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Chris Aiken, MD
Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Adult ADHD

Learning Objectives

After reading these articles, you should be able to:

1. Diagnose borderline personality disorder by recognizing its symptoms and using effective communication strategies.
2. Evaluate the advantages of nonstimulant medications in treating ADHD and their impact on comorbid conditions.
3. Summarize some of the current research findings on psychiatric treatment.

How to Diagnose Borderline Personality Disorder

C. Jason Mallo, DO. Division Medical Director, Maine Medical Center Department of Psychiatry, Adult Outpatient Psychiatry. Assistant Clinical Professor, Tufts University School of Medicine.

Dr. Mallo has no financial relationships with companies related to this material.

Diagnosing borderline personality disorder (BPD) is a daunting task—so much so that we sometimes defer or ignore the diagnosis. BPD is common, however, occurring in 10% of psychiatric outpatients and 20% of inpatients, and missing it can delay effective treatment (Biskin RS, *Can J Psychiatry* 2015;60(7):303–308). In this article, I will break down how to identify BPD and offer therapeutic strategies.

Categorical approach

The symptoms that patients with BPD present with rarely align with the DSM-5 criteria. Rather, their complaints take after major depression, bipolar disorder, generalized anxiety disorder, etc. Of course, these disorders are not

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Highlights From This Issue

Feature article. Ask about affective instability—rapid swings of intense emotions—to screen for borderline personality disorder.

Q&A. Nonstimulants are a little less effective than stimulants in ADHD, but they have unique benefits for common comorbidities.

Research update on page 6. When using quetiapine in schizophrenia, start with immediate release. As the dose goes beyond 300 mg, extended release may bring better results.

Q&A With the Expert

ADHD: Beyond Stimulants
Nicholas J. Nissen, MD

Concierge psychiatrist, specializing in nonstimulant management of ADHD and anxiety disorders. Austin, TX.

Dr. Nissen has no financial relationships with companies related to this material.

TCPR: What is the advantage of nonstimulants in ADHD?

Dr. Nissen: One advantage is safety. Stimulants have an abuse potential, particularly the amphetamines and the short-acting versions, which can be crushed or snorted. Diversion is pretty common—8.5% of college students use nonprescribed stimulant medications. Then there are cardiovascular risks, which are worse with long-term use. The risk of heart disease—mainly hypertension and arterial disease—increased steadily by 4% per year in children and adults, according to a recent large case-controlled study (Zhang L et al, *JAMA Psychiatry* 2024;81(2):178–187).

TCPR: But aren't stimulants more effective?

Dr. Nissen: Yes, but not by as much as people think. Here's how their effect sizes compare:

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How to Diagnose Borderline Personality Disorder

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mutually exclusive and may be comorbid with BPD. Focusing on them, however, can interfere with picking up on the full story and establishing a path toward recovery.

A BPD diagnosis requires at least five of nine DSM-5 criteria, which fall into four categories: unstable emotions, impulsive behaviors, inaccurate perceptions, and unsteady relationships (see the table "BPD DSM-5 Criteria and Questions to Ask" on page 3). These categories are interrelated. For example, unsteady relationships can trigger unstable emotions, and vice versa.

When assessing for BPD, a good starting place is to ask about affective instability that lasts minutes to hours. In Mark Zimmerman's research, this stood out as a core feature of the disorder. His team evaluated 3,674 patients and found that asking about affective instability was 92.8% sensitive and had a 99% negative predictive value. This suggests that further investigation of the BPD criteria is warranted if your patient has affective instability (Zimmerman M et al, *J Clin Psych* 2019;80(1):18m12257).

Assessing the DSM-5 criteria for BPD can be done in less than 10 minutes. For patients who are squeamish about diagnostic labels, review the criteria before naming the disorder. The DSM's categorical approach is useful but incomplete, as it does not identify patient strengths or shed light on what happens intrapsychically.

Dimensional approach

The dimensional approach was born out of psychoanalysis and regards personality as existing on a spectrum from more neurotic to psychotic, with borderline in the middle. At any time, people can move across this spectrum. However, most of the time, their patterns of thinking, feeling, and behaving exist in a particular zone.

