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IN THIS ISSUE

Focus of the Month:
Psychotic Depression

Learning Objectives

After reading these articles, you should be able to:

1. Evaluate the efficacy of quetiapine to prevent and treat bipolar depression.
2. Describe how to diagnose psychotic depression.
3. Identify appropriate clinical scenarios for benzodiazepines.
4. Summarize some of the current research findings on psychiatric treatment.

Quetiapine Reconsidered

Paul Riordan, MD. Assistant Consulting Professor of Psychiatry, Duke University.

Dr. Riordan has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

It is the best of drugs; it is the worst of drugs. Quetiapine (Seroquel) has benefits in some disorders that are unmatched by other medications, but it is also one of the most difficult antipsychotics to tolerate. In this article, I'll look at where this medication fits and whether its numerous off-label uses are justifiable, including PTSD, generalized anxiety, insomnia, and delirium.

Different effects at different doses

Quetiapine is challenging to use because it acts differently at different doses. Why? It has markedly distinct binding affinities for different receptors. At low doses (25–150 mg), quetiapine binds first to the histamine 1 receptor, which drives its sedative properties. Unfortunately, quetiapine also has alpha 1 adrenergic and muscarinic 1 antagonism ("anticholinergic") properties in this range, which contribute to sedation

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Highlights From This Issue

Feature article
Quetiapine is one of the more effective treatments for bipolar depression, helping sleep and anxiety as well as mood, but it also has some major drawbacks.

Q&A page 1
One in three cases of psychotic depression are missed, and the usual treatments for depression are not likely to work in these cases.

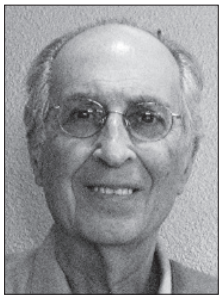
Q&A page 6
Benzodiazepines need not be feared. They are risky in some situations (eg, when combined with opioids or used in the elderly) but very effective in others (eg, panic disorder).

Q&A With the Expert

Psychosis During Depression
Conrad M. Swartz, MD, PhD

Professor Emeritus, Southern Illinois University, Springfield, IL.

Dr. Swartz has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.



TCPR: Is psychotic depression difficult to diagnose?

Dr. Swartz: Psychotic depression is often missed and often misdiagnosed. A study of hospital units at four academic medical centers found that one in three cases of psychotic depression were missed (Rothschild AJ et al, *J Clin Psychiatry* 2008;69(8):1293–1296). This is important because these patients aren't going to respond very well to common antidepressants like SSRIs, and they may not respond well to medication at all.

TCPR: What gets in the way of detecting psychotic depression?

Dr. Swartz: Number one is subjectivity. All of the symptoms—depression and hallucinations or delusions—depend on patients' self-reports, and the DSM encourages a kind of bureaucratic accounting of them. But patients cannot reliably identify or describe their own symptoms,

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particularly in psychosis. Even in nonpsychotic disorders where self-awareness is relatively intact, like anxiety disorders, I find that patients are unable to recognize improvements that are visible to me in their mental status—as when they are more relaxed, no longer fidgeting, and no longer hyperventilating.

TCPR: How can we move beyond self-report?

Dr. Swartz: Mental status and behavior. In psychotic depression, you may notice a complete rigidity of thought or poverty of thought in the interview. You may pick up on hallucinatory or delusional behaviors through the relatives.

TCPR: How do you screen for psychotic depression?

Dr. Swartz: I ask, "Do you feel guilty about anything? Do you believe you're sick, physically sick? Do you believe the symptoms you have are due to a physical illness? Do you think about death a lot, and what are your thoughts about it?" Nihilism, especially in elderly patients, is a common symptom of psychotic major depression with melancholic features. Patients believe they're sick or dead or guilty of some horrible thing they can't put into words.

TCPR: Suppose the patient answers, "Yeah, I feel sick. I feel empty. I feel like I may as well be dead." How would you proceed?

Dr. Swartz: I would tease it out more and look for cognitive rigidity or behavioral evidence of delusions. "You feel sick, but are you sick? And what have you been doing to figure out the cause of the sickness?" Often patients do odd things to prove their sickness. They hound doctors. They collect urine or other bodily substances. I am trying to identify something out of the range of common thought and behavior, so if they feel guilty, I might ask, "What punishment do you deserve?" If the patient says, "I deserve death; I am dead," that would be a psychotic answer.

"Every symptom that occurs in schizophrenia can be seen in mood disorders, including unusual mannerisms and inappropriate laughter. The difference is in the course. In mood disorders, the symptoms fully resolve, while in schizophrenia the course is chronic."

Conrad M. Swartz, MD, PhD

TCPR: Which symptoms tend to be more prominent—the psychosis or the depression?

Dr. Swartz: It can go either way, and I'm glad you asked that because there are two common types of psychotic depression. I call them depression-dominant and psychosis-dominant. Both can be misdiagnosed. In the depression-dominant, the psychotic features may not be readily apparent, and the patient is often misdiagnosed as having major depression. In the psychosis-dominant, it's the mood symptoms that need to be teased out. When they are missed, the patient is usually misdiagnosed with delusional disorder or schizophrenia, or the psychotic symptoms might be misunderstood as dissociation, conversion disorder, or PTSD.

TCPR: Can you describe a psychosis-dominant patient?

Dr. Swartz: A woman believed she was being electrocuted by people who were spying on her. She felt electric shocks in her body, and she complained about this obsessively, so it dominated all conversation with her. But once I reviewed the symptoms of major depression, it became clear she had them. She experienced no pleasure. Her sleep was disrupted. Her appetite and energy were low.

TCPR: What if she was just worn down by the intense delusions—too scared to sleep, too distracted to eat or enjoy anything?

Dr. Swartz: That's psychological reasoning, which is valid in its place, but it doesn't apply to psychiatric diagnosis. Signs and symptoms have to be assessed in their own right, regardless of what we may think about their cause or context.

TCPR: Tell us about a typical patient with depression-dominant psychosis.

