Afraid to leave home

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

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.

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.[1] 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.[1]

Possible causes of unusually high rates of anxiety disorders in schizophrenia

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Table 1

Treatment options for comorbid schizophrenia and anxiety

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

CBT: cognitive-behavioral therapy; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor

include trauma history, delusional conviction and inflexibility of abstract thought,[2] and passive coping mechanisms.

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

- develop into more profound psychopathology
- 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.[3]

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.[4]

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

- increased hallucinations
- poor psychosocial function
- hopelessness.[5]

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).[6] Treatment options for comorbid anxiety and schizophrenia include psychopharmacology and psychotherapy (***Table 1***).

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.

continued

Clinical Point

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

Table 2

Anxiety: How to differentiate disorders and symptoms

Disorder/symptom	Keys to differential diagnosis
Panic disorder	≥2 panic attacks
Agoraphobia	Fear of 'no escape,' 'no options,' 'loss of control'
Generalized anxiety disorder	Constant worriers
Specific phobias	Fear of an object itself, not the response it will elicit within the patient
Obsessive-compulsive disorder	Patterns of intrusive thoughts followed by an action to undo or avoid anxiety
Residual paranoia	Feeling of insecurity associated with episodes of decompensation that have remained inter-episode
Drug-seeking behaviors	Secondary gain, in direct relationship to request for medication
Akathisia, other side effects	Inner restlessness that is constant, without trigger

Clinical Point

Higher anxiety levels in schizophrenia patients are associated with increased hallucinations

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)

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dose was also associated with maternal toxicity (clinical signs, decreased body weight gain). The developmental no-effect dose was 56 mg/kg/day. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of racemic citalopram of up to 16 mg/kg/day. Thus, teratogenic effects of racemic citalopram were observed at a maternally toxic dose 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) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose. The no-effect dose was 12.8 mg/kg/day. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses ≥ 24 mg/kg/day. A no-effect dose was not determined in that study. There are no adequate and well-controlled studies in pregnant women; therefore, escitalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pregnancy-Nonteratogenic Effects Neonates exposed to Lexapro and other SSRIs or SNRIs, 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*]. Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective, case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk. When treating a pregnant woman with Lexapro during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment [*see Dosage and Administration*]. Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication. **Labor and Delivery**-The effect of Lexapro on labor and delivery in humans is unknown. **Nursing Mothers**-Escitalopram is excreted in human breast milk. Limited data from women taking 10-20 mg escitalopram showed that exclusively breast-fed infants receive approximately 3.9% of the maternal weight-adjusted dose of escitalopram and 1.7% of the maternal weight-adjusted dose of desmethylcitalopram. There were two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a racemic citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of racemic citalopram by its mother and, in the second case, no follow-up information was available. Caution should be exercised and breastfeeding infants should be observed for adverse reactions when Lexapro is administered to a nursing woman. **Pediatric Use**-Safety and effectiveness of Lexapro has not been established in pediatric patients (less than 12 years of age) with Major Depressive Disorder. Safety and effectiveness of Lexapro has been established in adolescents (12 to 17 years of age) for the treatment of major depressive disorder [*see Clinical Studies*]. Although maintenance efficacy in adolescent patients with Major Depressive Disorder has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of escitalopram pharmacokinetic parameters in adults and adolescent patients. Safety and effectiveness of Lexapro has not been established in pediatric patients less than 18 years of age with Generalized Anxiety Disorder. **Geriatric Use**-Approximately 6% of the 1144 patients receiving escitalopram in controlled trials of Lexapro in major depressive disorder and GAD were 60 years of age or older; elderly patients in these trials received daily doses of Lexapro between 10 and 20 mg. The number of elderly patients in these trials was insufficient to adequately assess for possible differential efficacy and safety measures on the basis of age. Nevertheless, greater sensitivity of some elderly individuals to effects of Lexapro cannot be ruled out. SSRIs and SNRIs, including Lexapro, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [see *Hyponatremia*]. In two pharmacokinetic studies, escitalopram half-life was increased by approximately 50% in elderly subjects as compared to young subjects and C_{max} was unchanged [*see Clinical Pharmacology*]. 10 mg/day is the recommended dose for elderly patients [*see Dosage and Administration*]. Of 4422 patients in clinical studies of racemic citalopram, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. 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 responses between the elderly and younger patients, but again, greater sensitivity of some elderly individuals cannot be ruled out.

