[28-30]
- Benzodiazepines do not appear to relieve acute or chronic PTSD-related distress, and discontinuation could cause rebound symptoms.[31]

Because no outcome studies have addressed PTSD management in patients with bipolar spectrum disorders, clinicians must rely on their judgment when formulating treatment plans. One strategy is to treat patients with mood stabilizers, then leave well enough alone if both the mood and anxiety symptoms remit (which is possible but unlikely in my experience). I often start treatment for the bipolar spectrum disorder and co-existing PTSD using mood stabilizers (including atypical antipsychotics) and prazosin, an α-1 antagonist originally used for treating hypertension.

Prazosin can help diminish nightmares, dreams, and other painful recollections of trauma.[32,33] The drug does not affect time to sleep onset. It also has been reported to reduce avoidance behavior and hyperarousal, such as irritability and anger.[34] This has been my experience.

Prazosin to treat PTSD-related symptoms in children or adolescents has not been studied, but it can be useful in adults over a wide range of doses. As little as 1 mg at bedtime may confer benefit, although the mean prazosin dose in an 8-week, placebo-controlled study of 40 combat veterans was 13.3 mg in the evening.[33]

I often initiate prazosin treatment as follows:

- 1 mg on the first night of treatment
- 2 mg on the second night
- 3 mg on the third night
- then, if tolerated, 1 mg upon waking, 1 mg 8 hours later, and 3 mg at bedtime.

I then slowly adjust the dose schedule based on the patient's needs, such as minimizing painful re-experiencing of the trauma. Reducing avoidance and hyperarousal also are reasonable targets. For example, when using prazosin to treat extremely angry men with PTSD stemming from exposure to violent crimes, I have observed that even "murderous" rage ceases with

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Box

Psychotherapies for PTSD with comorbid affective illness

Cognitive-behavioral therapy (CBT) involving prolonged exposure (PE) to trauma-related stimuli has been shown to be effective for posttraumatic stress disorder (PTSD) in controlled studies.[17,18] PE is an individual CBT designed to help patients process traumatic events and reduce psychological distress. It involves education about reactions to trauma, relaxation techniques, imaginal reliving of the trauma, exposure to cues associated with the trauma, and cognitive restructuring.

Administering D-cycloserine before behavioral treatment sessions facilitates fear extinction, and its use to enhance prolonged PE constitutes state-of-the-art treatment.[19] Eye movement desensitization and reprocessing also may be effective.[18,20]

PE is a reasonable first-line treatment for PTSD patients with comorbid bipolar spectrum disorders when PTSD symptoms persist after pharmacologic treatment for the bipolar spectrum disorder. PE also is a first-line treatment for PTSD in patients with comorbid major depressive disorder. Barriers to PE treatment include its cost and finding professionals who are expert in its use.

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SSRIs and venlafaxine are first-line treatments for PTSD in depressed patients who do not have a bipolar spectrum disorder

Overall, of the total number of subjects in schizophrenia clinical studies of INVEGA® (n = 1796), including those who received INVEGA® or placebo, 125 (7.0%) were 65 years of age and older and 22 (1.2%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with moderate to severe renal impairment *[see Clinical Pharmacology (12.3) in full PI]*, who should be given reduced doses. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Dosage and Administration (2.5) in full PI]*.

Renal Impairment: Dosing must be individualized according to the patient's renal function status *[see Dosage and Administration (2.5) in full PI]*.

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Paliperidone is the major active metabolite of risperidone. Overdose experience reported with risperidone can be found in the OVERDOSAGE section of the risperidone package insert.

Management of Overdosage: There is no specific antidote to paliperidone, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers. Consideration should be given to the extended-release nature of the product when assessing treatment needs and recovery. Multiple drug involvement should also be considered.

In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of paliperidone. Similarly the alpha-blocking properties of bretylium might be additive to those of paliperidone, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of paliperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered.

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prazosin treatment, only to reappear when prazosin is discontinued.

In treating approximately 100 patients with prazosin, I have not exceeded 16 mg/d. Dosages used for treating hypertension usually are 5 to 20 mg/d. When using prazosin, I always:

- warn patients that faintness or fainting is a side effect and record this caveat in their chart
- obtain sitting and standing blood pressure and pulse before starting treatment and subsequently
- ask patients if they feel dizzy when changing posture before and after initiating treatment.

Most of my PTSD patients are suffering so much that they are willing to accept the risk of fainting associated with prazosin use. For PTSD comorbid with severe panic disorder,[12,13] I find that a benzodiazepine with antipanic properties such as alprazolam or clonazepam often works well in conjunction with prazosin.

Some patients with bipolar spectrum disorders might benefit from the addition of an SSRI after mood stabilizer treatment proves effective. However, I have never managed a patient in this manner, and like my own treatment strategy, this has not been subjected to rigorous empiric inquiry. In my view, psychological treatment is much preferred to antidepressant therapy.

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Related Resource

• Benazzi F. Bipolar disorder—focus on bipolar II disorder and mixed depression. Lancet. 2007;369:935-945.

Drug Brand Names

Alprazolam • Xanax
Bupropion • Wellbutrin
Clonazepam • Klonopin
D-cycloserine • Seromycin
Fluoxetine • Prozac
Paroxetine • Paxil
Phenelzine • Nardil
Prazosin • Minipress
Sertraline • Zoloft
Venlafaxine • Effexor

Disclosure

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

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Bottom Line

Because posttraumatic stress disorder (PTSD) is common among persons with affective disorders, routinely screen these patients for PTSD. Pharmacologic and psychological treatments are effective. Antidepressants—although often considered first-line treatment for PTSD—may cause hypomanic or manic switching in patients with bipolar spectrum disorders.

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I often start treatment of bipolar spectrum disorders and co-existing PTSD with mood stabilizers and prazosin