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Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Schizophrenia

Learning Objectives

After reading these articles, you should be able to:

1. Identify the advantages and disadvantages of off-label uses of gabapentin in treating psychiatric disorders.
2. Distinguish depression from negative symptoms of schizophrenia.
3. Summarize some of the current research findings on psychiatric treatment.

An Off-Label Guide to Gabapentin

Rajesh R. Tampi, MD, MS, DFAPA. Professor of Medicine, Case Western Reserve University. Chairman, Department of Psychiatry & Behavioral Sciences, Cleveland Clinic Akron General, and Chief of Geriatric Psychiatry, Cleveland Clinic.

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The authors have disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Gabapentin (Neurontin) is not a medication that would make the FDA proud. Less than 1% of its outpatient use is for an FDA indication, and a good portion of the off-label use takes place in psychiatry. These trends sparked a backlash in the 2000s, when Pfizer paid a $1.3 billion fine for misleading marketing practices. Recent reports of misuse of gabapentin and its GABAergic cousin, pregabalin (Lyrica), have added to those concerns. In this article, we'll look at where gabapentin fits in psychiatric practice.

Highlights From This Issue

Gabapentin missed the mark in bipolar disorder, but it has support in anxiety, insomnia, and alcohol and cannabis use disorders, although pregabalin (Lyrica) is the better option for anxiety.

Clozapine should be offered after two failed antipsychotic trials in schizophrenia, and Dr. Brian Miller has ideas for what to do when clozapine does not work.

Lumateperone (Caplyta) has new evidence in bipolar I and II depression.

Anxiety disorders

Gabapentin may be effective for social anxiety and panic disorders at a dose of 900–3600 mg/day. The supporting clinical trials are industry sponsored, and while the methodology is solid (randomized, double blind, placebo controlled), the

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Q&A With the Expert

Raising the Bar in Schizophrenia Treatment
Brian Miller, MD, PhD, MPH

Professor of Psychiatry at the Medical College of Georgia, Augusta, and President of the Georgia Psychiatric Physicians Association.

Dr. Miller receives research support from Augusta University, the National Institute of Mental Health, the Brain and Behavior Research Foundation, and the Stanley Medical Research Institute.

TCPR: Antipsychotics are the standard of care in schizophrenia, but what can we do beyond that?
Dr. Miller: Several things come to mind. Therapeutic alliance, addressing the full symptom picture, and greater use of clozapine in treatment-resistant cases.
TCPR: Let's start with therapeutic alliance.
Dr. Miller: Nonadherence with medications is the rule in this population, so it's very important to develop rapport. I use any means possible to find out about what interests them, whether it's movies, music, video games, sports, or art. Ask, "What are your interests? What do you like to do?" or "How do you spend your time?" If they draw a blank, ask, "Are there things you used to do in the past that you haven't been doing so much lately?" I look for interests that

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get them physically active and out of the house and try to encourage those. It's important to assess psychopathology, but we can build a stronger alliance by finding out what's going well for them.

TCPR: What types of symptoms do you address in addition to psychosis?

Dr. Miller: Depression, insomnia, and physical health are common ones. For depression, I'll often start an antidepressant or psychotherapy. Patients with schizophrenia do respond to cognitive behavioral therapy. In terms of antidepressants, I tend to use SSRIs, SNRIs, and bupropion. There is a theoretical concern that the dopaminergic effects of bupropion could exacerbate psychosis, but that risk didn't pan out in controlled studies, including smoking cessation studies in schizophrenia. Smoking cessation is a good reason to prefer bupropion in this population, as is bupropion's low risk of sexual side effects, which are often a problem with antipsychotics.

TCPR: Any tips on distinguishing depression from negative symptoms?

Dr. Miller: Depression will usually cause distress for the patient, but negative symptoms are more likely to cause distress for the family. Patients with negative symptoms may have apathy, amotivation, and anhedonia, but they are unlikely to complain of sadness or depressed mood. On the mental status examination, you'll see restrictions in emotional expression, like a blunted affect that doesn't change even when talking about positive things. They use short sentences and give one- or two-word answers—alogia, a poverty of speech.

