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Chris Aiken, MD

Editor-in-Chief

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Helping Patients Tolerate Anti-Manic Treatments

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

Mania is a psychiatric emergency. From job loss to arrest, it can destroy a person’s life in a few days. It calls for rapid treatment, but poor tolerability and low insight often stand in the way of adherence. In this article, I’ll look at how to make first-line treatments more tolerable and suggest options when FDA-approved treatments aren’t feasible.

First-line agents: How to maximize tolerability

The most effective agents for treating mania are lithium, carbamazepine,

valproate, and the antipsychotics. Here are some ways to make them more tolerable:

- Start with the lowest possible dose and raise slowly. For lithium, that may mean 150 mg, or even lower with the liquid form.
- Use controlled-release versions. Carbamazepine XR is better tolerated than ER. With valproate, the ER is the better tolerated formulation.
- Give the entire dose at night. With lithium, this also protects the kidneys.
- Select an agent based on which side effects you most want to avoid (see the table “Tolerability of Anti-Manic Medications” on page 2).
- Pretreat for side effects (see the table “Pretreatment for Mood Stabilizer Side Effects” on page 2).

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Diagnosing Borderline Personality

Mark Zimmerman, MD

Chief of Ambulatory Psychiatry and Behavioral Health, South County Psychiatry. Former professor of psychiatry and human behavior, Warren Alpert Medical School, Brown University.

Dr. Zimmerman reports he is on the speaker’s bureau of Intra Cellular Therapies and a research consultant with GH Research. This article was reviewed by Dr. Aiken, Editor-in-Chief, who has concluded that there is no evidence of commercial bias in this educational activity.

Q&A
With
the Expert

TCPR: Is borderline personality disorder (BPD) underdiagnosed or overdiagnosed?

Dr. Zimmerman: I think underdiagnosis is the bigger problem. We interviewed 500 patients who presented to a private outpatient clinic with a general, unstructured interview. We also interviewed a separate sample of 409 patients with a structured interview: the Structured Interview for DSM-IV Personality (SIDP-IV). With the structured interview, which is the gold standard, the rate of BPD was 14.4%, but it was only 0.4% with the unstructured interview (Zimmerman M and Mattia JI, *Am J Psychiatry* 1999;156(10):1570-1574). Other groups have come up with similar findings.

TCPR: What gets in the way of recognizing BPD?

Dr. Zimmerman: One reason is that mood, anxiety, and substance use disorders are common in patients with BPD, and they usually



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Highlights From This Issue

Feature Article. When patients don’t respond to or cannot tolerate standard therapies for mania, off-label meds and dark therapy offer hope.

Feature Q&A. Dr. Mark Zimmerman explains why borderline personality disorder is underdiagnosed and how to distinguish it from bipolar disorder.

Research Update on page 7. Insights on PTSD, alcohol misuse, and antipsychotic-induced weight gain.

Benzodiazepine augmentation can rapidly reduce agitation, insomnia, and anxiety during mania, while alleviating mood stabilizer side effects like nausea and akathisia (eg, clonazepam 0.5–2 mg every 12 hours or lorazepam 1–2 mg every 8–12 hours). This strategy works best in the inpatient setting

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where misuse can be monitored and is best kept short term. Long-term benzodiazepine use is associated with worse functional outcomes in bipolar disorder (Cañada Y et al, *Aust N Z J Psychiatry* 2021;55(10):1005–1016).

Off-label options for mania

When the FDA-approved routes don't work or aren't tolerated, off-label medications are worth considering. Although the evidence supporting them is weaker, they are generally better tolerated than traditional mood stabilizers, allowing them to be used as augmentation without burdensome side effects. Non-pharmacologic approaches also have a role here. Dark therapy is a behavioral strategy with potent anti-manic effects that fit well in any treatment regimen (see sidebar on page 3).

Clonidine

This alpha-2 agonist is FDA approved in ADHD and hypertension. Small trials have explored it in mania since the 1990s, but more solid evidence arrived only recently when it successfully augmented lithium in an RCT (Ahmadpanah M et al, *J Psychiatr Res* 2022;146:163–171).