Patients in the borderline zone have intact reality testing much of the time. With stress, however, their reality testing becomes compromised and presents as paranoia, dissociation, or even illusions. Splitting is a common defense mechanism in BPD. Patients tend to idealize or devalue themselves and others, and their sense of self and others fluctuates. With adequate support and structure, however, their relationships can appear to thrive. A patient's ability to adapt in this manner can help differentiate BPD from psychosis or mania.

To get a sense of where your patient falls dimensionally, here are a couple of useful questions:

- "Can you tell me about yourself so I can get a real picture of you as a person?"
- "Can you describe someone close to you so I can get a full sense of who they are?"

Pay attention to how detailed, multilayered, and relatable the patients' responses are. Patients with BPD often give answers that are vague, inconsistent, or exaggerated with caricatures of heroes and villains (Yeomans F et al. *Transference-Focused Psychotherapy for Borderline Personality Disorder: A Clinical Guide*. Washington, DC: American Psychiatric Publishing; 2015: 83–98).

Other considerations

Rating scales

Self-rating screens help us know when to probe further for BPD and track a patient's course. These screens cast a wide net, so interpret them with caution. A positive screen does not mean your patient has BPD, but a negative screen does a pretty good job of ruling it out.

Comorbidity

Comorbidity can also indicate when to look for BPD. In another study by Zimmerman and colleagues, BPD was common in patients presenting for bipolar disorder, posttraumatic stress disorder, panic disorder with agoraphobia, and major depressive disorder. BPD was found in 33.8% of patients with bipolar I (odds ratio [OR] 4.52; 95% confidence interval [CI] 2.7–7.5) and in 27.1% with bipolar II (OR 3.28; 95% CI 2.1–5.2; Zimmerman M et al, *Ann Clin Psychiatry* 2017;29(1):54–60).

Gender

BPD is wrongly stereotyped as a female disorder. The rates are similar across genders, though the presentations differ (Grant J et al, *J Clin Psych* 2008;69(4):533–534). Men present more often with anger, substance use, and difficulty engaging in treatment, while women are more likely to have emotional instability, identity diffusion, and self-harm (Bayes A and Parker G, *Psychiatry Res* 2017;257:197–202).

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Countertransference

Take stock of your thoughts and feelings about the patient. Reactions to BPD may include frustration, hatred, guilt, anxiety, helplessness, and rescue fantasies. These feelings commonly vacillate and vary considerably.

Genetics

Ask about family history and temperament. A Swedish population-based study estimated the heritability of BPD at 46% (95% CI 39%–53%; Skoglund C, *Mol Psychiatry* 2021;26(3):999–1008). Intense emotionality early in life has been implicated as a risk factor (Stepp S et al, *BPD Emot Dysregul* 2014;1:18).

Communicating the diagnosis

After you review the diagnostic steps above, it is time to share your formulation. By and large, this goes well, especially when you use familiar terms, connect your impressions with details of the patient's history, and recognize their strengths.

If the patient struggles with the diagnosis, hedge your bets. Let them know you believe BPD applies, but do not force it. With more time, education, patience, and persistence, they can come around. When done collaboratively, this diagnostic process fosters an alliance around a shared understanding of your patient's struggles. It reduces their sense of isolation and anchors the hope of recovery to a rational plan of treatment. BPD is not a life sentence. Two-thirds of cases eventually achieve remission or recovery (Stone MH, *Psychodyn Psych* 2016;44(3):449–474).

BPD DSM-5 Criteria and Questions to Ask

Unstable Emotions	
Mood instability	Have you struggled with mood instability?
Inappropriate anger	Do you often feel angry or have outbursts?
Feelings of emptiness	Do you often feel empty?
Impulsive Behaviors	
Self-damaging acts	Have you done risky/dangerous things without thinking them through?
Suicidal or nonsuicidal self-harm	Have you hurt yourself for nonsuicidal reasons or made a suicide attempt?
Inaccurate Perceptions	
Identity disturbance	Have you felt that you do not really know yourself or what direction your life is heading in?
Transient paranoia or dissociation	Are you distrustful of others or feel that the world is against you?
	Have you felt unreal or that the environment around you is unreal?
Unsteady Relationships	
Abandonment issues	Have you worried about people leaving you?
Interpersonal difficulty	Have close relationships been affected by arguments or major shifts in how you perceive others?