Dr. Swartz: Here the depression is usually a melancholic type, and the psychosis usually presents as delusions with a depressive theme. Themes of sickness, guilt, and nihilism are common, as in an emaciated young man who quit eating because he believed his body could not metabolize food, or an elderly woman who spent two days in a bathtub believing she was too sick and weak to get out. Hallucinations are less common. Now, when I say "melancholic," I'm talking about classical melancholic depression, and the DSM criteria do not capture the classical definition very well (Chelminski I et al, *J Clin Psychiatry* 2000;61(11):874–875).

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TCPR: In DSM-5, melancholia means a total loss of pleasure along with early-morning awakening, low appetite, excessive guilt, and psychomotor changes. How is that different from classical melancholia?

Dr. Swartz: What I'm referring to is impairment of problem solving, inability to understand complexity, and visible apathetic behavior, including withdrawal from pleasurable activities. Their faces are unreactive—lacking in spontaneous expression—and they lack spontaneous thought. Sometimes they have a very interesting physical sign: the omega sign. This is the appearance of the Greek letter Ω between the eyes just above the nose.

TCPR: Some of that sounds like cognitive symptoms of psychosis: thought blocking, concrete and distorted thinking.

Dr. Swartz: To clarify, we often see those cognitive symptoms in psychotic patients, but they are not psychotic symptoms, and we see them in nonpsychotic disorders as well. In the past, some psychiatrists used the term "psychosis" to describe those cognitive symptoms, like the Maudsley group in the UK back in the 1970s, but that is not the mainstream view. Psychotic depression has delusions or hallucinations, not simply distorted or impaired cognition.

TCPR: How do those delusions and hallucinations differ from the psychosis we see in schizophrenia?

Dr. Swartz: Actually, schizophrenia can be difficult to distinguish from mood disorders. Every symptom that occurs in schizophrenia can be seen in mood disorders, including unusual mannerisms and inappropriate laughter. The difference is in the course. In mood disorders, the symptoms fully resolve, while in schizophrenia the course is chronic. How you define "chronic" is a matter of experience and judgment. Personally, I favor two to three years rather than six months.

TCPR: Why not six months?

Dr. Swartz: Because mood episodes often last that long or more. The natural history of psychotic and melancholic depression is about one year, and the average manic episode lasts six months if untreated or if nonresponsive to treatment. If these cases are misdiagnosed as schizophrenia and the psychiatrist prescribes an antipsychotic, then it's likely the patient will stay on that drug for the long term. Few clinicians will stop the drug, because it's just too risky if the patient carries a schizophrenia diagnosis.

TCPR: OK, so that might be one clue between the two. Does family history ever help you distinguish between schizophrenia and psychotic depression?

Dr. Swartz: I would have to say family history is not reliable. It distinguishes the presence of severe psychiatric disturbances, but it doesn't help you identify which disturbance it is. I think the twin studies have shown remarkable discordance for identical twins where one has schizophrenia and the other one is seriously ill with a mood disorder and not schizophrenia.

TCPR: Another disorder with psychotic-like symptoms is PTSD: flashbacks, paranoia, and dreams that intrude on waking life. How do you distinguish that from psychotic depression?

Dr. Swartz: We do see psychotic symptoms in PTSD, in an estimated 15%–60% of cases, but I do not think PTSD is a psychotic illness. Mark Zimmerman's group found that nearly all the psychotic symptoms in PTSD could be better explained by comorbidities that can cause psychotic symptoms, such as schizophrenia, bipolar, substance use, and borderline personality disorder (Gaudiano BA and Zimmerman M, *Br J Psychiatry* 2010;197(4):326–327). On the other hand, I often see PTSD symptoms in people with psychotic depression, and I think that's something we need to pay attention to.

TCPR: Tell us about that.

Dr. Swartz: The experience of having a serious mental illness like psychosis is traumatic. Being hospitalized, stigmatized, disempowered, losing your family, losing your job, losing your identity. Childhood trauma is also very common in this population. Patients with psychotic depression are two or three times more likely to have experienced physical or sexual abuse in their childhood than those with nonpsychotic depression (Gaudiano BA and Zimmerman M, *Acta Psychiatr Scand* 2010;121(6):462–470).

TCPR: How do you address that?

Dr. Swartz: Psychotherapy and antianxiety medication. There is some evidence that psychotherapy helps psychotic depression, but I suspect that it's treating these PTSD symptoms. Sometimes patients with psychotic depression tell me they are still depressed after a course of ECT, but it's very different from the depression they came in with. It's PTSD from the illness.

TCPR: Anything else we should look for when a patient has psychotic depression?

Dr. Swartz: Well, psychotic depression is a marker for bipolar disorder, so you'd want to look carefully for past manias. In the elderly, you should think about vascular depression, particularly if it's their first episode. Vascular depressions are usually melancholic, though not necessarily psychotic. So, new-onset melancholia is a hint for the clinician to look for cardiac risk factors, blood pressure, and cholesterol. Medical morbidity is high in psychotic depression, and they have twice the rate of death compared with severe nonpsychotic depression (Vythilingam M et al, *Am J Psychiatry* 2003;160(3):574–576). Their risk of suicide is also much higher (Gaudiano BA et al, *Depress Anxiety* 2009;26(1):54–64).

TCPR: Why is that?

Dr. Swartz: These individuals are more disturbed, more hopeless, and more desperate than other patients. They can't see past their delusions, and their judgment is more impaired.

TCPR: What's your first-line treatment for psychotic depression?

Dr. Swartz: It's pretty frustrating to treat psychotic depression with medications. Tricyclics are a good choice, and in women I'll often augment with triiodothyronine (Cytomel) 25 mcg QD. There's some evidence that thyroid augmentation works better in women, and I've seen good results. I also use bupropion (Wellbutrin). If the antidepressants do not work, I'll add

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lithium, which has open-label evidence as augmentation in psychotic depression (Birkenhäger TK et al, *J Clin Psychopharmacol* 2009;29(5):513–515). But the treatment I've relied on the most is ECT (Petrides G et al, *J ECT* 2001;17(4):244–253); most of these patients are receptive and sign consent forms to receive ECT.

TCPR: The 2010 APA guidelines recommend lithium augmentation for psychotic depression, but they seem to favor antipsychotic augmentation.

Dr. Swartz: For me antipsychotics are second or third line.

TCPR: Why is that?