Clonidine is well tolerated, and patients often appreciate its sedative

qualities during mania. Orthostatic falls are the main risk and improve with extended-release forms.

Levetiracetam

Levetiracetam (Keppra) is an anticonvulsant that can normalize the overly excited calcium signaling seen in manic patients—an ability it shares with lithium and carbamazepine. It is one of the better-studied off-label agents for mania, with support from five randomized trials involving 240 patients. All but one of those trials were positive, and the negative trial also had the most limited design (small, open label). Levetiracetam was used as augmentation, with doses ranging from 250 to 3000 mg (Kishi T et al, *Bipolar Disord* 2022;24(8):834–835; Mirzazadeh H et al, *J Affect Disord* 2025;387:119526).

Most patients tolerate levetiracetam. It is weight neutral but can cause sedation, dizziness, and dyscoordination. The XR form is better tolerated and available generic. It may also improve executive function, cognition, and tardive dyskinesia (Lin CY et al, *CNS Drugs* 2024;38(1):1–14; Woods SW et al, *J Clin Psychiatry* 2008;69(4):546–554). However, it can cause rare

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Tolerability of Anti-Manic Medications

Less sedation	Lithium, cariprazine, aripiprazole, risperidone
Less weight gain	Lithium, carbamazepine, ziprasidone
Less akathisia	Non-antipsychotics or quetiapine, olanzapine, iloperidone, asenapine

Pretreatment for Mood Stabilizer Side Effects

Nausea	<ul style="list-style-type: none"> Ondansetron 4 mg PRN Ginger capsules 1,000–2,000 mg every 12 hours PRN Lorazepam 0.5–1 mg every 8 hours PRN Olanzapine 5 mg every 12 hours PRN
Akathisia	<ul style="list-style-type: none"> Propranolol 80–240 mg/day Lorazepam 1–3 mg/day divided BID or TID Vitamin B6 150–300 mg BID (as pyridoxal 5'-phosphate)*
Weight gain	<ul style="list-style-type: none"> Metformin ER 500–1,000 mg/day with food Melatonin 3–5 mg HS Probiotics 1 capsule/day

*Vitamin B6 treats akathisia, extrapyramidal symptoms, prolactinemia, and possibly tardive dyskinesia on antipsychotics, as well as tremor on lithium. The standard form (pyridoxine) carries a risk of neuropathy, while the active form (pyridoxal 5'-phosphate) appears free of this risk (Hadjistefani F and Vrolijk M, *Adv Nutr* 2021;12(5):1911–1929).

psychiatric side effects, including aggression, suicidality, and psychosis.

Allopurinol

Allopurinol is FDA approved in gout. In five placebo-controlled trials involving 425 patients, it augmented mood stabilizers with a small effect size (Bartoli F et al, *Br J Psychiatry* 2017;210(1):10–15). Among those trials, allopurinol worked when added to lithium, but not to antipsychotics, raising the untested possibility that its synergy depends on lithium or is blocked by antipsychotics.

Allopurinol is well tolerated with rare joint pain or edema. The main risk is an allergic rash (1:2,500) that—like lamotrigine—requires immediate discontinuation of the drug.

Natural therapies

Palmitoylethanolamide (PEA) is a

Off-Label Options for Mania	
Treatment	Dose
Allopurinol	Start 100 mg/day, raise by 100 mg every 3–7 days toward 300–600 mg/day (divided BID)
Clonidine	Start 0.1 mg QHS, raise by 0.1 mg every 3 days (target 0.1–0.6 mg QHS)
Levetiracetam	Start XR 500 mg QHS, raise by 500 mg every 5–7 days toward 1000–3000 mg QHS
Palmitoylethanolamide	600 mg BID

natural fatty acid with neuroprotective and anti-inflammatory effects. It has been used successfully for pain since the 1970s. In psychiatry, the trials are new and small. So far it has shown promise as augmentation in unipolar depression and bipolar mania, based on results from small, placebo-controlled trials (Abedini T et al, *Psychiatry Clin Neurosci* 2022;76:505–511).

PEA has no significant side effects or risks. It occurs naturally in peanuts, eggs, and soybeans, but there is no cross-allergy with these.