TCPR: Can antipsychotics cause negative symptoms?

Dr. Miller: They can, particularly first-generation antipsychotics, but some of them may also improve negative symptoms to a limited extent. One thing that's important to rule out is negative symptoms that are caused by psychosis, such as threatening voices telling the patient not to move or speak.

TCPR: Some antipsychotics also help depression. Does that have any relevance here?

Dr. Miller: It may, but I'm not aware of any evidence that the antipsychotics approved for use in bipolar or unipolar depression improve mood in schizophrenia.

TCPR: A lot of medications have a little bit of evidence for negative symptoms, from antidepressants to lithium to antibiotics. Do you use any of those?

Dr. Miller: Sometimes I use anti-inflammatory treatments. Inflammation can contribute to negative symptoms. Obesity, poor diet, sedentary lifestyle, smoking, and chronic health problems are all risk factors for inflammation, and you can screen for inflammation with a high-sensitivity C-reactive protein (cutoff > 3 mg/L). Anti-inflammatories that may help negative symptoms include minocycline (200 mg QHS), the NSAID celecoxib (200 mg BID), and possibly high-dose aspirin (1000 mg Qday) (Correll CU et al, *JAMA Psychiatry* 2017;74(7):675–684).

TCPR: How do you treat insomnia in schizophrenia?

Dr. Miller: I try to maximize sleep hygiene before adding a hypnotic. Caffeine use and evening blue light from TVs or smartphone screens are good places to intervene. In terms of hypnotics, I use a lot of trazodone (50–200 mg QHS) and hydroxyzine (20–100 mg QHS). There are also some data showing that melatonin (3–5 mg QHS) has metabolic benefits and reduces oxidative stress (Porfirio MC et al, *Neuropsychiatr Dis Treat* 2017;13:2167–2174). I take a good substance use history before prescribing benzodiazepines or the z-drugs such as zolpidem.

TCPR: What do you look for in patients' physical health?

Dr. Miller: Metabolic and cardiovascular health are particularly important. These patients develop cardiovascular disease 20 years earlier than the average population. I'll check in on nutrition and physical activity, and screen for blood pressure, lipids, and glucose. If I find abnormalities, I'm comfortable starting a first-line medication and referring to primary care from there.

TCPR: Which medications do you start with?

Dr. Miller: For hypertension, White patients are more likely to respond to ACE inhibitors and beta-blockers, so I tend to start with a low-dose ACE inhibitor like lisinopril 10 mg Qday. Black patients are more likely to respond to calcium channel blockers or diuretics, so hydrochlorothiazide 12.5–25 mg Qday or amlodipine 5 mg Qday. For hyperlipidemia, any of the statins are fine—I tend to start with simvastatin 10 mg qday.

TCPR: How do you educate patients about schizophrenia?

Dr. Miller: Patients differ in their cognitive abilities and their level of recovery, so we need to tailor their education appropriately. Start by

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EDITORIAL INFORMATION

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asking, "What questions do you have for me? They can be about this illness, your medications, or other treatments." In general, I'll want them to know that schizophrenia is a treatable illness, that they can lower their risk of relapse by about 80% if they stay on their medication, and that I'm open to adjust the dose if it's difficult to take. But I also inform them that physical activity, a healthy diet, and good social connections are part of their recovery. It's also important to educate families and caregivers, and the National Alliance on Mental Illness is a great resource for them.

TCPR: Sounds like you try to instill hope. That's not easy to do in this illness, where full recovery is not the norm.

Dr. Miller: That is true, and you need to be realistic. One avenue where I do see hope is clozapine. Many patients are able to go back to school or return to work after starting clozapine.

TCPR: Are we using enough clozapine?

Dr. Miller: We're not. The guidelines are consistent on the evidence for clozapine. Patients should be offered a clozapine trial if they have a partial or non-response to two antipsychotic trials, assuming those antipsychotic trials are an adequate dose and duration (four to eight weeks). About 25%–30% of patients with schizophrenia have crossed that threshold, but only 5% are taking clozapine in the US.

TCPR: Which antipsychotics do you try before clozapine?