Dr. Swartz: If you read those guidelines closely, they admit the combination may be no better than an antidepressant alone. The only paper they cite in support of the combination is a small randomized controlled trial of 18 patients (Spiker DG et al, *Am J Psychiatry* 1985;142(4):430–436). The other papers they cite—which include two meta-analyses and a randomized controlled trial—actually concluded that antidepressant monotherapy was just as effective as the antipsychotic combination (Wijkstra J et al, *Br J Psychiatry* 2006;188:410–415). Now, I think antipsychotics can improve symptoms, particularly symptoms of depression, which they are FDA approved for in low doses. And I will use antipsychotics if there is a risk of violence or suicide and ECT is not available. But my concern is that antipsychotics don't improve functioning and might even worsen it.

TCPR: What do you mean?

Dr. Swartz: They can cause frontal lobe syndromes: apathy, difficulty solving problems or dealing with complexity in relationships. These patients have trouble multitasking and taking initiative. They become dependent, passive, and quiet. We see these syndromes in case reports, and there are imaging studies showing a reduction in frontal lobe activity with antipsychotic use (Swartz C and Walder M, *Ann Clin Psychiatry* 1999;11(1):17–19; Cohen RM et al, *Arch Gen Psychiatry* 1997;54(5):481–486). It's not something researchers look for in clinical studies, but some antipsychotic trials mention "personality changes," and this is what I think they are talking about.

TCPR: I'm familiar with those side effects, but I thought they only happened at high doses.

Dr. Swartz: Yes, and the studies are pretty clear that to treat psychotic depression you need high doses of antipsychotics, so not the low doses you use in depression. We're talking about the doses you'd use in acute schizophrenia. Anyway, frontal impairment is just one reason to avoid them. There's also the metabolic and cardiovascular risks, which this population is already vulnerable to. Then there's the possibility of *tardive psychosis,* which is where chronic antipsychotic use upregulates the D_2 receptors and withdrawal of the antipsychotic then causes a rebound psychosis. There are case reports of psychosis developing in people after abrupt withdrawal of an antipsychotic, even in those who were taking metoclopramide and had no history of psychiatric problems (Lu ML et al, *Ann Pharmacother* 2002;36(9):1387–1390).

TCPR: Thank you for your time, Dr. Swartz.

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Quetiapine Reconsidered

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and cause the adverse side effects of dry mouth, dizziness, orthostatic hypotension, constipation, and urinary hesitancy.

At higher doses, those side effects start to plateau and more therapeutic properties kick in. At doses of 150–300 mg, quetiapine has serotonergic and noradrenergic properties, which is why it shines as an antidepressant in that range. Finally, quetiapine has antipsychotic properties, but only at doses of at least 300 mg, when it starts to antagonize the dopamine 2 receptor. This is why the average dose in schizophrenia is around 500 mg (Leucht S et al, *Am J Psychiatry* 2020;177(4):342–353).

Mood and anxiety disorders

In mood disorders, quetiapine stands out as one of the two atypical antipsychotics with efficacy in both the manic and depressive phases, the other being cariprazine (Vraylar). But what really sets quetiapine apart is its efficacy in bipolar depression, which is about twice that of cariprazine's, judging by their numbers needed to treat (NNT) of 6 vs 11. Lumateperone, lurasidone, and olanzapine-fluoxetine combination also have robust efficacy in bipolar depression, but these three lack evidence in mania (Kadakia A et al, *BMC Psychiatry* 2021;21(1):249).

When it comes to side effects, however, quetiapine is one of the worst offenders. Patients gained an average of 2.6 pounds in trials lasting less than two months, as compared to lurasidone at 0.53 pounds and aripiprazole at 0.44 pounds. Only olanzapine did worse at 6.35 pounds. Over the long term, one in five patients gained more than 7% of their body weight after nine or more months on quetiapine (Bak M et al, *PloS One* 2014;9(4):e94112).

In acute mania, antipsychotics are usually favored over lithium when rapid action is needed or when mixed features are prominent. Quetiapine's antimanic efficacy is about average for the antipsychotic family, but some consider it first line for its ability to prevent postmanic depression. That's an important consideration, as depression is much more common than mania throughout the lifespan in this illness. Surprisingly, no other antipsychotic has robust evidence in preventing bipolar depression, with the possible exception of asenapine (Szegedi A et al, *Am J Psychiatry* 2018;175(1):71–79).

In the maintenance phase of bipolar disorder, quetiapine works particularly well when combined with lithium, where it lowers the odds of recurrence four-fold over lithium alone (Nestsiarovich A et al, *Eur Neuropsychopharmacol* 2022;54:75–89). Some of these benefits may be due to quetiapine's effects on sleep, which are

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more than just sedating. Quetiapine is the only atypical antipsychotic with evidence to improve sleep *quality*.

Unipolar depression

In unipolar depression, quetiapine has FDA approval only as an augmenting agent, not as monotherapy. It is mildly helpful at doses of 200–300 mg with a small effect size of 0.32 and an NNT of roughly 7 (Davies P et al, *Cochrane Database Syst Rev* 2019;12(12):CD010557). There was a stark difference in dropout rates between the high and low doses in the unipolar studies, with no increase in dropouts at 150 mg/day but an 82% increased dropout risk at 300 mg/day.

Anxiety

In generalized anxiety disorder, a meta-analysis showed that quetiapine had the largest effect of all medications as measured by the Hamilton Anxiety Rating Scale, edging out escitalopram, duloxetine, and even benzodiazepines. However, people taking quetiapine were also more likely to drop out of the study, with a 44% increased likelihood compared to placebo (Slee A et al, *Lancet* 2019;393(10173):768–777). That side effect burden caused the FDA to decline quetiapine's application for approval in generalized anxiety, and we would only consider it third or fourth line for severe cases.

However, these anxiolytic properties are more useful in bipolar disorder, where there is a paucity of therapies for comorbid anxiety. Quetiapine reduced anxiety that was comorbid with a mood disorder in 20 out of 27 placebo-controlled trials (Crapanzano C et al, *J Clin Psychopharmacol* 2021;41(4):436–449). This benefit may extend to OCD, according to a small placebo-controlled trial that tested quetiapine 350 mg in patients with bipolar I disorder and OCD (Sahraian A et al, *CNS Spectr* 2021;1–5).