Another fatty acid, omega-3s (fish oil), is also useful in bipolar disorder, but not for acute mania. Omega-3s may prevent new episodes and treat acute bipolar depression (dose 1,000–3,000 mg/day with an EPA:DHA ratio of at least 2:1).

Dark Therapy

Dark therapy is a behavioral approach that was developed at the National Institute of Mental Health for insomnia and bipolar disorder. The original strategy required patients to stay in a pitch-dark room all night long, but we've since learned that eliminating just the blue wavelength of light has a similar stabilizing effect on circadian rhythms. In this *virtual* dark therapy, patients wear blue-light blocking glasses or are in a pitch-dark room from 6:00 PM to 8:00 AM.

Virtual dark therapy was tested in a small, randomized trial of inpatient mania, where it improved symptoms within a week with a large effect size (1.05–1.86; Henricksen TE et al, *Bipolar Disord* 2016;18(3):221–232). Three tips are critical to its success:

1. Most blue-light glasses don't block enough to work, so use a brand that has been tested clinically (eg, Uvex Skyper S1933X, Noir Insight ARG, or pairs available at <https://lowbluelights.com>).
2. Likewise, patients need 100% darkness when not wearing the glasses. Strategies include blackout curtains, electrical tape over LED lights, towels over door cracks, or sleeping in the basement. For patients who are afraid of the dark, lowbluelights.com makes nightlights that don't emit blue light.
3. Sleep is not the goal. Some patients give up on dark therapy because it doesn't help them fall asleep. In the research, it improves sleep quality and regularity but is not directly sedating.

As patients improve with dark therapy, they can ease the protocol, gradually moving the start time up by an hour every two to five days until they are donning the glasses one or two hours before bed to maintain stability. Dark therapy can be added to any anti-manic treatment, and many patients appreciate the opportunity to take a more active role in their recovery.

Not recommended

Other off-label anticonvulsants are unlikely to work. Most have failed in large trials of mania, including lamotrigine, topiramate, and gabapentin. Among them, oxcarbazepine is most likely to work, but its trials trend toward the negative and it is not a reliable mood stabilizer.

Calcium channel antagonists are a promising but unproven strategy. They include the antihypertensives amlodipine, nimodipine, isradipine, and verapamil. Only verapamil has controlled trials, where it largely failed against placebo (Cipriani A et al, *Mol Psychiatry* 2016;21(10):1324–1332). The others have only observational studies, which show potential benefits in patients with ultra-rapid cycling (where mood episodes change every week or two).

CARLAT VERDICT Off-label options for mania shine on tolerability, but rest on less solid evidence. Consider them for augmentation or for mild manic symptoms that don't pose a danger. Otherwise, stick with FDA-approved agents for this dangerous state of mind.

Expert Interview

Continued from page 1

present with symptoms associated with those disorders as their chief complaint. They don't come in and say, "I'm here because I have real problems with abandonment" or "I don't know who I am." Another problem is that there is no obvious gate. The DSM-5 lists nine criteria for BPD, but none are identified as required in the way that "sudden attacks of anxiety" is for panic disorder.

TCPR: How do you screen for BPD?

Dr. Zimmerman: I ask patients about affective instability. Among the DSM-5 criteria, this one had the highest sensitivity for diagnosing BPD in our sample of over 3,500 outpatients who were evaluated with a semi-structured diagnostic interview, and other studies back this up. Not only does this item have a sensitivity of over 90%, but it has a negative predictive value of 99%, which means if it's absent you don't have to worry about the person having the disorder (Zimmerman M et al, *Br J Psychiatry* 2017;210(2):165–166). It's more sensitive than self-harm, which only occurs in about one-half to two-thirds of individuals with BPD.

TCPR: Is self-harm not as reliable of a criterion?

Dr. Zimmerman: Correct. Depending on the setting, about one-half to two-thirds of individuals with BPD have a history of self-harm. It can also lead to overdiagnosis. About half of patients who self-harm do not have a diagnosis of BPD.

TCPR: How do you ask about affective instability?

