Afraid to leave home

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CASE Disabling anxiety

Mr. B, age 35, has a history of schizophrenia, chronic paranoid type and has been hospitalized more than 12 times since its onset 10 years ago. He received clozapine during his most recent hospitalization approximately 5 years ago and experienced full symptom response without the motor side effects he developed in response to other medications. He visits a psychiatrist monthly for medications and supportive psychotherapy, and he receives intensive case management and housing from a community mental health center.

When Mr. B is assigned to my (CK) care, his psychotic symptoms are in remission, but he complains of anxiety that leaves him almost homebound. He has intense fear of bridges, upper-floor windows, express buses, subways, riding in speeding vehicles, and having a seizure. If Mr. B faces any of these triggers, he experiences harmful thoughts—such as jumping out a window or off a bridge—even though he does not endorse suicidality. These thoughts are intrusive, ego-dystonic, and ruminative. He avoids these triggers at all costs, which compromises his housing and employment opportunities. He experienced a single panic attack in the subway 1 year earlier. Mr. B firmly believes that any intense anxiety he experiences will trigger a psychotic episode. When faced with sudden urges, he believes his illness would interfere with his ability to control his impulses.

He reports that these symptoms started when he began clozapine and have worsened. Mr. B says he experiences a feeling of “uneasiness” approximately 2 hours after taking clozapine that is exacerbated if he faces a trigger. He describes the uneasiness as “the feeling of being about to have a seizure” during which he would “lose control” of his body.

When I begin treating Mr. B, he is receiving clozapine, 125 mg bid. In an effort to combat Mr. B’s anxiety, a previous psychiatrist had titrated clonazepam up to 5 mg/d as needed. Mr. B is compliant with his medications and appointments but refuses to change his psychotropic or psychotherapy regimen.

Clozapine alleviates Mr. B’s schizophrenia symptoms, but he develops anxieties that leave him virtually homebound. Is the antipsychotic to blame?

The authors’ observations

Approximately 50% of patients with schizophrenia have at least 1 anxiety disorder, and close to 30% meet criteria for >1 anxiety disorder. Social anxiety disorder (SAD), generalized anxiety disorder, panic disorder, posttraumatic stress disorder, and obsessive-compulsive disorder (OCD) have been found comorbid with schizophrenia, with rates as high as 30% for each.

Possible causes of unusually high rates of anxiety disorders in schizophrenia

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Treatment options for comorbid schizophrenia and anxiety

<table>
<thead>
<tr>
<th>Modality</th>
<th>Options</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Psychopharmacology</td>
<td>Antipsychotics</td>
<td>Favor monotherapy at full dose for full trial period before considering adjunct therapy with a second antipsychotic, for which evidence is still equivocal</td>
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<tr>
<td></td>
<td>• Increase antipsychotic dose</td>
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<td></td>
<td>• Change antipsychotic</td>
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<td>• Add an atypical with serotonergic action (ziprasidone, aripiprazole)</td>
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<td></td>
<td>Antidepressants</td>
<td>Avoid bupropion because of possible dopamine agonism</td>
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<td>• SSRI</td>
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<td>• SNRI</td>
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<td></td>
<td>Benzodiazepines</td>
<td>Weigh risks of sedation and potential for addiction vs benefits of immediate relief</td>
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<td></td>
<td>Gabapentin</td>
<td>Use high doses to obtain symptomatic response</td>
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<tr>
<td>Psychotherapy</td>
<td>CBT (for psychosis and anxiety)</td>
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<td>Supportive (for decompensating psychosis)</td>
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<td>Behavioral</td>
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<td>Activity and vocational</td>
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CBT: cognitive-behavioral therapy; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor

include trauma history, delusional conviction and inflexibility of abstract thought, and passive coping mechanisms.

Schizophrenic illnesses may be linked to anxiety antecedents such as panic or social phobia that:

• develop into more profound psychosis
• or bring about anxiety symptoms, given the severity of the subjective psychotic experience.

In a twin pairs study, the schizophrenic twin had an almost threefold increase in rates of comorbid psychiatric disorders compared with their non-schizophrenic twins; social or environmental factors may not account for this.

Comorbid OCD, panic disorder, and SAD frequently persist after remission of psychotic symptoms. Comorbid anxiety disorders may play a role in the psychotic symptoms themselves (such as panic and social anxiety related to paranoia, OCD, and bizarre behavior) and negatively impact quality of life.

In patients with schizophrenia, higher anxiety levels are associated with:

• increased hallucinations
• poor psychosocial function
• hopelessness.

Accurately assessing and diagnosing anxiety disorders in patients with schizophrenia is challenging because there is inconsistency among clinical interviewers (poor reliability scores), and anxiety scales are not as accurate as we would like them to be (poor construct validity). Treatment options for comorbid anxiety and schizophrenia include psychopharmacology and psychotherapy (Table 1).

**Clinical Point**

Comorbid OCD, panic disorder, and SAD frequently persist after remission of psychotic symptoms.