Schizophrenia

In schizophrenia, quetiapine is favored more for its relative lack of akathisia and Parkinsonism than its efficacy. Its effect size is in the medium range (0.4) but smaller than the effect size for clozapine (0.9), olanzapine (0.55), and risperidone (0.55). In addition, its metabolic profile is unfavorable; only clozapine and olanzapine have worse metabolic effects. Anticholinergic burden is another problem, particularly in the higher doses used for schizophrenia, as these side effects are linked to cognitive impairment in schizophrenia (Joshi YB et al, *Am J Psychiatry* 2021;178(9):838–847).

Quetiapine: Indications and Dosing

Indication	FDA Approved?	Target Dose/Day	When to Use
Augmentation for unipolar depression	Yes	150–300 mg	Best used with depression with anxious features that persist despite first-line treatment with SSRI/SNRI
Bipolar depression	Yes	300 mg	If no response to lithium and lurasidone or if significant comorbid anxious features
Bipolar maintenance	Yes	600 mg	Approved when combined with lithium or divalproex; lower doses may be effective for bipolar II disorder
Bipolar mania	Yes	600 mg (400–800 mg)	Best for mixed features and insomnia, as well as to prevent future episodes of depression
Delirium	No	50–200 mg	Avoid if possible; no antipsychotics have been shown to have benefit for delirium
Dementia with behavioral disturbance	No	50–200 mg	Avoid if possible; given side effects and anticholinergic burden, consider only as fourth or fifth line after trials of escitalopram, risperidone, carbamazepine, and valproic acid
Generalized anxiety disorder	No	150–300 mg	Given side effects, consider third/fourth line after trials of SSRIs/SNRIs and pregabalin
PTSD	No	150–400 mg	Given side effects, consider third or fourth line after a trial of two of the following: sertraline, venlafaxine, fluoxetine, and paroxetine
Schizophrenia	Yes	400–600 mg	Best for patients with extrapyramidal side effects who cannot tolerate clozapine or olanzapine

PTSD, delirium, and behavioral symptoms of dementia

While quetiapine is often used off-label for PTSD, delirium, and dementia, the quality of evidence for these indications is weak. Two placebo-controlled trials in delirium were negative, and quetiapine had little benefit in psychosis related to Parkinson's dementia (Nikooie R et al, *Ann Intern Med* 2019;171(7):485–495; Jethwa KD et al, *BJPsych Open* 2015;1(1):27–33). Quetiapine fared a little better in PTSD, where it improved reexperiencing and hyperarousal (but, surprisingly, not sleep) in a randomized trial with 80 participants, most of whom were combat veterans (Villarreal G et al, *Am J Psychiatry* 2016;173(12):1205–1212).

How to use

In the outpatient setting, slowly titrating quetiapine by 50 mg every three to four days helps mitigate its most common side effects of somnolence, dry mouth, and dizziness. It's best to stick to the target dose for each indication (see table), as higher doses led to more dropouts, particularly in the elderly. In the inpatient setting, going faster by 100 mg/day is often necessary to treat mania and psychosis. Avoid using with carbamazepine, which can render quetiapine inert, and watch for a little-known interaction with lamotrigine, which can reduce quetiapine levels by up to 30%.

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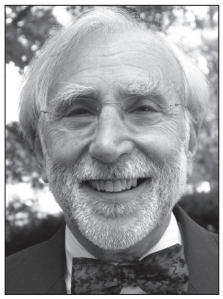
Q&A With the Expert

Benzodiazepines: A Reevaluation of Their Benefits and Dangers



Carl Salzman, MD

Professor of Psychiatry at Harvard Medical School and past chairman of the American Psychiatric Association Benzodiazepine Task Force.

Interview by Marcia L. Zuckerman, MD. Board member of The Carlat Psychiatry Report; *outpatient psychiatrist, Hallmark Health, Medford, MA; clinical assistant professor in psychiatry, Tufts School of Medicine. Edited by Chris Aiken, MD. Editor-in-Chief of* TCPR; *practicing psychiatrist, Winston-Salem, NC.*

Drs. Salzman, Zuckerman, and Aiken have disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

TCPR: Benzodiazepines were the most commonly prescribed drug—of all drugs—in the 1970s. Are they still that popular?

Dr. Salzman: I think benzodiazepines are still widely used, both appropriately and inappropriately. The SSRIs were supposed to replace the benzos for long-term treatment of anxiety, but while the use of these antidepressants has increased in anxiety disorders, the use of benzos has barely fallen.

TCPR: Why is that?

Dr. Salzman: I'm speculating, but one reason is that the benzos are more potent anxiolytics. In generalized anxiety disorder, their effect size is in the medium range (0.5) compared to SSRIs, which have a small effect size of 0.3 (Gomez AF et al, *Expert Opin Pharmacother* 2018;19(8):883–894). The second reason is the benzos work faster. Finally, they are helpful for sleep. They may not always be the best drugs for sleep, but they are reliable.

TCPR: On the other hand, physicians seem to have more negative attitudes about benzos today than they did in the 1970s.

Dr. Salzman: Yes. I call it "benzo hysteria." It's very hard to get a doctor to prescribe a benzodiazepine, though on their own they are almost never fatal in overdose. Some benzo use is inappropriate: the wrong patient, the wrong dose, the wrong duration, or the wrong interaction with other drugs like alcohol, opioids, or other sedative-hypnotics. But if you take away those situations and just look at the legitimate medical use of benzos, these are good drugs and they are effective. We know the pharmacology. We know how they work in the brain. They are sedative-hypnotics and can cause dependence, but that depends on the dose and duration.

TCPR: What do you consider the appropriate dose and duration for benzodiazepines?

Dr. Salzman: Once you're above 3 mg/day of clonazepam, you begin to think, "Why does this person need more? Am I missing something?" Or when their dose keeps increasing and you're getting calls saying, "I'm still anxious and can't sleep." We don't like to use benzodiazepines long term, but there are many people who suffer from serious chronic anxiety that is not well managed by antidepressants but is well managed by modest doses of a benzo. Benzos are also useful for short-term control of agitation, and they are very good for panic disorder and phobias. Two are FDA approved in panic disorder—alprazolam and clonazepam—and we have the best data supporting their use in panic disorder.

TCPR: Do you see tolerance with long-term use?