Dr. Zimmerman: I ask, "Do you often have days where your mood changes, meaning you'll go from depressed to angry to happy all in the same day? How typical is that for you? Have others commented that your mood changes a lot—that you're often irritable and that you have mood swings?" I include that in all psychiatric assessments, and if they answer yes, I ask about the other eight criteria for BPD.

TCPR: How do people with bipolar disorder (BD) respond to that question?

Dr. Zimmerman: We actually published a study of this screening in a mood disorder sample, and the psychometrics were very similar to what we found in a general psychiatric sample (Zimmerman M et al, *J Clin Psychiatry* 2019; 80(1):18m12257).

TCPR: So it helps identify people with mood disorders who also have BPD?

Dr. Zimmerman: Yes. About 20% of people with BD have BPD, and 20% of people with BPD have bipolar (more often bipolar II).

TCPR: For the rest who only have one diagnosis, how do you distinguish BD from BPD?

Dr. Zimmerman: There is some overlap in the features, but this is a superficial resemblance. Both have "mood swings," but in BPD these are time-limited reactions to how they perceive other people are treating them. In BD, mood symptoms may be stress-related, but they are more sustained and accompanied by other characteristic symptoms. Impulsivity is common in both, but in BD impulsivity is out of character and occurs along with other manic symptoms. The best way to tell the disorders apart is simply to apply the diagnostic criteria of each. Admittedly, that is not always easy, but you don't have to get it right on the first assessment.

TCPR: Why is it important to distinguish BD from BPD?

Dr. Zimmerman: The foundation of treatment for BD is medication. For BPD, the foundation of treatment is psychotherapy. Medications are also helpful for comorbidities in BPD, and psychotherapy is helpful in BD, but the core treatment is different.

TCPR: People with BD have long periods of sustained recovery. Can we see that in BPD as well?

Dr. Zimmerman: Absolutely. Mary Zanarini's group did a prospective follow-up study on 290 patients who were admitted to McLean Hospital with a diagnosis of BPD. About half of them had a sustained recovery, meaning their functioning improved and their symptoms resolved. For many others, the symptoms fluctuated, often going away for two to four years and returning again (Zanarini MC et al, *Am J Psychiatry* 2010;167(6):663–667). Another 10-year follow-up study, the Collaborative Longitudinal Personality Disorders Study, found similar results. In my own practice, I look at the last five years when asking patients about symptoms of BPD.

TCPR: Should we tell people with BPD about the diagnosis?

Dr. Zimmerman: I do, but I understand that a lot of clinicians do not. In my group at Brown, we routinely surveyed patients about their satisfaction with the assessment, and there are no differences between patients who were told they had BPD and those who were told they had other disorders. In fact, many patients with BPD are reassured to know that there's a name for their problems and hope for recovery. There is one small subgroup who does not like being diagnosed with BPD: mental health professionals.

“The foundation of treatment for bipolar disorder is medication. For borderline personality disorder, it is psychotherapy.”

Mark Zimmerman, MD

TCPR: Suppose I work in an area without a DBT program. How will this diagnostic information help my patient?

Dr. Zimmerman: Well, one of the benefits of COVID has been the rapid expansion of telehealth services, so you might find that DBT is more available than before.

TCPR: What if my patient can't afford therapy?

Dr. Zimmerman: John Gunderson and Lois Choi-Kain developed a treatment model for BPD that can be used outside of formal psychotherapy: "Good Psychiatric Management." Patients work toward realistic goals, like gaining financial independence or having stable relationships, rather than just symptom reduction. As part of this, they are encouraged to participate in a structured social group outside of treatment. It may be a sports team or a religious or community group (*Editor's note: See our interview with Dr. Choi-Kain in TCPR June/July 2020*).

TCPR: If you could include a screening instrument for every new patient at an outpatient practice, what would it be?

Dr. Zimmerman: I'm biased here. Our group developed the Psychiatric Diagnostic Screening Questionnaire (PDSQ), which screens for 13 common disorders in outpatient settings. Admittedly, it doesn't assess for BPD. The PDSQ has questions like, "Over the past two weeks, did you worry obsessively about dirt, germs, or chemicals? Did you think that you were in danger because someone was plotting to hurt you?" It has been validated by independent groups, and it was used in the STAR-D trial.