**HISTORY** Propensity for violence

Mr. B was born in a large city and raised by his single mother. He denies childhood physical or sexual abuse. Mr. B reports engaging in violent activity since he was an adolescent, but this activity is undocumented because he has never been arrested. Mr. B still belongs to a gang he joined after being assaulted at age 16.
Mr. B was diagnosed with schizophrenia at age 20 following an overt psychotic episode and suicide attempt by hanging. During his psychotic episodes, he thinks groups of people are plotting to kill him. He hears people talking about him or voices telling him about others’ plots against him. Mr. B probably has experienced these symptoms since early childhood, as evidenced by reports of attention-deficit/hyperactivity disorder, oppositional defiant disorder, conduct disorder, and tics.

His health records contain no mention of anxiety symptoms until approximately 3 months after he started clozapine, when he reported brief episodes of unexplained phobia of windows and bridges. Approximately 1 year later, he reported obsessive-compulsive symptoms—ruminating and intrusive thoughts of jumping off a bridge with no suicidal intent. Mr. B’s outpatient therapist at the time believed these symptoms began before Mr. B started clozapine.

Numerous medication trials failed. Antipsychotics were ineffective or poorly tolerated because of motor side effects or intense sedation. Mr. B did not tolerate selective serotonin reuptake inhibitors (SSRIs) because of akathisia or sexual side effects. Mr. B had a history of poor medication compliance until he began clozapine treatment.

Mr. B used cannabis daily until 10 years ago. He smokes cigarettes and reports occasional alcohol use. He has no history of chronic substance or alcohol use, withdrawal symptoms, or complications from intoxication.

Mr. B is unemployed and receives Supplemental Security Income. He has never married or had children.

Medical comorbidities include a white blood cell count and absolute neutrophil count that have been chronically in the lower limit range, and dyslipidemia and diabetes, for which Mr. B receives statins and oral hypoglycemics. He has no history of seizures or brain trauma. His family history includes substance dependence on his mother’s side and schizophrenia in 2 paternal cousins.

Mr. B best meets criteria for which of the following disorders?

a) panic disorder
b) OCD
c) agoraphobia without panic
d) specific phobia

The authors’ observations

Mr. B’s anxiety disorder has not been clearly elucidated. He does not seem to meet criteria for:

- panic disorder (only 1 panic attack)
- OCD (no compulsions to diminish anxiety)
dose was also associated with maternal toxicity (clinical signs, decreased body weight gain). The developmental no-effect dose was 50 mg/kg/day. In a rat study, no adverse effects on embryo/fetal development were observed at doses of racemic citalopram of up to 35 mg/kg/day. Thus, the teratogenic effects of racemic citalopram are observed at a single high dose in the rat. Although no evidence was observed for teratogenic effects of racemic citalopram in the rat, these findings emphasize that caution should be exercised in the interpretation of animal data, and the potential teratogenic effects of escitalopram should be considered in women of childbearing potential. Yet, the range of doses that were teratogenic in the rat were not reported.

In the rat, when dams were treated throughout gestation and early lactation at doses up to 24 mg/kg/day, there was no evidence of fetal toxicity, decreased maternal weight gain, or decreased fetal survival. However, there was a significant decrease in fetal body weight. Fetal malformations were not observed in rats. When male and female rats were treated with racemic citalopram (1.25, 4.8, or 16 mg/kg/day) and mated, the no-effect dose was 1.25 mg/kg/day. However, the no-effect dose in the rabbit was not established, since the maximum dose examined was 16 mg/kg/day.

In a teratology study conducted in the beagle dog, escitalopram was administered at doses up to 16 mg/kg/day for 14 days. There were significant decreases in maternal body weight and maternal body weight gain, and decreases in pup body weight, pup body weight gain, and pup survival. In the rat, when dam was treated with racemic citalopram (4.8, 12.8, or 32 mg/kg/day) throughout gestation, there were maternal body weight decreases, decreased maternal food consumption, and decreases in pup survival. These effects were dose-related and were not observed in the rabbit. In addition, adverse effects on the offspring were observed in the rat and were not observed in the rabbit. When female rats were treated with racemic citalopram (4.8, 12.8, or 32 mg/kg/day) throughout gestation and lactation, the offspring showed decreased maternal weight gain, decreased pup birth weight, decreased pup survival, and increased pup mortality. However, no pup effects were observed at a dose of 1.25 mg/kg/day.

In a recombinant inbred strain analysis, the rat pup provides a model to study the potential of offspring of SSRI users. Therefore, the progression of offspring can be evaluated in terms of their potential for offspring to develop a specific phobia. However, the results of this study would not be directly applicable to humans, since the potential for offspring to develop a specific phobia is not a direct consequence of exposure to an SSRI. Nevertheless, the results of this study suggest that the potential for offspring to develop a specific phobia is not a direct consequence of exposure to an SSRI.