Dr. Salzman: Tolerance develops to the sedative effect, but usually not to the anxiolytic effect. It depends on the patient. If the patient regularly uses alcohol or any other sedative-hypnotic, you want to be very careful. I don't recommend long-term benzos for patients who drink on a daily basis, but if they have a drink on Saturday night at dinner, that's not a prohibition—though it depends how much they drink on Saturday night.

TCPR: What would be too much for you?

Dr. Salzman: More than one cocktail or a glass or two of wine a day for most people, unless they are elderly or in poor health—then any alcohol would be too much. I would ask if they ever mixed the two and what happened, and I would warn about the interaction with alcohol. At high levels the two can be fatal in overdose, and at moderate levels both of them increase the risk of car accidents.

TCPR: Are there any other populations where benzodiazepines would give you pause?

Dr. Salzman: Yes, I would try not to prescribe in borderline and antisocial personality disorders. Elderly patients and those with chronic obstructive pulmonary disorder are also high risk. I would avoid in patients with substance use disorders, even when they are in recovery. A history of an opioid use disorder or of accidental overdose on opioids would be a red flag. Opioids and benzos are risky together, but it isn't that people who are taking benzos then add opioids. Instead, it's the other way around: People who are taking opioids add the benzos. This is because sedative-hypnotics increase the high of an opioid, which is well known. Any sedative-hypnotic will do it, and barbiturates will do it as well.

TCPR: What if they are legitimately taking a benzodiazepine for anxiety, and then have an acute pain situation that requires an opioid? Or if they have chronic pain from rheumatoid arthritis or a congenital deformity, along with social anxiety?

Dr. Salzman: That's still a risk. If benzodiazepine therapy is appropriate, I'd want the pain doctor to prescribe both in those cases. I'd call the doctor and explain, "The patient needs some benzodiazepines. Could one doctor prescribe both drugs so that you can keep track of dosing and whether there's potential abuse?"

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TCPR: What about patients with a history of alcohol use disorder?

Dr. Salzman: I do prescribe to some patients who have a distant history of an alcohol use disorder and are active in AA. We don't have a lot of data in this group, but an outpatient psychiatric clinic followed people with past alcohol abuse who were prescribed benzos for up to 12 years and found no problems with tolerance or relapse (Mueller TI et al, *Alcohol Clin Exp Res* 2005;29(8):1411–1418).

TCPR: They didn't tend to relapse into alcohol or benzo use?

Dr. Salzman: Right. Now, I should warn you about another group of patients. As benzos and opioids have come under more regulatory scrutiny, we're seeing more patients referred by primary care physicians who no longer feel comfortable prescribing benzodiazepines to those patients. I know one psychiatrist whose office got flooded with these cases, and sometimes the patients were very loud and even threatening. Some of the prescribing was appropriate, but many of the patients were just angry and unhappy about their lives, and they were demanding Klonopin. They abused alcohol; they had bad marriages; they were out of work. He put up a sign in his waiting room that said, "This doctor does not prescribe Klonopin for any reason." Over the next couple of weeks, the office emptied out, and the people who remained were legitimate patients for benzodiazepines.

TCPR: A lot of people are stressed out and unhappy. They may not have a genuine psychiatric disorder, but what is the harm if a benzo makes them feel better?

Dr. Salzman: Well, it might make them feel better, but then they start to increase the dose, and pretty soon you have somebody taking 10 mg/day of clonazepam. That person needs help managing their stress, and a benzodiazepine won't do that.

TCPR: What are the risks in the elderly?

Dr. Salzman: Older patients are more susceptible to falls, traffic accidents, and respiratory suppression on benzos. Whether benzos raise the dementia risk is less clear.

TCPR: Why are you less worried about the dementia risk?

Dr. Salzman: There were studies showing an association, but that doesn't prove causality, and more recent studies have cast doubt. In a prospective follow-up study with 3,434 patients, the risk of dementia actually went down as the dose exposure went up (Gray SL et al, *BMJ* 2016;352:i90). Another study with 616,256 patients found the same risk of dementia in people taking benzodiazepines as in those on antidepressants, suggesting that these meds are just a marker for another variable, like having a psychiatric disorder (Baek YH et al, *J Am Med Dir Assoc* 2020;21(2):201–211.e2). In the early phases, dementia can present with anxiety and depression, and that can confound the association. Recently a Danish group tried to get around that by removing patients from their study who developed dementia within the first two years of starting the benzo, as those were more likely to be cases where early signs of dementia were misdiagnosed as anxiety or depression. They found no association between benzos and dementia (n = 235,465; Osler M and Jørgensen MB, *Am J Psychiatry* 2020;177(6):497–505).

> **"Some benzo use is inappropriate: the wrong patient, the wrong dose, the wrong duration, or the wrong interaction with other drugs. But if you take those away and look at the legitimate medical use of benzos, these are good drugs and they are effective."**
>
> Carl Salzman, MD

TCPR: How do you take people off benzodiazepines?

Dr. Salzman: A slow taper is important. If the patient is taking 2 mg/day of clonazepam, you would go down by, say, 0.25 mg per week until you get to 1 mg. Then at 1 mg you've got to go even slower. The reason is that the receptors where benzos work are beginning to upregulate and are becoming more sensitive to the withdrawal of the drug. The brain makes benzodiazepines, and it stops doing so when you start prescribing, so you've got to give the brain a chance to reestablish its normal benzodiazepine level while you're tapering. So taper slowly.

TCPR: Are you saying the brain produces benzodiazepines on its own?

Dr. Salzman: Yes, the term for these is "endozepines." We don't know exactly what they are, but several compounds have been put forth as candidate endozepines that modulate the benzodiazepine receptor (Tonon MC et al, *Pharmacol Ther* 2020;208:107386).

TCPR: Back to withdrawal. What do you do when you need to lower by smaller increments than you can get to by cutting the pill in half?

Dr. Salzman: Alprazolam, diazepam, and lorazepam are available as liquids. For others, like clonazepam, patients can grind the 0.5 mg tablet into a fine powder with a mortar and pestle, or just spill out the contents for benzos that come as capsules. Next, they dissolve the solids into a measured amount of water—say, four ounces. You'd need to guide them with the ratio of pills to liquid to get the right dose, then use that to continue a very slow taper, adjusting as you evaluate how tolerable the withdrawal symptoms are.

TCPR: Do you ever use other medications to help with benzo withdrawal?