DRUG ABUSE AND DEPENDENCE: Abuse and Dependence; Physical and Psychological Dependence-Animal studies suggest that the abuse liability of racemic citalopram is low. Lexapro has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. The premarketing clinical experience with Lexapro did not reveal any drug-seeking behavior. However, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate Lexapro patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE: Human Experience-In clinical trials of escitalopram, there were reports of escitalopram overdose, including overdoses of up to 600 mg, with no associated fatalities. During the postmarketing evaluation of escitalopram, Lexapro overdoses involving overdoses of over 1000 mg have been reported. As with other SSRIs, a fatal outcome in a patient who has taken an overdose of escitalopram has been rarely reported. Symptoms most often accompanying escitalopram overdose, alone or in combination with other drugs and/or alcohol, included convulsions, coma, dizziness, hypotension, insomnia, nausea, vomiting, sinus tachycardia, somnolence, and ECG changes (including QT prolongation and very rare cases of torsade de pointes). Acute renal failure has been very rarely reported accompanying overdose. **Management of Overdose**-Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric evacuation by lavage and use of activated charcoal should be considered. Careful observation and cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive care. Due to the large volume of distribution of escitalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. There are no specific antidotes for Lexapro. In managing overdosage, 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.

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Box

Clozapine and OCD: The jury's still out

Clozapine has been associated with the emergence or worsening of obsessive-compulsive symptoms, although conclusions of studies that investigated this link are equivocal.[7] Most of the literature consists of isolated case reports, some of which advocate clozapine for treating obsessive-compulsive disorder rather than for its role as a causative agent.

A case report has associated clozapine with the development of panic disorder in a 34-year-old woman receiving 400 mg/d for paranoid schizophrenia.[8] She developed daily attacks of sudden chest compression, dizziness, fear of dying, and intense anxiety. These symptoms progressively improved and eventually resolved after she was switched to olanzapine, 10 mg/d. Clozapine also has been associated with cardiomyopathy presenting as panic attacks.[9]

- specific phobia (phobias were too broad and lacked fear of an object itself).

In addition, he does not seem to have residual paranoia, akathisia, or drug-seeking behavior. Based on numerous evaluations, Mr. B's anxiety symptoms seem most consistent with agoraphobia without panic (***Table 2, page 62***).

The phenomenology of his symptoms appears to be linked to his psychodynamic development, but previous therapists had not explored this. In addition, his relationships with his therapists, illness, and medications are complex. Mr. B is poorly engaged, lacks motivation toward recovery goals, and does not trust me. However, he holds high expectations of the potential damage or benefits of medication.

Mr. B's pharmacologic management is complicated by several relative contraindications. Clozapine may be associated with or increase the incidence of OCD, panic, and agoraphobia (***Box***).[7-9] Combining clonazepam with clozapine is not recommended because of the possibility of intense sedation. Even so, in a patient with a history of substance use and illegal activity—such as Mr. B—cautious use of benzodiazepines is warranted to avoid addiction or drug diversion.

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 biweekly 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).

Related Resource

- Garrett M, Lerman M. CBT for psychosis for long-term inpatients with a forensic history. Psychiatr Serv. 2007;58(5):712-713.

Drug Brand Names

Aripiprazole • Abilify
Bupropion • Wellbutrin
Clonazepam • Klonopin
Clozapine • Clozaril
Gabapentin • Neurontin
Olanzapine • Zyprexa
Ziprasidone • Geodon

Disclosure

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

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.

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.

continued

TREATMENT An effective drug

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.

Clinical Point

Mr. B was willing to try gabapentin because he feared seizures and the drug lacked sexual side effects

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predominant state and who no longer want to live with minds that are bombarded day and night with inescapable, racing thoughts?

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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 al[1,2] 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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