

Subscribe today!
Call 866-348-9279

AN UNBIASED MONTHLY COVERING ALL THINGS PSYCHIATRIC

Chris Aiken, MD
Editor-in-Chief
Volume 17, Issue 1
January 2019
www.thecarlatreport.com

IN THIS ISSUE

Focus of the Month: Deprescribing

Prescription CBD Is Available, But Are We Ready to Use It?	— 1
Expert Q&A: Barbara Farrell, PharmD Deprescribing Medication	— 1
Ask the Editor: Wellbutrin Augmentation: When Does It Work?	— 4
Tables: <ul style="list-style-type: none">• Cannabinoids From CBD to THC — 2• 5 Medications to Consider Deprescribing — 5	
Research Updates: <ul style="list-style-type: none">• Cannabidiol for Schizophrenia — 6• Is Ketamine Just Another Opiate? — 6	
CME Test	— 7
News of Note: <ul style="list-style-type: none">• Brexanolone: A New Treatment for Postpartum Depression — 7	

Learning Objectives

After reading these articles, you should be able to:

1. Discuss the differences between tetrahydrocannabinol (THC) and cannabidiol (CBD), two marijuana-derived cannabinoids.
2. Identify when deprescribing medications could be beneficial to a patient.
3. Summarize some of the current research on psychiatric treatment.

Prescription CBD Is Available, But Are We Ready to Use It?

Chris Aiken, MD, Editor-in-Chief of The Carlat Psychiatry Report. *Practicing psychiatrist, Winston-Salem, NC.*

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

Your patient comes in with a new medication on his list: CBD oil. He started taking it for anxiety and wants to know if it's safe. You hedge, explaining that there is limited information available on unregulated products, but the patient is persistent. He says CBD oil is available as a prescription, and wonders if you could write one for it.

Cannabidiol, or CBD, is a derivative of marijuana that has recently become available as a prescription drug, Epidiolex.

In Summary

- Marijuana contains over 100 cannabinoids. One of them, cannabidiol (CBD) oil, is growing in popularity as an over-the-counter remedy for psychiatric symptoms.
- CBD recently became available as a prescription for epilepsy, but should not be confused with "medical marijuana," which contains a more dangerous cannabinoid: tetrahydrocannabinol (THC).
- THC is responsible for the cognitive impairment and psychosis seen with marijuana, whereas CBD may actually improve psychosis and anxiety.

Continued on page 2



Deprescribing Medication Barbara Farrell, PharmD

Assistant Professor, Department of Family Medicine, University of Ottawa and Adjunct Assistant Professor, School of Pharmacy, University of Waterloo. Co-founder of the Canadian Deprescribing Network.

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

There's no shortage of information on prescribing medications, but when and how do we stop them? The Bruyere Deprescribing Guidelines Research Team is a group of clinicians and researchers who've set out to answer those questions. They've recently published 5 deprescribing guidelines, 3 of which are for psychiatric medications: benzodiazepines, antipsychotics in dementia, and cholinesterase inhibitors. We caught up with the leader of this research program, Barbara Farrell, to learn more.



TCPR: What is deprescribing?

Dr. Farrell: Deprescribing refers to lowering or stopping medications that might be causing harm or no longer providing benefit. It's done in a planned, collaborative, and supervised way rather than simply the patient stopping the medications independently.

TCPR: Sounds like something we should have been doing all along. Why now?

Dr. Farrell: I think people have been doing it all along, though maybe not defining it in that way. The term "deprescribing" first appeared in 2003.

Continued on page 3

Prescription CBD Is Available, But Are We Ready to Use It?

Continued from page 1

Cannabinoids From CBD to THC

Name	Regulation	Effects and Indications
Cannabidiol oil (CBD)	Over the counter	Benefits in psychosis and possibly anxiety. Sedation.
Epidiolex (CBD)	Schedule V Rx	This prescription form of CBD oil was recently FDA-approved for rare forms of childhood epilepsy.
Dronabinol (Marinol) and nabilone (Cesamet)	Schedule III Rx	FDA-approved for nausea during chemotherapy and anorexia in AIDS, these synthetic versions of THC carry similar risks as THC.
Tetrahydrocannabinol (THC)	Illegal in most states	THC is the cannabinoid responsible for marijuana's highs. It is addictive and can cause psychosis and cognitive impairment, particularly in adolescents.