CARLAT VERDICT

Recognizing BPD paves the way to effective treatment. When the diagnosis is explained in a personalized, collaborative way, your patient will feel understood, possibly for the first time.

Expert Interview

Continued from page 1

- Stimulants: 0.8–0.9
- Clonidine (Kapvay): 0.7–0.8
- Guanfacine (Intuniv): 0.4–0.9
- Viloxazine (Qelbree): 0.5–0.6
- Atomoxetine (Strattera): 0.4–0.6
- Bupropion (off-label): 0.3–0.5

To put that in perspective, the average effect size for psychiatric treatments is 0.5. So while the stimulants are clearly at the top, the nonstimulants still have a respectable effect. One limitation here is that most of those figures come from trials in children and adolescents (Childress A, *Expert Opin Pharmacother* 2024;25(7):853–866).

TCPR: Do the nonstimulants work in adults and children?

Dr. Nissen: Atomoxetine and viloxazine are approved in both age groups, but the alpha-2 agonists, clonidine and guanfacine, are only approved in children. Of those two, guanfacine is the only one with trials in adult ADHD (Ota T et al, *Drug Des Devel Ther* 2021;15:1965–1969). Bupropion is off-label in ADHD, and it has trials in children and adults.

TCPR: So their benefits are a little lower. Do they affect different symptoms?

Dr. Nissen: In terms of ADHD subtypes, the inattentive type is more common in adults, but no medication stands out as more effective for particular subtypes. One difference is that stimulants are going to make people feel more energized. The nonstimulants are not going to do that, and the alpha-2 agonists, particularly clonidine, can cause sedation. On the other hand, the alpha-2 agonists can improve sleep, and that's where the nonstimulants have an edge: in treating comorbidities.

TCPR: How so?

Dr. Nissen: I'd consider viloxazine and bupropion for ADHD with depression, and bupropion for nicotine cessation. Atomoxetine and viloxazine are both repurposed antidepressants. They are norepinephrine reuptake inhibitors, with additional serotonin activity for viloxazine. Viloxazine is approved for depression outside the US, where it's been used since the 1970s. Atomoxetine doesn't have approval for depression anywhere because it failed in those trials, but it does help

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anxiety disorders that are comorbid with ADHD in adults and children—social and generalized anxiety (Khoodoruth MAS et al, *Res Dev Disabil* 2022;128:104275).

TCPR: What about clonidine and guanfacine?

Dr. Nissen: I'd consider those for anxiety as well, particularly clonidine. It has small studies in PTSD and panic disorder, and it may help nightmares, but these studies are very preliminary. A related alpha-2 agonist, dexmedetomidine, is currently being explored by the industry for posttraumatic stress disorder. Clonidine also improved mania in small trials (Ahmadpanah M et al, *J Psychiatr Res* 2022;146:163–171). Both of the alpha-2 agonists are effective for tics, which are a rare side effect of stimulants. In my own practice, I go with guanfacine more because it has better evidence in adults. It is also less sedating, and I see fewer complaints of "brain fog."

TCPR: When do you give up on nonstimulants?

Dr. Nissen: After one or two failures, I'll usually go with a stimulant, in which case my go-to is a methylphenidate product, usually an extended-release (ER) formulation like methylphenidate ER (Concerta). However, if the patient has a history of substance use disorder, I'm likely to stick with the nonstimulant category.

TCPR: What formulations of guanfacine and clonidine do you use?

Dr. Nissen: I tend to use the ER versions. Those are the ones that are FDA approved, but some of the earlier studies used immediate release, so that is feasible. I usually dose it all at night to prevent sedation during the day. I'll start with the lowest dose and raise it every week based on tolerability and efficacy (see the table "Nonstimulants in ADHD" on page 5).

TCPR: When a patient is already taking an antihypertensive, how do you work with clonidine and guanfacine?

Dr. Nissen: Certainly it's a good idea to check blood pressure before starting and to monitor it closely. I also check if they've had any history of hypotension, falls, or syncope and might avoid these medications if so. I'll coordinate with their primary care physician, but most patients can remain on their blood pressure regimen while starting these alpha-2 agonists. Also exercise caution with mirtazapine, which has the opposite action at the alpha-2 receptor. There are a few case reports of hypertensive urgency when mirtazapine is combined with an alpha-2 agonist (Abo-Zena RA et al, *Pharmacotherapy* 2000;20(4):476–478).