TCPR: Does the PDSQ make a diagnosis or just screen for them?

Dr. Zimmerman: It is a screening instrument, not a diagnostic instrument. Screening instruments are designed to have high sensitivity so you don't miss the disorder, as well as a high negative predictive value so you can be confident that when the screen is negative, the patient doesn't have that disorder. The PDSQ has a sensitivity of 90% and a negative predictive value of 97% across all 13 disorders, based on a study of more than 2,000 psychiatric outpatients (Zimmerman M and Mattia JI, *Compr Psychiatry* 2001;42(3):175-189).

TCPR: Are there pen-and-paper screening instruments for BPD?

Dr. Zimmerman: Yes. The McLean Screening Instrument is one of the best out there, but it should not be relied on. Its positive predictive value is around 50%, which means a lot of people who screen positive do not actually have BPD (Zimmerman M and Balling C, *J Pers Disord* 2021;35(2):288-298).

TCPR: What is the gold standard for a BPD diagnosis?

Dr. Zimmerman: Many say it is a semi-structured interview like the SCID, but Robert Spitzer, who was editor of the DSM-III, has suggested a LEAD standard: Longitudinal Evaluation of All Data. That includes the semi-structured interview, follow-up over time, mental status, and collateral information from people who know the patient well (Spitzer RL, *Compr Psychiatry* 1983;24(5):399-411).

TCPR: Some of those LEAD elements are not in the DSM.

Dr. Zimmerman: I view the DSM as a guide. It's a test, and like the other tests we've talked about, it can yield false positives and false negatives. For example, I have seen patients with depression who describe one or two past hypomanic episodes. They met the DSM criteria for bipolar II disorder, but I did not think they had it. The episodes were too infrequent, and the rest of the LEAD information did not fit. So I didn't treat them with a mood stabilizer, and they have done well. On the other hand, I've seen patients who have clear and frequent hypomanias that only lasted two to three days. By the DSM's four-day duration criterion, they did not technically have BD, but when I looked at the whole picture, I thought they did. I diagnosed bipolar unspecified and treated them as if they had BD.

TCPR: Structured interviews like SCID and MINI have licensing fees. Are there more affordable options?

Dr. Zimmerman: Not really, but keep in mind there are no magic questions on structured interviews. They simply inquire about the DSM criteria using everyday language. Their real advantage is in providing a structure for a thorough assessment, but the DSM itself provides a similar structure. I have written a book that suggests DSM-based questions, *Interview Guide for Evaluating DSM-5-TR Psychiatric Disorders and the Mental Status Examination*. It is not a structured interview, but if used with the DSM, it could serve as a low-budget structured interview.

TCPR: What mistakes do clinicians make when they use a structured interview?

Dr. Zimmerman: Being overly rigid. You can go beyond the questions that are printed to make sure the patient understands them.

TCPR: You've conducted hundreds of studies on diagnosis. Did any of your findings surprise you?

Dr. Zimmerman: Yes. When the revisions to the DSM-IV were first proposed, they suggested changing the personality disorders section to a dimensional system. I thought this would not work, so I did a study comparing patients who met zero criteria with those who met only one for BPD. My intention was to kill the dimensional idea by showing that people who met only one did not differ from those who met zero. Much to my surprise, there were rather robust differences between the two, such as in rates of comorbidities, suicidality, and overall functioning. So meeting one criterion makes a difference, but ultimately, they stuck with the categorical system.

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

Research Updates IN PSYCHIATRY

PTSD

Do “Other” Events Trigger PTSD?

Alex Evans, PharmD, MBA. Dr. Evans has no financial relationships with companies related to this material.

REVIEW OF: Scoglio AAJ et al, *Eur J Psychotraumatol* 2025;16(1):2506759

STUDY TYPE: Parallel mixed methods study

What if the most distressing event in someone’s life doesn’t show up on a trauma checklist—or even meet the DSM’s Criterion A definition of trauma? Under the DSM-5, trauma requires exposure to actual or threatened death, serious injury, or sexual violence, yet many life events that patients find shattering—like a loved one’s illness, a painful breakup, or a moral injury at work—don’t qualify. That gap was the focus of this study, which analyzed 2,653 female nurses in the Nurses’ Health Study II who had listed an “other” event as their worst lifetime trauma.