Dr. Salzman: They aren't very helpful, but sometimes I use propranolol. It reduced the severity of withdrawal symptoms in a double-blind study (60–120 mg/day). Some people use gabapentin (Neurontin), though there's not much literature on that, but pregabalin (Lyrica) improved sleep in a controlled trial of benzodiazepine withdrawal (200–400 mg/night). There are also small controlled studies supporting carbamazepine at doses of 200–800 mg/day (Tyrer P et al, *Lancet* 1981;1(8219):520–522; Rubio G et al, *Eur Addict Res* 2011;17(5):262–270; Di Costanzo E et al, *Minerva Psichiatr* 1992;33(4):301–304).

TCPR: Do you have a go-to benzo?

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Dr. Salzman: I don't have a favorite. Some people do better on different benzos for reasons we don't understand. I prefer lorazepam for sleep and for short-term use. I also prefer lorazepam in the elderly as it doesn't have hepatic drug interactions and doesn't accumulate metabolites. I'm less likely to use a benzodiazepine with a long half-life like clonazepam in an elderly patient, because that can raise the fall risk.

TCPR: What do you warn patients about before starting a benzo?

Dr. Salzman: I tell them that the drug can interfere with driving. It slows their reaction time, particularly when the serum levels peak, which is 30–60 minutes after taking it. That's still true if they've been on a steady dose for a long time, so they wouldn't want to drive when the level is at its peak, although there is also evidence that high anxiety can impair driving. Next, I say, "If you take this drug on a steady basis, you're probably going to develop a physiologic dependence—not an addiction, a dependence—so you must never stop it abruptly unless there's an emergency or under a doctor's supervision. If you want to stop the drug, call me and we'll work out a taper." Finally, I warn them not to mix it with opioids, other sedative-hypnotics, or alcohol.

TCPR: Final thoughts?

Dr. Salzman: Don't be afraid of benzos. They are among the safest drugs we have. Even in overdose, they are safer than most psychiatric medications, unless they are taken with another sedative-hypnotic like alcohol or an opiate or the patient has chronic obstructive pulmonary disorder.

TCPR: Thank you for your time, Dr. Salzman.

❖ ❖ ❖

New Feature!

Uncommon Tips: Which Is Better—Citalopram or Escitalopram?

Editor's note: We're pleased to introduce the new feature "Uncommon Tips." In this series, Dr. Aiken will discuss little-known pearls about commonly used medications. The series starts with a comparison of citalopram and escitalopram.

The rivalry between these two SSRIs began in 2002 when the Lundbeck pharmaceutical company split citalopram (Celexa) into its two mirror-image enantiomers, releasing the active enantiomer (escitalopram) as Lexapro and leaving behind the inactive one (R-citalopram). With Celexa's patent about to expire and Lexapro's extended for another decade, Lundbeck scurried to convince doctors that escitalopram was the better choice.

Lundbeck argued that R-citalopram was not a neutral bystander but actually interfered with escitalopram's ability to raise serotonin by blocking it at the serotonin transporter. The evidence came from animal studies, but it seemed confirmed by a series of head-to-head clinical trials showing slightly higher efficacy and faster onset with escitalopram than citalopram in major depression and panic disorder (Sánchez C et al, *Psychopharmacology (Berl)* 2004;174(2):163–176).

How well has that claim held up? Marginally. Although most of the 10 trials comparing the two SSRIs favor escitalopram, the difference is slight. When narrowed down to equidose comparisons (eg, citalopram 40 mg vs escitalopram 20 mg), only 5%–10% of patients have a meaningful response on escitalopram that they wouldn't have experienced on citalopram (Trkulja V, *Croat Med J* 2010;51(1):61–73).

Instead, a different reason to prefer escitalopram has arisen from the FDA, which placed a warning about QTc prolongation on citalopram in 2011. This risk is dose dependent, so the FDA capped citalopram's dose at 40 mg/day, or 20 mg/day in patients who are (1) over age 60; (2) poor metabolizers at the CYP2C19 enzyme that clears citalopram; or (3) taking strong CYP2C19 inhibitors like omeprazole or cimetidine.

However, the FDA's dosing guidelines can have unintended consequences. When the VA attempted to lower citalopram into the acceptable range for 35,848 veterans, they saw a sharp increase in all-cause hospitalizations and deaths without any decline in arrhythmias (Rector TS et al, *Am J Psychiatry* 2016;173(9):896–902). What, then, is an FDA-abiding clinician to do?

One approach is to switch to escitalopram, which is free of this FDA warning because it only causes about half as much QTc prolongation as citalopram at equivalent doses (citalopram 60 mg = 18.5 ms; escitalopram 30 mg = 10.7 ms). Even though actual cardiac problems are very rare on either drug, there is evidence that this difference in QTc interval has a real-world effect on cardiac outcomes. Two studies that examined large, diverse populations found higher rates of cardiac arrest and serious arrhythmias with citalopram than escitalopram (Qirjazi E et al, *PLoS One* 2016;11(8):e0160768; Weeke P et al, *Clin Pharmacol Ther* 2012;92(1):72–79).

If you choose this route, I'd suggest a gradual cross-taper, such as adding in escitalopram at 5 mg and titrating to half the original citalopram dose while tapering citalopram off over two to four weeks. We don't know much about the long-term effects of citalopram's R-enantiomer, and sudden shifts in a stable pharmacodynamic system may have unintended consequences of their own.

CARLAT VERDICT

Escitalopram is generally safer and possibly more effective than citalopram, but psychiatric practice is full of the unexpected. Be careful if you decide to cross-taper from one to the other.

—Chris Aiken, MD. Editor-in-Chief, *The Carlat Psychiatry Report*

Research Updates IN PSYCHIATRY

DEPRESSION

How Essential Is Antidepressant Continuation?

Michael Posternak, MD. Dr. Posternak has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

REVIEW OF: Lewis G et al, *N Eng J Med* 2021;385(14):1257–1267

TYPE OF STUDY: Randomized controlled trial

Most of us have been taught that long-term antidepressant therapy is crucial for patients who have had three or more episodes of depression. This idea is based on trials in which patients in remission were randomly assigned to medication continuation vs placebo. Those switched to placebo had a higher rate of relapse, especially if they'd had three prior episodes of depression.