Dr. Miller: The best antipsychotic is the one that they will take. If adherence is the issue, I will move to a long-acting injectable. After that, I look for what worked in the past. Antipsychotics that kept people well for a long time are often stopped because the patient moved, got hospitalized, or just stopped taking them. I also ask if any family members had psychosis and did well on particular medications, because genetic variations in CYP enzymes can influence antipsychotic serum levels. If the patient has a metabolic problem, which many do, I'm more likely to select an antipsychotic with a favorable metabolic profile such as aripiprazole or ziprasidone on the generic side, and brexpiprazole (Rexulti), lumateperone (Caplyta), or lurasidone (Latuda), which are more costly branded alternatives.

"In general, schizophrenia is a treatable illness, and patients can lower their risk of relapse by about 80% if they stay on their medication. I tell patients I'm open to adjust the dose if it's difficult to take. But also, I tell them that physical activity, a healthy diet, and good social connections are part of their recovery."

Brian Miller, MD, PhD, MPH

TCPR: All things being equal, what do you typically start with?

Dr. Miller: Risperidone. Stefan Leucht did a network meta-analysis that found slight superior efficacy for risperidone and olanzapine compared with other non-clozapine antipsychotics (Leucht S et al, *Lancet* 2013;382(9896):951–962). Olanzapine is also worth trying before clozapine, but I use it second line because of its metabolic risks. So a typical course is to start with risperidone, then olanzapine, and then clozapine. However, if the patient has metabolic problems, I might start with aripiprazole or lurasidone instead of risperidone.

TCPR: How high do you go on the dose for an adequate trial?

Dr. Miller: It depends. In general, patients who are in their first episode or early in the illness tend to respond to approximately half the usual maintenance dose of an antipsychotic. Quetiapine is one exception—it tends to require the same dosing early in the illness as it does in chronic schizophrenia. For risperidone, I usually start at 4 mg/day and go up to 6 mg/day for chronic illness, or start at 1–2 mg/day and go up to 3 mg/day in the early course. I usually divide it twice a day to reduce side effects, but it can be dosed all at night if patients have trouble remembering to take it.

TCPR: And what do you do if clozapine doesn't work?

Dr. Miller: First I'd want to make sure we've maximized the dose, and for that we rely on blood levels. Patients on clozapine are most likely to exhibit a therapeutic effect when total concentrations of clozapine + norclozapine are > 450 ng/mL. Eight weeks at a therapeutic dose is an adequate trial. After that, we don't have randomized controlled trials to guide us, so what I'm going to say is gathered from experience and uncontrolled studies. If they are tolerating clozapine and deriving at least a little benefit from it, I will keep it going and add something in, starting with a second antipsychotic—this is one of the rare situations where I would combine antipsychotics. Aripiprazole and risperidone have some evidence to augment clozapine (Lähteenvuo M and Tiihonen J, *Drugs* 2021;81(11):1273–1284). ECT should also be considered at this stage. It mainly treats positive psychotic symptoms, but it can also help mood, suicidality, and even substance use comorbidities (Wang G et al, *J Psychiatr Res* 2018;105:23–32).

TCPR: Any other options?

Dr. Miller: We have a few medications that may help the overall psychopathology, including positive and negative symptoms. Lamotrigine, for example, has some beneficial effects when added to clozapine, according to a small meta-analysis (dose 50–200 mg Qday after titration) (Tiihonen J et al, *Schizophr Res* 2009;109(1–3):10–14). Another meta-analysis found benefits for adjunctive topiramate—both for positive and negative symptoms and for metabolic parameters (start 25 mg Qday, titrate to max of 200 mg BID) (Correll CU et al, *J Clin Psychiatry* 2016;77(6):e746–e756).

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

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An Off-Label Guide to Gabapentin
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studies were small—only two trials with a total of 172 participants (Pande AC et al, *J Clin Psychopharmacol* 1999;19(4):341–348; Pande AC et al, *J Clin Psychopharmacol* 2000;20(4):467–471). Other studies report benefits in nonspecific anxiety, such as before surgery and in breast cancer survivors, where gabapentin worked better than placebo in two large trials (total n = 630) at a dose range of 300–1200 mg/day (Tirault M et al, *Acta Anaesthesiol Belg* 2010;61(4):203–209; Lavigne JE et al, *Breast Cancer Res Treat* 2012;136(2):479–486).