It is FDA-approved for two rare forms of childhood epilepsy, Lennox-Gastaut and Dravet syndromes, and was fast-tracked for that indication because of the dire need for treatment in children with these intractable

seizures. Meanwhile, the same drug has been available as a supplement for the past decade, called CBD oil. Many patients take this oil for its rumored mental health benefits, and you'll need to know the basics when they request prescriptions for it.

CBD vs THC

Marijuana (cannabis) is a blend of over 100 cannabinoids, only one of which is tetrahydrocannabinol (THC), the cannabinoid that is most responsible for the high people get from consuming pot. CBD, on the other hand, does not cause a "high," although many people consider it to be somewhat tranquilizing. CBD also does not cause some of the problems seen with THC, such as cognitive impairment, anxiety, and (more rarely) psychosis. Those dangers are particularly relevant to adolescents, where the latest data show that marijuana triples the risk of psychotic disorders (Jones HJ et al, *JAMA Psych* 2018;75(3):240–246). CBD has neuroprotective properties, and it may actually lower the risk of psychosis and anxiety with THC. For more information, see the table "Cannabinoids From CBD to THC" above.

CBD in psychiatric disorders

In one of the most paradoxical clinical findings in recent memory, it turns out that CBD, far from causing psychosis, may actually be an effective *treatment* for psychosis. So far, 5 out of 7 controlled trials of CBD's antipsychotic effects have been positive, and the latest of these is reviewed in this issue (*Epidemiol Psychiatr Sci* 2018;27(4):327–335). Another prescription CBD product, Arvisol, is undergoing phase I clinical trials in schizophrenia.

In addition to psychosis, there are a couple of small, placebo-controlled trials of CBD in social anxiety disorder. These

looked at the drug's acute effects when taken before a stressful social situation in 34 subjects. Compared to placebo, CBD had a significant effect, bringing anxiety down to the same levels reported by healthy controls (Blessing EM et al, *Neurotherapeutics* 2015;12(4):825–836).

Somnolence is the main side effect with CBD, but studies in sleep are mixed. Tolerance can develop to its sedative effects, and low doses (below 160 mg) can be stimulating (Babson KA, *Curr Psychiatry Rep* 2017;19(4):23). CBD does not appear to help bipolar mania or the cognitive impairments of schizophrenia.

CBD oil or Epidiolex?

Are CBD oil and Epidiolex really the same drug? They are both CBD, short for cannabidiol, but where they differ is in their purity and regulatory status. Epidiolex is a Schedule V prescription drug, the lowest level of regulation for a controlled substance. CBD oil is an over-the-counter supplement. It is legal in all states as long as it's extracted from the hemp plant, a variety of cannabis that contains little THC and produces no high.

In terms of purity, CBD oil is a gamble. In a study of 84 online products, only 30% contained the amount of CBD on the label, and 21% contained THC (Bonn-Miller MO et al, *JAMA* 2017;318(17):1708–1709). The FDA keeps a running tally of unacceptable products at www.fda.gov/NewsEvents/PublicHealthFocus/ucm484109.htm. Another good source is Consumer Labs, which tests products for purity and integrity. Among their recommended options, the best-priced oils are available at elixinol.com and bluebirdbotanicals.com.

The dosages used in psychiatric research range from 300 mg/day for

Continued on page 3

EDITORIAL INFORMATION

Publisher: Daniel Carlat, MD

Editor-in-Chief: Chris Aiken, MD

Deputy Editor: Talia Puzantian, PharmD, BCPP, associate professor, Keck Graduate Institute School of Pharmacy, Claremont, CA

Executive Editor: Janice Jutras

Editorial Board:

Ronald C. Albuchoer, MD, clinical associate professor of psychiatry, Stanford University, Palo Alto, CA

Richard Gardiner, MD, psychiatrist in private practice, Potter Valley, CA

Alan D. Lyman, MD, child and adolescent psychiatrist in private practice, New York City, NY

James Megna, MD, PhD, DFAPA, director of inpatient psychiatry, professor departments of psychiatry, medicine, and public health & preventive medicine, SUNY Upstate Medical University, Syracuse, NY