However, these studies have a number of flaws that may bias the results. Generally, these patients were in remission for only a short amount of time—typically from three to eight months. Second, antidepressant discontinuation was typically done rapidly, making it hard to tell whether patients actually relapsed or were suffering from withdrawal symptoms. Third, the switch to placebo took place at a fixed time instead of when patients felt ready to come off their antidepressant. That leaves open the question: Can patients who have been in sustained remission from depression and feel ready to come off medication safely discontinue antidepressants?

In this study, researchers recruited 478 adult patients from 150 general practices across England, all of whom had a history of at least two prior depressive episodes, were currently in remission, had been taking their antidepressant for at least nine months, and felt well enough to consider stopping their medication. Only antidepressants that are commonly prescribed and known to have low rates of withdrawal were included: citalopram, sertraline, fluoxetine, and mirtazapine. Consenting patients were randomized in a double-blind manner to either remain on their antidepressant or have it slowly replaced with a placebo over two months (fluoxetine was tapered over only one month due to its long half-life). Patients were then followed every three months for one year to ascertain relapse rates.

In total, 92 of 238 patients (39%) in the maintenance group relapsed compared to 135 of 240 (56%) in the discontinuation group over the course of 52 weeks (HR 2.06; $p < .0001$). Differences in rates of depression, anxiety, and quality of life all emerged within 12 weeks and persisted throughout the trial. Of the patients who stopped their trial medication, 20% of the maintenance group and 39% of the discontinuation group elected to resume antidepressant medication.

One potential limitation of the study is that reported rates of medication withdrawal symptoms were higher in the discontinuation group (3.1) than the maintenance group (1.9; 95% CI 1.5–2.3). Although this could represent an unmasking of depressive symptoms, it also suggests that despite the slow taper, physiological withdrawal cannot be ruled out as a contributing factor.

CARLAT TAKE

This landmark study puts the risks of antidepressant discontinuation in perspective. On the one hand, staying on the medication lowers the relapse risk by 17% over the course of a year. On the other hand, 44% of discontinuation patients *did* taper off their antidepressant without relapsing. Those figures challenge the black-and-white recommendation to remain on an antidepressant indefinitely after more than two episodes and move the question into the realm of collaborative decision-making between clinician and patient.

MOOD DISORDERS

Can TMS Turn On the Switch?

Edmund S. Higgins, MD. Dr. Higgins has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

REVIEW OF: Miuli A et al, *World J Psychiatry* 2021;11(8):477–490

STUDY TYPE: Literature review and meta-analysis

Some treatments for depression, particularly antidepressants, present risk of manic reactions, but whether this risk exists with transcranial magnetic stimulation (TMS) is less clear.

A group in Italy searched the world's literature for studies using TMS for mood disorders. They sought studies that were double blind or single blind and published in English to find reports of manic and hypomanic switching.

The authors found 25 studies (21 double blind and four single blind) with a total of 576 subjects in active treatment and 487 receiving sham treatment. The studies used a variety of TMS protocols, but the most common was administered over the left dorsolateral prefrontal cortex for two weeks at 10 Hz with 2000–3000 pulses per session. Only eight studies reported on adverse effects like manic switching. Of those, four reported manic or hypomanic switches—three in active treatment and one in sham. Although there was a trend toward switches, the difference was not statistically significant, leading the authors to conclude that TMS does not seem to increase the risk of these reactions.

The parameters of TMS can be opaque to those of us who are not fluent in electricity, so we sought out Mark S. George, MD, one of the founding fathers of TMS (George MS et al, *Neuroreport* 1995;6(14):1853–1856) and editor-in-chief of the journal *Brain*

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Stimulation. Dr. George was hesitant to embrace the authors' conclusion from this analysis.

He noted that the usual length of treatment is four to six weeks, so the majority of the studies reviewed here were underdosed at only two weeks. Furthermore, many of the studies used a gentler form of TMS with low-intensity pulses. More recent TMS protocols have raised the frequency of the magnetic pulse to produce faster results, a change that—in theory—could also raise the risk of mania.

CARLAT TAKE

This study provides some reassurance that TMS does not cause manic switching. However, many of the studies were underdosed, and few systematically looked for side effects. For all intents and purposes, this analysis does not answer the question.

PSYCHOSOMATICS

Hypothyroidism and Depression: Just How Related Are They?

C. Jason Mallo, DO. Dr. Mallo has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

REVIEW OF: Bode H et al, *JAMA Psychiatry* 2021;78(12):1375–1383

STUDY TYPE: Meta-analysis of epidemiologic and population-based studies

Hypothyroidism and depression are related, right? Actually, the connection is not so clear. Prior studies have supported a connection, but they had limitations, such as small sample sizes, patients with severe disease, and rating scale cutoffs that were not clinically relevant. In the current meta-analysis, a group of psychiatrists led by Henry Bode attempted to clarify the link between these conditions.

Investigators screened databases for epidemiologic and population-based studies with laboratory and diagnostic evidence of hypothyroidism and major depression, as defined by DSM or ICD criteria. Of the 4,350 studies screened, 25 passed muster according to the Newcastle-Ottawa Scale, a standardized quality assessment of nonrandomized studies.

In total, the analysis included 348,014 patients, of which 53.6% were female and the mean age was 45 years (range 18–91). The primary outcome was the association between depression and hypothyroidism or thyroid autoimmunity. Secondary outcomes included the impact of subclinical vs overt hypothyroidism, gender, and age.

Hypothyroidism and depression were associated, but much less than expected (odds ratio [OR] of 1.3, indicating a 30% increased risk, with a range [95% CI] of 1.08–1.57). The association was stronger for clinical hypothyroidism (OR 1.77; 95% CI 1.13–2.77) than subclinical (OR 1.13; 95% CI 1.01–1.28), which suggests a dose effect with the degree of hypothalamic-pituitary-thyroid axis disturbance. On the other hand, thyroid autoimmunity and depression were not associated (OR 1.24; 95% CI 0.89–1.74), indicating that the immune system is not involved. Age did not affect the outcome, but the association between hypothyroidism and depression was stronger for women than men.

One limitation of this meta-analysis is that the analyzed studies had varying methodologies, but the results did not change when those variations were removed in a subanalysis. Strengths of this meta-analysis include that it focused on patients from the general population; also, the study was funded by an independent university grant that did not introduce any apparent bias.