> **"While the stimulants are clearly at the top, the nonstimulants still have a respectable effect."**
>
> Nicholas J. Nissen, MD

TCPR: What are the risks with atomoxetine and viloxazine?

Dr. Nissen: The most common risks are GI side effects, which improve by taking them with food. These medications can be sedating, but they can also cause insomnia. Atomoxetine can be given once or twice a day; its half-life is five hours. Viloxazine has a shorter half-life (two to five hours) but is still given once a day as it comes as ER capsules that can also be opened and sprinkled. Both can raise blood pressure and heart rate. Atomoxetine has additional warnings about rare sudden cardiac death from arrhythmias, similar to the warnings on stimulants. Viloxazine isn't known to cause that and doesn't have that warning. Generally, atomoxetine is well tolerated, but around one in 10 patients can have problems with it because they are poor metabolizers at CYP2D6, which raises the blood levels by as much as 16-fold (Childress A, *Expert Opin Pharmacother* 2024;25(7):853–866).

TCPR: How long do atomoxetine and viloxazine take to work?

Dr. Nissen: I'd suggest a trial of four to six weeks before making a change; same timeline with bupropion.

TCPR: What about the modafinils (modafinil/Provigil; armodafinil/Nuvigil)?

Dr. Nissen: Modafinil is not FDA approved for ADHD. It does have support from randomized controlled trials, but I don't use it often. I know other people do, but as far as I'm concerned, at that point you might as well be considering a stimulant. So for me, I might try a modafinil if both the stimulants and nonstimulants have failed.

TCPR: How do you separate valid ADHD from other cognitive problems?

Dr. Nissen: First, rule out other psychiatric disorders that could be causing the problem, especially mood and anxiety disorders. Next, focus on childhood history. You need that to diagnose ADHD (onset before age 12), so ask about school performance and whether the patient required any neuropsych evaluations or accommodations as they were growing up. Finally, conduct a structured interview to assess all the symptoms, and look for real-life examples of those symptoms. In the end, ADHD is a clinical diagnosis, which means you don't need a neuropsych evaluation or a computerized battery like the QbTest to diagnose it. Those tools can help provide clarity when the diagnosis is unclear, though.

TCPR: Are any supplements useful for ADHD?

Dr. Nissen: They are promising, but here the evidence is much weaker. Those that have at least small controlled trials include phosphatidylserine, fish oil, ginkgo biloba, ginseng, and probiotics. One I find interesting is phosphatidylserine.

TCPR: That's a phospholipid, right?

Dr. Nissen: Yes. Phosphatidylserine is a naturally occurring membrane phospholipid that is thought to change neurotransmitter signaling by altering receptors, enzymes, and ion channels. We get phosphatidylserine from foods like egg yolks and soybeans, and taking more than what's in the usual diet led to improvements in children with ADHD in a small randomized trial (n=37, 200–300 mg/day) as well as in a few other trials where it was combined with omega-3 fatty acids, another membrane phospholipid with support in ADHD (Hirayama S et al, *J Hum Nutr Diet* 2014;27 Suppl

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Expert Interview
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2:284–291). This phosphatidylserine + omega-3 combo used to be sold as a prescription supplement for ADHD, Vayarin. I'd take this efficacy research with a grain of salt, but it is safe and well tolerated, although like omega-3 it does have a blood-thinning effect. Consumer Labs tested phosphatidylserine products and found good results with Puritan's Pride, Life Extension, GNC, Jarrow, Swanson, and Doctor's Best (Now and Nutricost did not pass).

TCPR: Which other supplements have you found useful?

Dr. Nissen: Ginkgo biloba (80–120 mg/day) has a small controlled trial where it augmented methylphenidate in children and adolescents with ADHD (Shakibaei F et al, *Complement Ther Clin Pract* 2015;21(2):61–67). Another supplement to know about is nicotine—clearly not recommended, but people with ADHD have higher rates of nicotine use, and some of this may be to treat symptoms. Nicotine patches and nicotine agonists improve ADHD symptoms. If patients are smoking, I'll recommend that they switch to a nicotine gum and/or patch.