By comparison, pregabalin has much better evidence in anxiety disorders, with eight randomized controlled trials at a dose range of 150–600 mg/day involving over 2000 patients with generalized and social anxiety disorders, including several with long-term follow-up (Generoso MB et al, *Int Clin Psychopharmacol* 2017;32(1):49–55). Pregabalin sees more use for anxiety in Europe, where it has regulatory approval in generalized anxiety disorder, while US psychiatrists lean toward gabapentin. The evidence is clearly in pregabalin's favor, but gabapentin does have a tolerability advantage, with lower rates of weight gain and ataxia (Shaheen A et al, *Pak J Med Sci* 2019;35(6):1505–1510).

Addictions

Despite concerns about gabapentin misuse, the medication does have a role in alcohol and cannabis use disorders. Patients who take it for alcohol use disorders report fewer days of heavy drinking, with an effect size in the medium range (0.4) from seven randomized controlled trials (Ahmed S et al, *Prim Care Companion CNS Disord* 2019;21(4):19r02465). Gabapentin also improves sleep quality during recovery from alcohol use. The dose range was 300–3600 mg/day, with most settling in around 900 mg/day.

Gabapentin may also be useful for alcohol withdrawal, but with a caveat. Although it was generally effective in controlled trials that compared it with benzodiazepines and phenobarbital, there were a few seizures during the gabapentin taper—not enough to raise statistical alarms, but enough to give us pause. It does improve cravings, anxiety, and sleep during withdrawal, so it may still have a role as an adjunct to more established methods like a benzodiazepine taper, or its use should be confined to patients with less severe dependence. A typical schedule starts at 1200–2400 mg/day in three or four divided doses, tapers to 600 mg/day over four to seven days, then drops in increments of 300 mg or smaller every few days until reaching zero (Leung JG et al, *Ann Pharmacother* 2015;49(8):897–906). Alternatively, it may be continued long term to prevent relapse, a use that is endorsed by the APA guidelines on alcohol use disorders.

We have only one controlled trial for gabapentin in cannabis use disorder, but this limitation is tempered by the fact that there are few pharmacologic options for this disorder. In this small, placebo-controlled study, gabapentin reduced cannabis withdrawal symptoms, increased abstinence, and improved executive functioning (Mason BJ et al, *Neuropsychopharmacology* 2012;37(7):1689–1698).

Gabapentin is by no means a panacea for addictions, however. It failed in controlled trials of cocaine, methamphetamine, benzodiazepine, and opioid use disorders. Recent reports suggest particular caution in patients with opioid use disorder, as gabapentin may increase the risk of overdose and hospitalization in this group (Evoy KE et al, *Drugs* 2021;81(1):125–156).

Bipolar disorder

Long ago, there was a consensus in psychiatry that all anticonvulsants had antimanic effects. In 2000, gabapentin became the first anticonvulsant to challenge that idea, with a negative trial in bipolar mania that was followed by similar disappointments from topiramate and oxcarbazepine (Pande AC et al, *Bipolar Disord* 2000;2(3 Pt 2):249–255).

Gabapentin is not reliable on its own in bipolar disorder, but two placebo-controlled trials suggest it may have a role as adjunctive therapy. It augmented lithium in acute mania and had mild preventive effects over a year when added to various mood stabilizers. As encouraging as these results are, both came from small trials with a total n of 85 (Astaneh AN and Rezaei O, *Int J Psychiatry Med* 2012;43(3):261–271; Vieta E et al, *J Clin Psychiatry* 2006;67(3):473–477). In practice, gabapentin is best reserved for treating bipolar disorder in patients with comorbidities like anxiety and alcohol or cannabis use disorders.