Michael Posternak, MD, psychiatrist in private practice, Boston, MA

Glen Spielmans, PhD, associate professor of psychology, Metropolitan State University, St. Paul, MN

Marcia L. Zuckerman, MD, outpatient psychiatrist, Hallmark Health, Medford, MA; clinical assistant professor in psychiatry at Tufts School of Medicine

All editorial content is peer reviewed by the editorial board. Dr. Carlat, Ms. Jutras, Dr. Aiken, Dr. Albuchoer, Dr. Gardiner, Dr. Lyman, Dr. Megna, Dr. Posternak, Dr. Puzantian, Dr. Spielmans, and Dr. Zuckerman have disclosed that they have no relevant financial or other interests in any commercial companies pertaining to this educational activity. This CME/CE activity is intended for psychiatrists, psychiatric nurses, psychologists, and other health care professionals with an interest in the diagnosis and treatment of psychiatric disorders.

Mailing Information

The Carlat Psychiatry Report (ISSN 2473-4128) is published 10 times per year by Carlat Publishing, LLC, 29 Water Street, Newburyport, MA 01950.

Application to mail at periodicals postage prices is pending at Newburyport, MA and additional mailing offices.

POSTMASTER: Send address changes to The Carlat Psychiatry Report, P.O. Box 626, Newburyport, MA 01950.

Prescription CBD Is Available, But Are We Ready to Use It?

Continued from page 2

anxiety to 800–1,200 mg/day for schizophrenia. The epilepsy dosage, 10–20 mg/kg/day, adds up to around the same amount used in schizophrenia for most adults. Cost is an issue with CBD, prescribed or not. A 300 mg dose is \$20–50/day in the over-the-counter form and around \$35/day for the prescription when paying out of pocket.

CBD, Marinol, and medical marijuana

CBD is in a very different category than dronabinol (Marinol) and nabilone (Cesamet), the other prescription cannabinoids. These are synthetic isomers of THC (Δ-9-THC) and are under tighter regulation than CBD (Schedule III vs Schedule V). They are only approved for nausea during chemotherapy and, in the case of dronabinol, anorexia in AIDS. As pure THC compounds without the protective effects of CBD, they may have even more psychedelic effects than marijuana

(Bhattacharyya S et al, *Neuropsychopharmacology* 2010;35(3):764–774). “Medical marijuana” can refer to any marijuana component, such as CBD, or to the plant itself. It usually refers to the plant, which is legal with a prescription in 33 states and Washington DC. Each state has its own list of conditions that medical marijuana is approved for.

Side effects and drug interactions

The World Health Organization concluded that CBD has “a good safety profile” (WHO, 2018). Somnolence is its main side effect, and the *PDR* warns of elevated liver enzymes. On drug screens, CBD can cause a false positive for THC.

CBD may raise the levels of psychiatric medications through inhibition at UGT2B7 (lamotrigine, lorazepam) and CYP2C19 (diazepam and several SSRIs and antipsychotics). CBD itself is metabolized by CYP3A4 and CYP2C19.

Risks vs benefits

The FDA fast-tracked the approval of Epidiolex (CBD) because its risk-benefit profile is favorable for rare forms of epilepsy that are difficult to control with current anticonvulsants. The bar is higher for disorders with existing treatments, like psychosis and anxiety, and the data in these conditions are scarcer.

While we sort out these dilemmas, patients will no doubt experiment with the readily available CBD oil, so what should we do in the interim? We recommend the following commonsense approach.

TCPR VERDICT: We don't have much evidence to endorse or warn against CBD. Though it's premature to prescribe CBD, we should guide patients to safer products if they are getting it on their own. That's harm reduction, like suggesting to casual drinkers that red wine is safer than vodka.

Expert Interview

Continued from page 1

It's come to the forefront because of growing awareness of the problems with polypharmacy: adverse effects, drug interactions, hospitalizations, emergency room visits, and even mortality.

TCPR: How do you talk to patients about deprescribing?

Dr. Farrell: I use plain language like, “A drug that was good for you then might not be good for you now.” I might add, “I want to make sure that you're only taking medications you're really benefitting from, and that we are always using the lowest effective dose. Over time the body may not get rid of drugs as easily, so it's normal to gradually lower the dose.”