Nonstimulants in ADHD

Medication	Dosing	Other Benefits	Risks
Atomoxetine	Start 40 mg QD; raise to 80–100 mg QD after 1–2 weeks (dose by weight in peds)	Generalized and social anxiety disorders (when comorbid with ADHD)	Hypertension, ventricular arrhythmias, fatigue, mania. Levels significantly increased by CYP2D6 inhibitors.
Bupropion (off-label)	Start 75–150 mg/day; raise by 75–150 mg/week to target 300–450 mg/day (give entire dose in morning as XL)	Depression, nicotine use	Mania, seizures. Strong CYP2D6 inhibitor.
Clonidine	Start 0.1 mg QHS; raise by 0.1 mg/week to target 0.2–0.4 mg/day (divide BID in higher dose range)	Hypertension, anxiety, insomnia, bipolar mania, pain, opioid use disorder, tics	Hypotension, bradycardia, rebound hypertension on withdrawal, sedation.
Guanfacine	Start 1 mg QHS; raise by 1 mg/week to target 2–7 mg/day (divide BID in higher dose range; dose by weight in peds)	Hypertension, insomnia, tics	Hypotension, bradycardia, rebound hypertension on withdrawal, sedation. Levels raised by high-fat meals and CYP3A4 inhibitors.
Viloxazine	Start 200 mg QD; raise by 200 mg/week to target of 200–600 mg in adults (max 400 mg QD in peds)	Depression	Hypertension, fatigue, mania. Strong CYP1A2 inhibitor.

TCPR: What lifestyle approaches do you recommend for ADHD?

Dr. Nissen: Exercise is top on my list. I recommend aerobic exercise 30 minutes a day at least three days a week, preferably five. There are studies showing benefits on cognitive tests, and physiologically it improves circulation, oxygenation, and neuroprotection through brain-derived neurotrophic factor production. Clinically, I often see ADHD worsen when young adults drop their high school sports teams as they transition to college.

TCPR: What else is high on your list?

Dr. Nissen: Substance use is a low-hanging fruit, in particular cannabis. In online forums, many lay people discuss cannabis as if it were effective self-medication for ADHD (Mitchell JT et al, *PLoS One* 2016;11(5):e0156614). That's the perception, but in the studies cannabis impairs verbal learning, memory, and attention, especially in people under age 25 (Broyd SM, *Biol Psychiatry* 2016;79(7):557–567). GABAergic substances like alcohol and benzos can also impair attention and focus, and with alcohol we need to look at next-day effects from sleep disruption and hangover.

TCPR: How important is sleep for ADHD?

Dr. Nissen: That's also top on my list. Sleep deprivation will worsen most cognitive symptoms, including impulsivity. I ask not just if they have trouble falling asleep but also about their sleep quality, nocturnal awakening, and signs of sleep apnea like loud snoring or waking up short of breath. For people with ADHD who are also night owls, addressing their sleep schedule with chronotherapeutics can help. In one controlled trial of 51 adults with ADHD with a delay in sleep onset, melatonin 0.5 mg at night helped them fall asleep earlier and improved their ADHD symptoms a little (van Andel E et al, *Chronobiol Int* 2021;38(2):260–269).

TCPR: What about psychotherapy for ADHD?

Dr. Nissen: Definitely. There are three approaches I recommend: cognitive behavioral therapy (CBT), cognitive remediation, and coaching. There is a new form of CBT for ADHD that combines emotional skills and executive functioning skills like managing calendars and task lists, removing distractions, prioritization, and organization. There's a great Treatments That Work manual called *Mastering Your Adult ADHD* that has a workbook for the patient (Safren SA et al, Oxford University Press; 2017). Cognitive remediation (also called cognitive training) is typically done by neuropsychologists. It includes the skills from CBT and adds memory training games, often computerized, to improve specific deficits. Finally, lay persons often offer coaching. Executive functioning coaches help build planning, organization, and time management skills. Coaching can be very helpful, but is usually not covered by insurance.

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

Research Updates IN PSYCHIATRY

PSYCHOPHARMACOLOGY

Immediate vs Extended-Release Quetiapine for Schizophrenia

Richard Moldawsky, MD. Dr. Moldawsky has no financial relationships with companies related to this material.