Off-Label Dosing of Gabapentin

Use	Total Daily Dosage
Akathisia	300–2400 mg
Alcohol use disorder	600–2400 mg
Anxiety disorders	300–3600 mg
Bipolar disorder (as an adjunct)	900–4800 mg
Insomnia	200–900 mg
Restless legs syndrome	300–2400 mg

Restless legs syndrome and pain

Gabapentin has only three FDA indications: partial seizures, post-herpetic neuralgia, and restless legs syndrome (RLS). Although used widely in pain disorders, it only has clear benefits in post-herpetic neuralgia and diabetic peripheral neuropathy, and is not considered effective for low back pain, sciatica, spinal stenosis, or migraines (Mathieson S et al, *BMJ* 2020;369:m1315).

Gabapentin's RLS approval is reserved for gabapentin enacarbil (Horizant), a prodrug that delays absorption by attaching the medication to an enacarbil molecule. However, there are three reasons to prefer the original gabapentin when treating RLS besides the higher cost of the patented Horizant:

1. *Convenience.* Horizant must be taken with a meal at 5:00 p.m. Gabapentin can be taken before bed regardless of food.
2. *Driving.* The *PDR* warns of "significant driving impairment" for two hours after taking Horizant, a problem that is compounded by alcohol, which quickens Horizant's release. This is an issue for patients who dine out, while gabapentin can be taken right before bed without affecting driving the next morning.
3. *Toxicity.* The enacarbil in Horizant breaks down into acetaldehyde, the same byproduct responsible for the carcinogenic and hangover effects of alcohol. The FDA originally rejected the drug over this issue, and Horizant still carries a warning about "chromosomal aberrations" in human lymphocytes "attributed to acetaldehyde."

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Research Updates IN PSYCHIATRY

PSYCHEDELICS

MDMA-Assisted Therapy for Severe PTSD

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

REVIEW OF: Mitchell JM et al, *Nat Med* 2021;27(6):1025–1033

STUDY TYPE: Randomized controlled trial

MDMA (3,4-methylenedioxymethamphetamine, more commonly known as ecstasy or molly), is an amphetamine analog that also increases transmission of both serotonin and oxytocin. Prior to the FDA banning it from further research in 1985, MDMA had been developing a reputation for its ability to enhance the benefits of psychotherapy. These same effects were also gleaned on the street, where its perceived prosocial qualities and absence of violent tendencies led to its popularity in raves. In 2017, the FDA reversed course, granting MDMA breakthrough status to pursue an indication as an adjunct to psychotherapy for severe posttraumatic stress disorder (PTSD). This trial is the first phase III trial for that use.

In this study, researchers randomized 89 patients with PTSD to receive either MDMA or placebo in conjunction with manualized therapy for PTSD. Participants received three monthly doses of MDMA or placebo delivered over an eight-hour period. Each dose was followed by three weekly 90-minute "integration" sessions to help patients understand and incorporate their experience. The primary outcome of interest was reduction in PTSD scores on the Clinician-Administered PTSD Scale (CAP-5), while secondary outcomes evaluated changes in functioning.

The results were unusually robust. Reduction in CAP-5 scores were significantly greater in the active treatment cohort ($p < 0.0001$), and the effect size was large: 0.9 (by way of comparison, SSRI effect sizes for PTSD are typically in the 0.3–0.6 range). In addition, depression scores and functioning improved, and 67% of patients in the MDMA arm no longer met criteria for PTSD at endpoint (compared with 32% in the placebo arm). The benefits were apparent almost immediately and both accrued and persisted throughout the study. They appeared unhindered by duration or severity of PTSD symptoms, type of trauma, or degree of treatment resistance.

MDMA was well tolerated, with the most common side effects being muscle tightness, nausea, decreased appetite, and hyperhidrosis. There were no reports of suicidality, abuse, or serious adverse events associated with MDMA.

The major limitation of the study, as with many such studies, is that there is no way to ensure adequate blinding. To their credit, the investigators asked subjects to guess which medication they thought they had received. Many, though not all, were in fact able to guess correctly.