Researchers classified traumatic events using the Brief Trauma Questionnaire (combat, car accidents, natural disasters, life-threatening illnesses, child abuse, sexual abuse, serious injuries, losing a close family member to violence, or witnessing violence) plus five additional items (miscarriage or stillbirth, traumatic complications of pregnancy or birth, death of one’s child, sexual harassment at work, or treating civilian trauma). Events that didn’t fit these checkboxes were the sole focus of this study. PTSD symptoms were assessed using DSM-5 criteria, excluding functional impairment or duration.

A total of 56 types of trauma were grouped into 6 categories: a family member being harmed (35.8%), a non-violent death of a family member or close friend (31.1%), a personally distressing event or problem (16.3%), a family member managing a distressing problem (11.3%), problems with an

intimate partner (8.5%), and a distressing event occurring in the workplace (7.2%).

Despite not appearing on standard trauma checklists, in this study these events were associated with significant distress and PTSD symptom rates comparable to, or higher than, Criterion A events. The percentage of women experiencing events in each of these categories who met criteria for provisional lifetime PTSD ranged from 19% to 33.7%, and for past-month PTSD from 2.7% to 7.6%. Women who experienced verbal or emotional abuse or harassment had the highest prevalence of both lifetime (43.8%) and past-month (7.9%) PTSD. The authors note that prior evidence is mixed regarding whether non-Criterion A events lead to comparable rates of PTSD as official traumas.

CARLAT TAKE

We can’t rely entirely on the DSM to tell us what counts as a trauma. Ask open-ended questions, give patients room to describe what has truly shaken them, and focus on treating the symptoms of trauma rather than whether something should be called PTSD vs adjustment disorder or an unspecified trauma-related disorder. Be especially vigilant for distress among female patients reporting verbal or emotional abuse.

ALCOHOL USE DISORDER

Prazosin and Cyproheptadine for Alcohol Use Disorder: A Promising Combination

Christine Tran-Boynes, DO. Dr. Tran-Boynes has no financial relationships with companies related to this material.

REVIEW OF: Aubin H et al, *Addiction* 2024;119:1211–1223

STUDY TYPE: Randomized double-blind placebo-controlled trial

Treating alcohol use disorder (AUD) is challenging, even with FDA-approved medications like naltrexone and acamprosate. Serotonin and norepinephrine, respectively, have been implicated in cravings and impulsivity associated with AUD. This study examines whether prazosin, an alpha-1b antagonist, and cyproheptadine, a 5-HT_{2A} antagonist, can be taken together to reduce alcohol consumption. (Cyproheptadine has similar properties to mirtazapine and is sometimes used for anorexia, nightmares, sexual dysfunction, or serotonin syndrome, at a dose of 4–12 mg.)

This Phase 2 study was funded by Kinnov Therapeutics, maker of an investigational prazosin-cyproheptadine combo pill, although the study drugs here were separate. A total of 154 patients with severe AUD and high-risk drinking (defined as about 4 or more daily standard drinks for men or about 3 for women) were recruited from addiction treatment centers in France. Patients were randomly assigned to 3 groups for 12 weeks: high dose (prazosin ER 10 mg and cyproheptadine 12 mg daily), low dose (prazosin ER 5 mg and cyproheptadine 8 mg daily), or placebo. All received therapy focused on treatment adherence and alcohol use reduction. The primary outcome was a change in alcohol consumption at three months.

Compared to placebo, patients in both treatment groups decreased their alcohol consumption. The reduction was about three standard drinks per day for the high-dose group and two to three standard drinks for the low-dose group. Among patients with the heaviest drinking, the reduction was even greater, at about 3.8 drinks per day. There was a significant dose-response relationship, with a decrease in alcohol consumption by about 1.3 drinks per day between the low- and high-dose groups.