TCPR: Are the risks of polypharmacy greater in the elderly?

Dr. Farrell: Yes. As people get older, they absorb, process, and excrete drugs differently than they did when they were younger, and they also become more sensitive to CNS side effects. We also have more body fat as we age, and that can make fat-soluble drugs like diazepam accumulate because it lengthens their half-life.

TCPR: One of your guidelines focuses on benzodiazepines. When do you recommend deprescribing these?

Dr. Farrell: Anyone over age 65 who is taking a benzo for insomnia would be a good candidate for deprescribing. For younger people, if they've been taking a benzo for insomnia for over 4 weeks, coming off it should be considered. We should also consider deprescribing when the underlying problem, like anxiety, is already well-managed. On the other hand, our guidelines mention cases where continuing the benzo is reasonable, like for anxiety or other psychiatric illnesses that aren't well-managed, or when the benzodiazepine is needed to treat an anxiety disorder. **Editor's note:** See the table “5 Medications to Consider Deprescribing” on page 5.

TCPR: How do you recommend coming off the benzo?

Dr. Farrell: Our general guide is to lower it by 25% every 2 weeks, and then by 12.5% near the end of the taper. That needs to be fine-tuned for the patient, though, so monitoring for problems every 1–2 weeks is important. Also keep in mind that this is what we recommend for insomnia and well-managed anxiety. It may be too fast for other patients.

TCPR: Some doctors switch to diazepam for benzo withdrawal because it has a long half-life, but you mentioned that may cause problems, particularly in the elderly where it can accumulate.

Dr. Farrell: In our deprescribing guideline, we don't recommend automatically switching to diazepam. Generally, we recommend tapering with the benzo the patient is already on.

TCPR: Are there medications that can ease benzodiazepine withdrawal?

Dr. Farrell: We didn't find any medications with good evidence to treat withdrawal, but we focused on insomnia, and there may be medications that help in individual cases. We do recommend cognitive behavioral therapy for insomnia (CBT-i), which is actually just as effective as a benzodiazepine for sleep (Pottier K et al, *Can Fam Physician* 2018;64(5):339–351).

Continued on page 4

Expert Interview

Continued from page 3

TCPR: What are some high-yield behavioral interventions you recommend for sleep?

Dr. Farrell: One of the big things I do is work with patients on lowering caffeine. They'll say, "Oh, caffeine doesn't bother me," and I'll reply, "Well, why are you taking a sleeping pill then?" Caffeine also has a big impact on anxiety and tremor. Another one that can keep patients up at night is bronchodilators like albuterol.

TCPR: What about alcohol at night?

Dr. Farrell: That's a problem. It tends to automatically wake people up at about 3 a.m. If someone is drinking 1–2 glasses at night, I'll negotiate trying 1 week of not having a wine or beer in the evening to see if that helps the patient sleep, and invariably it does.

TCPR: A lot of people are using hydroxyzine (Vistaril) in place of the benzos. Any thoughts on deprescribing that one?

Dr. Farrell: Well, it's highly, highly anticholinergic and sedating. Anticholinergic effects can easily add up with polypharmacy. A useful tool to keep track of that is the Anticholinergic Cognitive Burden Scale (see <https://tinyurl.com/yc8ftvk8>). I work in a geriatric day hospital, and we usually discourage people from hydroxyzine and similar meds like diphenhydramine (Benadryl). Most people don't realize that Tylenol PM, Nytol, Nyquil (anything with "Night" or "Ny" in its name) contains an antihistamine that can increase the risk of dizziness, falls, and confusion.

TCPR: What about the z-hypnotics: zolpidem (Ambien), eszopiclone (Lunesta), and zaleplon (Sonata)? Are these any safer for sleep than benzos?

Dr. Farrell: Probably not. They have similar side effects, and there are growing claims that these z-drugs also have some withdrawal associated with them. Our benzodiazepine deprescribing guideline team doesn't recommend switching to another sedative because we didn't feel comfortable that any of them were safer than benzodiazepines. Trazodone is often seen as a more benign hypnotic, but a recent study of over 7,000 nursing home residents found that it had about the same fall risk as the benzodiazepines (Bronskill SE et al, *J Am Geriatr Soc* 2018;66:1963–1971). Physicians are also shifting from benzos to low-dose antipsychotics for sleep, but the risks usually outweigh the benefits there, especially if the patient doesn't have an underlying psychiatric problem.