TCPR'S TAKE

This rigorously conducted study is almost unparalleled in the annals of psychopharmacology for its effect size and safety. While it remains to be seen whether the gains are enduring, two questions naturally arise: Why might MDMA be so effective, and what took us so long? The answer to the second question is straightforward. MDMA fell victim to the antidrug wave of the 1970s and 1980s that shunned research involving any illicit substances. As to the first question, while enhanced serotonin release is hardly novel, keep in mind that the brain is not a monolithic organ. MDMA seems to preferentially target the amygdala, which is believed to be integral to the pathophysiology of PTSD. The release of serotonin and oxytocin there holds out promise of offering a truly targeted biological approach when used in conjunction with PTSD-focused therapy.

BIPOLAR

Lumateperone in Bipolar Depression

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

REVIEW OF: Calabrese JR et al, *Am J Psychiatry* 2021. Epub ahead of print

STUDY TYPE: Randomized, placebo-controlled trial

In 2019, lumateperone (Caplyta) became the 13th atypical antipsychotic with FDA approval in schizophrenia. Compared to other atypicals, it is relatively well tolerated, with low rates of akathisia and metabolic side effects. On December 20, 2021, the FDA approved the drug for bipolar I and II depression, and here we report on one of the trials that led to that approval.

This large, randomized, placebo-controlled, multi-center trial involved 377 patients with both bipolar I (n = 301) and bipolar II (n = 76) depression. The study was "quadruple blind," meaning the subjects, providers, investigators, and people administering the rating scales were all blinded to the assigned treatment. The primary outcome measure was the clinician-rated Montgomery-Åsberg Depression Rating Scale (MADRS). Lumateperone was started and maintained at 42 mg/day and used as monotherapy.

After six weeks, lumateperone outperformed placebo with a medium effect size (0.56) on the primary outcome of change on MADRS. Response (51.1% vs 36.7%, $p < 0.001$) and remission rates (39.9% vs 33.5%, $p < 0.018$) were also significantly greater with lumateperone. It was well tolerated, with minimal risk of metabolic, EPS, and prolactin side effects. A post-hoc analysis found greater benefits in bipolar II vs bipolar I depression (effect size of 0.81 vs 0.49) and revealed that a subgroup of patients with mixed features benefited from the medication.

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Research Updates
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The FDA reviewed two other trials that tested lumateperone in bipolar I and bipolar II depression with a similar design. These have not been published but were made available as a press release. One study was negative (study 401) and the other positive (study 402). Both were large, six-week trials, enrolling 554 and 529 patients. Unlike the Calabrese study, they tested three arms: lumateperone 28 mg, lumateperone 42 mg, and placebo. The positive study tested lumateperone as an adjunct to lithium or valproate and arrived at a small effect size (0.27) for the 42 mg dose and a non-significant effect with the 28 mg dose. A fourth trial is underway for unipolar depression with mixed features, a new disorder in DSM-5 that recognizes manic features in depressed patients who do not meet criteria for a bipolar diagnosis.

These trials are unique in their inclusion of bipolar II patients. Among the antipsychotics, only quetiapine and cariprazine have large studies in bipolar II depression, and only quetiapine's studies were positive.

TCPR'S TAKE
Lumateperone joins quetiapine as the only atypical antipsychotic with evidence in both bipolar I and bipolar II depression. Its main advantage is its favorable tolerability, while disadvantages include cost and the lack of research in the manic and maintenance phases of bipolar disorder.

SUBSTANCE USE

A Novel Treatment for Methamphetamine Use Disorder

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

REVIEW OF: Trivedi MH et al, *N Engl J Med* 2021;384(2):140–153

STUDY TYPE: Randomized, double-blind, placebo-controlled trial with sequential parallel comparison design

Methamphetamine use disorder is an increasing cause of overdose deaths in the US. Pharmacologic options are scarce, but pilot studies suggest that bupropion and naltrexone may be effective, either alone or in combination. This study tested them in combination.

The authors designed this double-blind, randomized, placebo-controlled study in two phases. First, patients were randomized to treatment or placebo for six weeks, with three times as many assigned to placebo. In the second stage, patients who responded to placebo were removed, and the remaining placebo non-responders were re-randomized to either more placebo or active treatment for another six weeks, this time with equal numbers in the placebo and treatment arms. The point of this design was to dampen the placebo response in the second phase of the study.