No serious adverse events were associated with the prazosin-cyproheptadine combination, and more than 90% of adverse events were considered mild

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CME Post-Test

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- According to Dr. Zimmerman, what did research comparing structured and unstructured interviews show about the diagnosis of borderline personality disorder (BPD)?
 - a. Structured and unstructured interviews diagnose BPD at similar rates
 - b. Unstructured interviews diagnose BPD more frequently than structured interviews
 - c. Structured interviews diagnose BPD much more frequently than unstructured interviews
 - d. Neither structured nor unstructured interviews reliably diagnose BPD
- Which strategy has been shown in an RCT to significantly improve symptoms of inpatient mania within one week when added to treatment?
 - a. Omega-3 fatty acids (EPA:DHA ratio \geq 2:1)
 - b. Virtual dark therapy using blue-light blocking glasses
 - c. Verapamil augmentation
 - d. Gabapentin augmentation
- In the study of female nurses who reported an "other" traumatic event not listed on standard trauma checklists, what percentage met criteria for provisional lifetime PTSD?
 - a. 5%–10%
 - b. 10%–15%
 - c. 19%–33.7%
 - d. 40%–50%
- According to Dr. Zimmerman, why is affective instability a particularly useful screening criterion for BPD?
 - a. It occurs in nearly all psychiatric disorders, making it highly specific for BPD
 - b. It has a sensitivity of over 90% and a negative predictive value of 99% for BPD
 - c. It is required by the DSM-5 for the diagnosis of BPD
 - d. It is more common than impulsivity in bipolar disorder
- Which off-label medication successfully augmented lithium in an RCT for mania?
 - a. Allopurinol
 - b. Clonidine
 - c. Levetiracetam
 - d. Oxcarbazepine

Research Updates

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or moderate. Sedation and orthostatic hypotension were similar in all three groups. Using ER prazosin likely resulted in an incidence of orthostatic hypotension that did not differ between the placebo and prazosin groups.

CARLAT TAKE

This study suggests that prazosin and cyproheptadine may reduce alcohol intake, particularly in patients with more severe drinking. The combination could be a useful off-label option when standard treatments like naltrexone and acamprosatate are ineffective. Industry funding and short duration are caveats.

SIDE EFFECT MANAGEMENT

Treating Antipsychotic-Induced Weight Gain With GLP-1 Agonists

Christine Tran-Boynes, DO.

REVIEW OF: Siskind D et al, *Lancet Psychiatry* 2025;12:493–503; Patino LR et al, *J Affect Disord* 2025;382:116–122

STUDY TYPE: Two RCTs

GLP-1 receptor agonists (GLP-1 RAs) have revolutionized obesity treatment. Can they

reverse antipsychotic-related weight gain? Two RCTs put this question to the test.

In the first study, Siskind et al ran a 36-week, multi-site trial in Australia involving 31 participants with schizophrenia on clozapine. (Recruitment ended early due to global semaglutide shortages.) Subjects received once-weekly semaglutide (titrated to 2.0 mg) or placebo. The primary endpoint was reduction in body weight. Semaglutide yielded a 13.88% reduction in body weight versus 0.42% in the placebo group, with a large effect size of 1.66. Two-thirds of participants lost at

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least 10% of their body weight, with no changes in PANSS scores or clozapine concentrations.

In the second study (which was industry funded), Patino and colleagues conducted a 16-week trial where 54 adults with obesity and taking olanzapine for schizophrenia, schizoaffective disorder, or bipolar disorder were randomized to twice-daily exenatide (titrated to 10 mcg BID) or placebo. This study's primary outcome was also reduction in body weight. Patients on exenatide lost 0.6% of total body weight, while those on placebo gained 2.8%.

Across both studies, psychiatric symptoms remained stable in both the treatment and placebo groups, and GLP-1 RAs were safe, effective, and well tolerated—with diarrhea being the most common side effect.

CARLAT TAKE

Although the semaglutide trial was small and ended early, it was on par with other evidence that 68 weeks of semaglutide for obesity yielded approximately 15% total body weight loss at a dose of 2.4 mg (Wilding JPH et al, *N Engl J Med* 2021;384:989–1002). Exenatide also prevented weight gain in patients on olanzapine. The studies support recent guidelines from INTEGRATE and Germany that recommend GLP-1 RAs for antipsychotic-induced obesity.

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