In conclusion, the results of the studies conducted in the rat and human subjects suggest that exposure to an SSRI during pregnancy is not associated with an increased risk of developing a specific phobia. However, the results of these studies do not exclude the possibility of a direct association between exposure to an SSRI and the development of a specific phobia. Therefore, further studies are needed to determine whether exposure to an SSRI during pregnancy is associated with an increased risk of developing a specific phobia.
Mr. B was taking clonazepam when our work began, and discontinuing it would have increased his risk for seizures and the possibility of him seeking illicit benzodiazepines. Furthermore, discontinuing clonazepam might have thwarted an emerging therapeutic relationship that would become key to enhancing his motivation and exploring the antisocial and narcissistic traits that were limiting his recovery.

**Which would be best to treat Mr. B’s anxiety symptoms?**

- a) clozapine, at a higher dosage
- b) a different antipsychotic
- c) a different benzodiazepine
- d) an SSRI
- e) bupropion

I slowly increase the frequency of my sessions with Mr. B from monthly to bi-weekly to weekly. We focus on strengthening the therapeutic alliance, motivational enhancement, emotional expression, and verbal identification of feeling states. We explore anxiety symptoms and psychosis using cognitive-behavioral therapy techniques informed by psychodynamic aspects of his experience, with the goal of resuming his prior level of functionality, including employment.

I carefully and slowly change Mr. B’s medications. First I increase his clozapine to 300 mg/d in 150 mg divided doses in an attempt to cover the possibility of residual paranoia, and for anxiolytic sedation without introducing a new medication. However, Mr. B’s anxiety symptoms worsen, so I resume the baseline dosage (125 mg bid).

I choose not to switch to another antipsychotic because the risk for psychotic decompensation outweighs the potential benefits. I lower clonazepam to 2 mg/d in split doses. I teach Mr. B anxiety management techniques, including distraction, exposure, and anxiety tolerance training.

Because Mr. B refuses to start an SSRI for his anxiety symptoms, I prescribe bupropion and monitor him closely for dopamine agonism as evidenced by a re-emergence of psychosis. Once again, his anxiety symptoms worsen.

I stop bupropion and switch Mr. B to gabapentin, titrated to 400 mg tid. I chose this medication because of its sedation properties and relatively safe side effect profile. Mr. B was willing to try gabapentin—which was first approved to treat epilepsy—because he was afraid of having a seizure and also because it is not associated with sexual side effects. Furthermore, its GABA-mimetic actions made it a plausible alternative to replicate the benefits he was getting from clonazepam.

**Related Resource**


**Drug Brand Names**

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<thead>
<tr>
<th>Aripiprazole - Abilify</th>
<th>Gabapentin - Neurontin</th>
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<tr>
<td>Bupropion - Wellbutrin</td>
<td>Olanzapine - Zyprexa</td>
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<td>Clonazepam - Klonopin</td>
<td>Ziprasidone - Geodon</td>
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**Disclosure**

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

**Clinical Point**

Clozapine may be associated with or increase the incidence of OCD, panic, and agoraphobia.

**Bottom Line**

Case reports suggest clozapine may be associated with or increase the incidence of obsessive-compulsive disorder, panic, and agoraphobia. Treatment options for comorbid anxiety and schizophrenia include a combination of psychopharmacology and psychotherapy.
Mr. B tolerates gabapentin well and his anxiety symptoms are much more sporadic, shorter, and more easily controlled by conscious exercise. The content of his thoughts is less disastrous and less ego-dystonic. He feels less dysphoria associated with clozapine and does not need as much clonazepam. He overcomes his avoidance of all fear-provoking triggers except walking across bridges.

Mr. B and I explore issues of object relationships and intimacy, establishing emotionally significant relationships with others, and the association between these and his distrust and paranoia. We also investigate the relationship between his criminal activity and feelings of loneliness or lack of control. Mr. B is able to verbalize positive and negative feelings and to feel in cognitive control of them.

Mr. B continues his regimen of clozapine, clonazepam, and gabapentin. He moves to independent housing and applies for employment.

References

Drs. Miller and Noel respond
We agree that manic episodes can be debilitating for the patient. Marital strife, job loss, legal problems, financial extravagance, sexual indiscretion, and embarrassment are some potential adverse consequences of untreated mania.

However, it is uncommon to see patients in whom mania is the predominant state. While classical elated mania rarely is seen in clinical practice, patients with bipolar depression often describe concurrent manic symptoms such as racing thoughts without fully meeting DSM-IV-TR criteria for a mixed state. The therapeutic guidance we offer for such patients is to begin with a mood stabilizer (eg, divalproex) and an atypical antipsychotic (eg, aripiprazole), to assess thyroid status and supplement if necessary, and—as a last resort if these measures fail to achieve stability for the patient—to start an antidepressant (eg, sertraline) at a low dose.

Unlike bipolar depression with or without manic features, mania is relatively easy to treat and responds to virtually every antipsychotic—both old and new—most mood stabilizers, benzodiazepines and, in olden days, barbiturates.

In their prospective natural history studies of bipolar I and II patients, Judd et al1,2 found that depression—not mania or hypomania—is the predominant feature of bipolar disorder. Treatment of bipolar depression presents the greatest challenge to clinicians and is the subject of the controversy about use of antidepressants discussed in our article.

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References