TCPR: What are some signs that a sleep medicine may no longer be safe?

Dr. Farrell: Cognitive impairment, sedation, dizziness, and falls. Also, if you ask, "How do you feel when you wake up in the morning?" and a patient says, "I feel exhausted," "It takes me 3 hours to get dressed," or "I go right back" ————— *Continued on page 5*

Ask the Editor

Each month, Editor-in-Chief Chris Aiken, MD, gives advice on a different practice challenge.

Wellbutrin Augmentation: When Does It Work?

Dear Dr. Aiken: In the July/August 2018 issue, you wrote that bupropion (Wellbutrin) augmentation does not work in treatment-resistant depression (TRD). So why do we see it work so often in practice?

Dr. Aiken: When all of the studies are averaged together, bupropion augmentation does not seem to work, but it's possible that something is lost in the averaging. What if there were two types of depressed patients—some who got worse with bupropion augmentation and others who got better? When lumped together, they would cancel out and give the impression that bupropion makes no difference. That's what a new analysis of the large CO-MED trial suggests. This study randomized 665 depressed patients into three treatment arms:

1. Escitalopram + placebo
2. Escitalopram + bupropion
3. Venlafaxine + mirtazapine

Outcomes were similar for all three groups after 12 weeks and again after 7 months. That's not a surprise, as our July/August issue suggested that none of those augmentation strategies perform much better than placebo. However, a different story emerges when the patients in that study are stratified by weight or inflammation. Compared to SSRI monotherapy, adding bupropion actually worsened outcomes when patients had

a BMI \leq 25 or low levels of C-reactive protein (CRP $<$ 1 mg/L), a marker for inflammation.

When CRP was \geq 1 mg/L or BMI was \geq 35, bupropion augmentation performed much better than SSRI monotherapy (remission rates were 1.75 times greater). For mild-moderate obesity (BMI 26–34), the three treatments did not differ (Jha MK et al, *J Affect Disord* 2018;234:34–37; Jha MK et al, *Psychoneuroendo* 2017;78:105–113).

These results need replication, but they did not come out of nowhere. Obesity is an inflammatory state, so it makes sense that BMI and CRP predicted similar outcomes. Bupropion is dopaminergic and noradrenergic, and has anti-inflammatory effects. Other research suggests that dopaminergic and noradrenergic antidepressants perform better in inflammatory states than the SSRIs.

Bottom line

Bupropion augmentation is not well-supported by the data, but if you use it, patients with obesity or inflammation may have the best outcomes. If combining bupropion with an SSRI, choose escitalopram or citalopram, as the others can alter its metabolism (see *TCPR*, Nov/Dec 2018). As for CRP, there's growing evidence that this biomarker can predict medication response, so look for an update in a future issue.



Expert Interview
Continued from page 4

to bed after breakfast,” that’s a sign of an issue. These problems come on gradually as people age, so a lot of physicians don’t recognize them as side effects.

TCPR: What are some risks with long-term antidepressant use?

Dr. Farrell: There can be additive side effects as the patient is put on more medications that would usually present as cognitive or anticholinergic problems, or falls. I’ve seen patients who wake up at night because of dry mouth on a medication like duloxetine, and then trazodone gets added because they can’t sleep. The result is an additive effect: more dry mouth and nocturnal awakenings.

TCPR: Stopping the antidepressant may be difficult, though, and some guidelines recommend continuing it indefinitely in patients who’ve had at least 3 depressive episodes.

Dr. Farrell: Yes. It may be that the answer is to reduce the dose, switch to another antidepressant, or lower off other drugs that may be contributing to the side effects. For example, if diarrhea develops after many years on an SSRI, you might end up lowering other meds that can cause diarrhea, like metformin or proton pump inhibitors.

TCPR: Do you see side effects start after many years on a drug?

Dr. Farrell: They can come on gradually as people age. We’ve had patients develop diarrhea after taking an SSRI for over a decade, and it goes away when we reduce the dose. Another problem is blood pressure. Someone on venlafaxine may have normal blood pressure at first, but we’ve seen cases where hypertension develops later in life and the blood pressure goes down to normal after the venlafaxine is stopped.