The subjects, recruited through advertisements and direct referrals, were adults with moderate to severe methamphetamine use disorder who wanted to quit or reduce use. On average, they had used methamphetamine on 27 of the previous 30 days. The active combo treatment was extended-release (ER) naltrexone 380 mg IM every three weeks and ER bupropion 450 mg daily.

There were 403 participants in stage 1, and 225 who did not respond to placebo were re-randomized to stage 2. Overall retention was good (77.4%). The primary outcome was response, defined as three out of four urine tests negative for methamphetamine in the last two weeks of stage 1 or stage 2.

In terms of results, naltrexone-bupropion was significantly more effective than placebo. The weighted average response was 13.6% for the active group and 2.5% for placebo ($p < 0.001$), and the number needed to treat (NNT) was 9. Serious adverse events, such as nausea, vomiting, and constipation, were evenly divided between active and placebo conditions.

TCPR'S TAKE
Naltrexone-bupropion combination is somewhat effective for methamphetamine use disorder. While the NNT of 9 is on the small side, this treatment was backed by a well-designed trial, and in a disorder with such devastating consequences, every tool is important.

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Although lacking in FDA approval, the original gabapentin was effective for RLS in half a dozen small studies. The usual dose is 300 mg before bed (which is equivalent to 600 mg of Horizant), but studies have gone as high as 2400 mg.

Akathisia, sleep, and hot flashes
Treatments for RLS often reduce akathisia, and gabapentin has promising results for this antipsychotic side effect, as evidenced in open-label trials at doses of 300–3600 mg/day.

Gabapentin is often used as a hypnotic, and this is supported by small controlled and open-label trials where it improved sleep duration and quality (eg, increased slow-wave sleep) at 200–900 mg/day (Furey SA et al, *J Clin Sleep Med* 2014;10(10):1101–1109). In practice, this means gabapentin may not help your patients fall asleep faster, but it can deepen their sleep and reduce nocturnal awakenings. Women with post-menopausal vasomotor symptoms are good candidates for this hypnotic use, as gabapentin reduced hot flashes in several controlled trials (Saadati N et al, *Glob J Health Sci* 2013;5(6):126–130).

Risks
Gabapentin has no serious warnings, but common adverse effects include sedation, fatigue, dizziness, imbalance, tremor, and visual changes from nystagmus.

Dosing tips
Gabapentin is one of the rare psychiatric meds with "nonlinear pharmacokinetics." That means serum levels start to plateau after a certain dose and rise sluggishly from there. For gabapentin, that dose is 900 mg. At 900 mg, 540 mg of the drug is absorbed; at 1200 mg, only 564 mg is absorbed; and at 2400 mg, a measly 816 mg makes it into the bloodstream. This slowdown occurs because the transporters that absorb gabapentin are easily saturated at higher doses (the prodrug Horizant was developed to overcome this limitation, but it does so at a cost).

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CME Post-Test

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1. According to recent studies, gabapentin has benefits in which substance use disorder(s) (LO #1)?
   - [ ] a. Benzodiazepine use disorder
   - [ ] b. Alcohol and cannabis use disorders
   - [ ] c. Opioid use disorder
   - [ ] d. Cocaine and methamphetamine use disorders

2. According to Dr. Miller, there is some evidence that melatonin has metabolic benefits and reduces oxidative stress in patients with schizophrenia receiving antipsychotic therapy (LO #2).
   - [ ] a. True
   - [ ] b. False

3. In a recent trial, lumateperone outperformed placebo in bipolar I and bipolar II depression on the primary outcome of change on the Montgomery-Åsberg Depression Rating Scale. What was the effect size (LO #3)?
   - [ ] a. Small
   - [ ] b. Medium
   - [ ] c. Large
   - [ ] d. No statistical difference from placebo

4. Which of the following is true about gabapentin versus pregabalin for anxiety disorders (LO #1)?
   - [ ] a. Gabapentin has higher rates of weight gain and ataxia compared to pregabalin
   - [ ] b. Gabapentin did not separate from placebo for nonspecific anxiety in breast cancer survivors
   - [ ] c. Pregabalin has eight randomized controlled trials supporting its use in generalized and social anxiety disorders, while gabapentin only has two
   - [ ] d. Gabapentin and pregabalin might be effective for anxiety at doses of 150–600 and 900–3600 mg/day, respectively