CARLAT TAKE

Few things in psychiatry are black and white, and this study moves the hypothyroidism-depression link into the gray area, particularly with subclinical cases. The results do not negate the importance of considering hypothyroidism, however, as we may still see depression develop in patients with overt disease, meaning clear physical symptoms of low thyroid in addition to lab evidence.

SPECIAL POPULATIONS

Topiramate Improves Weight in Schizophrenia in South Asians

Brian Miller, MD, PhD, MPH. Dr. Miller has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

REVIEW OF: Chandradasa M et al, *Asian J Psychiatr* 2022;68:102963

STUDY TYPE: Randomized placebo-controlled trial

People with schizophrenia have higher rates of cardiometabolic mortality. There is meta-analytic evidence that adjunctive topiramate reduces weight and improves psychiatric symptoms in schizophrenia. However, there are few studies of this medication in patients from South Asia, who are inherently more vulnerable to cardiometabolic disturbances. This study investigated topiramate's effects on weight and psychiatric symptoms in this population.

This was a randomized, double-blind, placebo-controlled trial of topiramate in 100 patients from Sri Lanka with a BMI >25 who had been on an antipsychotic for at least a year (mean age 41). Patients were treated with either topiramate (titrated to 50 mg twice daily) or placebo, in addition to their current antipsychotic, for three months. Weight and psychopathology (using the Brief Psychiatric Rating Scale [BPRS], baseline mean 24.3) were assessed monthly. All of the subjects completed the trial.

After three months, there was significantly greater weight reduction (-6.6 lbs vs +0.7 lbs) and improvement in BPRS score (-1.6 vs +0.3) in the topiramate group. Topiramate had a significantly higher prevalence of appetite loss (12% vs 0%); otherwise, there were no differences in adverse effects. The number needed to treat for a 5% body weight reduction was 4.

Potential limitations include that many patients were on antipsychotic polypharmacy, and that the dose of topiramate was relatively low. The

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CME Post-Test

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1. Which antipsychotic has the best evidence for preventing future episodes of depression after a manic episode in bipolar disorder (LO #1)?
   [ ] a. Olanzapine-fluoxetine
   [ ] b. Risperidone
   [ ] c. Quetiapine
   [ ] d. Cariprazine

2. According to Dr. Swartz, which of the following best describes depression-dominant psychosis (LO #2)?
   [ ] a. A depression with manic features and auditory hallucinations
   [ ] b. A melancholic-type depression with delusions that have depressive themes
   [ ] c. A depression with atypical features and visual hallucinations
   [ ] d. A depression with manic features and delusions of persecution

3. According to Dr. Salzman, what are the effect sizes of SSRIs and benzodiazepines, respectively, in generalized anxiety disorder (LO #3)?
   [ ] a. Small and medium
   [ ] b. Small and small
   [ ] c. Large and medium
   [ ] d. Medium and large

4. What was a limitation in a 2021 meta-analysis that investigated the risk of manic switching associated with transcranial magnetic stimulation (TMS) for mood disorders (LO #4)?
   [ ] a. The meta-analysis included only single-blind studies
   [ ] b. The studies used a harsher form of TMS with high-intensity pulses, whereas more recent TMS protocols use low-intensity pulses
   [ ] c. The meta-analysis was underpowered due to its small sample size
   [ ] d. The majority of studies included in the meta-analysis administered TMS for only two weeks, which is shorter than the usual treatment of four to six weeks

5. Quetiapine has sedative properties in the 25–150 mg dose range, antidepressant properties in the 150–300 mg dose range, and antipsychotic properties at doses ≥300 mg (LO #1).
   [ ] a. True
   [ ] b. False

6. Which of the following statements about psychotic depression is true (LO #2)?
   [ ] a. Suicide risk is equal in psychotic and nonpsychotic depression
   [ ] b. Medical morbidity is low in psychotic depression
   [ ] c. Childhood physical or sexual abuse is two to three times more likely in psychotic vs nonpsychotic depression
   [ ] d. The mortality rate is five times higher in psychotic vs nonpsychotic depression

7. Which medication improved sleep in a study of benzodiazepine withdrawal (LO #3)?
   [ ] a. Ramelteon
   [ ] b. Carbamazepine
   [ ] c. Propranolol
   [ ] d. Pregabalin

8. According to Dr. Swartz, a 2010 study revealed that nearly all psychotic symptoms in PTSD are better explained by comorbidities that are known to cause psychotic symptoms (LO #2).
   [ ] a. True
   [ ] b. False

Research Updates

Continued from page 10

authors also did not measure glucose, hemoglobin A1c, or lipids. Furthermore, all subjects were stable outpatients with chronic schizophrenia. Therefore, the generalizability of the findings to other patients and phases of illness is limited. Nevertheless, the authors studied topiramate in a resource-limited, vulnerable patient population.

CARLAT TAKE

Adjunctive topiramate significantly reduced weight and psychopathology in schizophrenia-stable outpatients in South Asia, consistent with previous meta-analyses. Further studies of optimal dosage are needed, but findings support the clinical utility of topiramate as a viable off-label treatment in this patient population.

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Quetiapine Reconsidered

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The XR formulation may be helpful if orthostatic hypotension is a problem, but it also has a slightly greater risk of morning fatigue. Quetiapine XR's release mechanism can break down in the presence of food or alcohol, causing it to release all of its sedating ingredients at once. For that reason, it should be taken 30–60 minutes away from a large meal, and—to minimize morning fatigue—12 hours before the patient plans to wake up (Kishi T et al, *J Psych Research* 2019;115:121–128).

When quetiapine was first released, there was concern about its potential to cause serious arrhythmias like torsades de pointes by prolonging the QTc interval. However, not all QTc prolongation leads to serious arrhythmias, and it now appears that the risk of arrhythmias with quetiapine is much lower than once thought (Hasnain M et al, *CNS Drugs* 2014;28(10):887–920).

CARLAT VERDICT

Quetiapine is not for everyone, but its ability to prevent and treat bipolar depression makes it a good choice in this condition, particularly when the mood problems are severe or mixed with anxiety or insomnia. For other disorders, it doesn't stand out from the pack, and its side effect burden makes it less desirable.

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