REVIEW OF: Terao I et al, *J Psychopharmacology* 2023;37(10);953–959

STUDY TYPE: Meta-analysis

Quetiapine is widely used in varying doses and formulations to manage schizophrenia. Given its extensive dose range in both immediate-release (IR) and extended-release (ER) forms, it can be challenging to determine which formulation is most appropriate to prescribe. This research offers a valuable comparison of IR and ER quetiapine across different dosages.

The study synthesized data from six double-blind, randomized, placebo-controlled trials involving 2,456 patients using a dose-response network meta-analysis. This analytical tool allows researchers to evaluate multiple doses within the same analysis, avoiding common issues found in traditional meta-analyses that mix different doses. The main outcomes were scores on the Positive and Negative Syndrome Scale and/or the Brief Psychiatric Rating Scale.

Both IR and ER quetiapine were more effective than placebo, which was not a surprise. However, there were significant differences across formulations and doses. IR quetiapine had a bell-shaped dose-response curve up to 500 mg, which peaked at a maximally effective dose of about 300 mg. ER quetiapine only had increasing efficacy above 300 mg, increasing linearly to a maximally effective dose around 550 mg and then decreasing somewhat to 800 mg (the highest dose studied). Superimposing these dose-response curves showed IR significantly outperforming ER at doses between 100 and 300 mg, with ER better in the 600–700 mg range.

The authors summarized their findings on quetiapine for schizophrenia with the following recommendations:

- Begin with an IR formulation for doses up to 300 mg.
- If the clinical response at 300 mg of IR is inadequate, switch to ER to titrate further.

CARLAT TAKE

This meta-analysis provides us with some updated recommendations for prescribing quetiapine for schizophrenia. It suggests using IR quetiapine for doses up to 300 mg. For higher doses, ER is likely more effective, but may have diminishing returns above 550 mg.

ANTIPSYCHOTICS

Strategies to Reduce Antipsychotic-Induced Hyperprolactinemia

Sarah Azarchi, MD. Dr. Azarchi has no financial relationships with companies related to this material.

REVIEW OF: Zhe L et al, *Transl Psychiatry* 2022;12(1):267

STUDY TYPE: Systemic review and network meta-analysis

Many patients on antipsychotic drugs—up to 70%—face a common side effect: increased levels of prolactin. This condition, which is typically seen when levels exceed 20 ng/mL in patients who are not pregnant, can lead to issues like reduced libido, breast enlargement, and galactorrhea. Men may experience erectile dysfunction, and postmenopausal women may see a decrease in bone density.

A comprehensive review involving 31 randomized controlled trials, with around 2,000 participants in total, investigated ways to lower elevated prolactin levels in patients who were taking antipsychotic medications. The study explored various methods: switching antipsychotic drugs, supplementing with vitamin B6 (200–1200 mg), using dopamine agonists such as bromocriptine and cabergoline, and even an herbal remedy (peony-glycyrrhiza decoction). Researchers also investigated the effectiveness of aripiprazole, a drug known from previous studies to lower prolactin levels, either when added to a patient's regimen or as a replacement for their current medication.

The findings varied based on patients' initial prolactin levels. For those whose starting levels were very high (above 100 ng/mL), adding a low dose of aripiprazole (5 mg daily) was the only method that significantly cut prolactin levels. For levels of 50–100 ng/mL, either switching to aripiprazole, adding aripiprazole as an adjunct (in doses of 5–10+ mg daily), or incorporating vitamin B6 significantly helped. When prolactin levels were below 50 ng/mL, none of the strategies made a significant difference. The study didn't delve into whether these reductions in prolactin also eased the related symptoms or affected psychotic symptoms, nor did it consider differences between genders.

CARLAT TAKE

When prescribing antipsychotics, it's crucial to keep an eye on your patients' prolactin levels. For patients with prolactin levels over 100 ng/mL, adding just 5 mg of aripiprazole can be beneficial. For those with prolactin levels of 50–100 ng/mL, adding or switching to aripiprazole are both viable alternatives, as is simply adding high-dose vitamin B6. This study did not investigate reducing the offending antipsychotic, which may also be helpful.