5. Compared with other non-clozapine antipsychotics, which antipsychotics were shown to have slightly superior efficacy for positive symptoms of schizophrenia (LO #2)?
   - [ ] a. Risperidone and olanzapine
   - [ ] b. Paliperidone and aripiprazole
   - [ ] c. Quetiapine and haloperidol
   - [ ] d. Asenapine and lurasidone

In Brief: Lybalvi: The Diet Olanzapine

Lybalvi is a new combo pill that aims to overcome the dreaded metabolic effects of olanzapine by pairing it with the opioid antagonist samidorphan. Patients still gain weight on Lybalvi, though not as much as they do on olanzapine. In the three controlled trials that compared the two drugs, the weight gain on Lybalvi was 5 lb less at six months, 3 lb less at three months, and no different at one month (Srisurapanont M et al, *Sci Rep* 2021;11(1):7583).

Where the drug falls short is in comparison to metformin, which reduced weight gain on various antipsychotics by 7 lb compared with placebo in a meta-analysis of 10 trials, most of which lasted three months, at a dose range of 750–2000 mg/day (Mizuno Y et al, *Schizophr Bull* 2014;40(6):1385–1403). Moreover, metformin improved insulin sensitivity, hemoglobin A1C, dyslipidemia, and prolactinemia on antipsychotics, while Lybalvi improved none of these.

Lybalvi could also be compared with naltrexone, an opioid antagonist with a similar pharmacodynamic profile to samidorphan. Naltrexone has weaker evidence when it comes to reducing weight gain on antipsychotics, showing effectiveness in only one of two trials. However, the naltrexone trials enrolled patients with actual obesity (BMI > 30 kg/m^2), while patients in the Lybalvi trials were barely overweight (BMI 18–30, mean 25). This may have made a difference, as Lybalvi tended to work better in patients with lower BMI.

Lybalvi is approved in schizophrenia and bipolar I disorder, although the studies were limited to schizophrenia. The drug does not seem to exacerbate psychosis or add to the side effect burden of olanzapine. The manufacturer also sought approval for schizophrenia with alcohol use disorder, but a negative phase II trial halted that pursuit. To prevent opioid withdrawal, Lybalvi should not be started within seven days of taking a short-acting opioid or 14 days of a long-acting one. Most insurers require documentation of significant weight gain on olanzapine or failure of two generic atypical antipsychotics to cover Lybalvi, which retails for $1300 per month.

TCPR'S TAKE

Metformin is preferred over Lybalvi for weight gain on antipsychotics, as it brings about more meaningful metabolic benefits beyond the reduction in BMI.

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

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An Off-Label Guide to Gabapentin

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Gabapentin is excreted entirely by the kidneys, which means it avoids hepatic drug interactions, but the dose needs to be lowered as creatinine clearance (CC) declines, a common problem in older patients. The usual dose range of 900–3600 mg/day is lowered to 400–1400 mg/day for a CC of 30–59 mL/min, 200–700 mg/day for a CC of 15–29 mL/min, and 100–300 mg/day for a CC below 15 mL/min (such patients usually require dialysis).

With a six-hour half-life, gabapentin can be divided three times daily for anxiety disorders and dosed at bedtime for sleep disorders. When stopping the medication, taper gradually to avoid withdrawal symptoms, which are rare and include tremor, sweating, restlessness, insomnia, and a lower threshold for seizures (Mersfelder TL and Nichols WH, *Ann Pharmacother* 2016;50(3):229–233). *(Editor's note: See the table "Off-Label Dosing of Gabapentin" on page 4.)*

TCPR VERDICT: Gabapentin is probably used more often than the evidence supports. Consider it for alcohol and cannabis use disorders, and insomnia with hot flashes or nocturnal awakenings. Both pregabalin and gabapentin are effective in anxiety disorders, but pregabalin should be tried first as it has the better data.

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