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CME Post-Test

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1. Which is a core feature that, when present, suggests further investigation for borderline personality disorder (BPD) is warranted (LO #1)?
   - [ ] a. Chronic feelings of emptiness
   - [ ] b. Affective instability lasting minutes to hours
   - [ ] c. Impulsive self-destructive behaviors
   - [ ] d. History of abuse or trauma

2. What advantage do nonstimulant medications provide for ADHD (LO #2)?
   - [ ] a. Greater efficacy in adults compared with stimulants
   - [ ] b. Reduced cardiovascular risks and abuse potential
   - [ ] c. Immediate effect upon initiation
   - [ ] d. Better efficacy and safety in young children

3. Which best summarizes Terao and colleagues' research findings on quetiapine for schizophrenia (LO #3)?
   - [ ] a. Extended-release (ER) quetiapine was more effective than immediate-release (IR) quetiapine at doses under 300 mg
   - [ ] b. IR quetiapine showed greater efficacy than ER quetiapine up to doses of 300 mg
   - [ ] c. Both IR and ER quetiapine had a bell-shaped dose-response curve peaking at 800 mg
   - [ ] d. The dose-response curves for IR and ER quetiapine were identical across all doses

4. When diagnosing BPD, what approach helps capture both the patient's symptoms and their psychological functioning on a spectrum (LO #1)?
   - [ ] a. Categorical approach using DSM-5 criteria
   - [ ] b. Dimensional approach focusing on personality dynamics
   - [ ] c. Comorbidity-focused assessment
   - [ ] d. Countertransference awareness

5. Which nonstimulant medication is most likely to treat depressive episodes in a patient with ADHD (LO #2)?
   - [ ] a. Atomoxetine (Strattera)
   - [ ] b. Clonidine (Kapvay)
   - [ ] c. Guanfacine (Intuniv)
   - [ ] d. Viloxazine (Qelbree)

6. In the study by Zhe et al, which intervention significantly reduced baseline prolactin levels of ≥100 ng/mL in patients taking antipsychotic medications (LO #3)?
   - [ ] a. Supplementing with vitamin B6
   - [ ] b. Switching to a different antipsychotic drug
   - [ ] c. Adding a low dose of aripiprazole (5 mg daily)
   - [ ] d. Drinking valerian tea

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DEPRESSION

Cariprazine Augmentation for MDD

Jeremy Mills, DNP, PMHNP-BC. Dr. Mills has no financial relationships with companies related to this material.

REVIEW OF: Sachs GS et al, *Am J Psychiatry* 2023;180(3):241–251

STUDY TYPE: Randomized double-blind placebo-controlled trial

When a patient with depression does not respond to an antidepressant alone, adding a second-generation antipsychotic is a well-known evidence-based strategy. Cariprazine (Vraylar), a dopamine D2 and D3 and serotonin 5-HT1A receptor partial agonist, is the latest option for such combination therapy. In December 2022, the FDA approved the drug as an adjunct to antidepressants for the treatment of major depressive disorder (MDD), and this AbbVie-funded Phase 3 trial was one of the key studies leading to that approval.

In this six-week double-blind study with participating sites in seven countries, 751 adults with MDD and inadequate response to antidepressant monotherapy were randomized in thirds to adjunctive cariprazine 1.5 mg/day, cariprazine 3 mg/day, and placebo groups. Participants had historically tried three or fewer antidepressants, but most had tried only one. No participants were using other psychiatric medications for affective symptoms during the trial period, and no one had attempted other options for treatment-resistant depression such as esketamine or ECT. Change in baseline

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was measured by the Montgomery-Åsberg Depression Rating Scale (MADRS).

The 250 individuals in the cariprazine 1.5 mg/day group fared best, seeing a statistically significant mean 14.1-point drop in MADRS scores compared to a mean 11.5-point drop among the 249 individuals in the placebo group. The cariprazine 3 mg/day group saw a mean 13.1-point drop that was not statistically significant when compared to placebo. Overall, remission of depression did not significantly differ between the three groups. Both cariprazine groups had double the rates of akathisia and nausea compared to placebo but were otherwise well tolerated.

CARLAT TAKE

Cariprazine joins similar second-generation antipsychotics as an option for MDD when antidepressants alone are ineffective, but improvements seem to be modest. Considering that cariprazine's side effect profile offers no clear advantages over generic aripiprazole, the outsized cost of this brand-name option might preclude its place as a first choice.

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