TCPR: We’re also using more blood pressure medications in psychiatry, like prazosin for nightmares, propranolol for akathisia, and clonidine or guanfacine for ADHD. What should we watch out for with those as people age?

Dr. Farrell: Definitely orthostatic hypotension. The elderly are more prone to that problem, so we often warn them to sit up on the edge of the bed for a minute before standing. Once upright, they should hold onto the dresser for a minute before they start to walk. Also, as people get into their 80s and 90s, we start worrying about both cognitive impairment and fall risk with low blood pressure. People can become easily confused when blood pressure falls too low.

TCPR: How should we manage antipsychotics in dementia?

Dr. Farrell: In dementia, antipsychotics are often used for psychosis, aggression, and agitation—what we call the behavioral and psychological symptoms of dementia (BPSD). They’re not absolutely contraindicated for BPSD, and they can work in the short term, but they carry unique risks in that population, including stroke, cardiac arrest, and premature death. What we recommend is gradually withdrawing the antipsychotic in these patients if the BPSD has stabilized for at least 3 months. At that point, withdrawal does not lead to worsened symptoms compared to continuation, according to controlled studies (Bjerre LM et al, *Can Fam Physician* 2018;64(1):17–27).

TCPR: How do you withdraw the antipsychotic?

Dr. Farrell: Our deprescribing guidelines recommend lowering the dose slowly by 25%–50% every 1–2 weeks. If the BPSD returns, consider non-drug interventions first. There’s good evidence for music therapy and behavioral interventions like structured activity, a safe place to walk, empathic communication skills, and offering the patient simple choices (Livingston G et al, *Health Technol Assess* 2014;18(39):1–226).

TCPR: Medications like donepezil, rivastigmine, galantamine, and memantine are supposed to slow the progression of dementia. What’s the harm in continuing them?

Dr. Farrell: The risks are gastrointestinal side effects and weight loss, particularly for elderly women, as well as dizziness, confusion, headache, insomnia, tremor, and agitation. Rarer side effects include urinary problems, bradycardia, pulmonary and dermatological complications, seizures, GI hemorrhage, and rhabdomyolysis. Our guidelines recommend a trial off these medications after a year if it’s not clear that they are helping, if the patient’s condition has worsened, or if the patient has end-stage dementia (<https://tinyurl.com/ycclo3g3>).

“As people get older, they absorb, process, and excrete drugs differently than they did when they were younger, and they also become more sensitive to CNS side effects. Anyone over age 65 who is taking a benzo for insomnia would be a good candidate for deprescribing.”

Barbara Farrell, PharmD

TCPR: What if deprescribing fails and the patient can’t manage withdrawal?

Dr. Farrell: Sometimes it’s worth another try later on. People’s situations change. For example, some people come off anxiety meds more easily after they’ve retired and aren’t stressed out from work.

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

Editor’s note: For deprescribing guidelines, visit www.deprescribing.org.

5 Medications to Consider Deprescribing	
Medication	Risks
Benzodiazepines	Dependence, falls, cognitive impairment, dementia, sedation, pneumonia, motor vehicle accidents
Antipsychotics in dementia	Metabolic syndrome, TD, EPS, adverse cardiovascular events, temperature imbalance, hypotension, falls, UTIs, death
Cholinesterase inhibitors and memantine	Gastrointestinal effects, dizziness, confusion, headache, insomnia, agitation, weight loss, and falls
Proton pump inhibitors	Fractures, infections, low magnesium and B12
Antidiabetic medications	Hypoglycemia

SCHIZOPHRENIA

Cannabidiol for Schizophrenia

REVIEW OF: McGuire P et al, *Am J Psychiatry* 2017;175(315). doi:10.1176/appi.ajp.2017.17030325

TYPE OF STUDY: Double-blind, randomized controlled trial

Traditional antipsychotic medications leave much to be desired. Their therapeutic response rate for schizophrenia is low, and their side effects are troubling and lead to high rates of noncompliance. Clearly, there is an urgent need for alternative agents. Although patients—including those diagnosed with schizophrenia—have long attested to the benefits of marijuana, only recently have researchers begun taking it seriously as a therapeutic option. In this pilot study, investigators evaluated the benefits of cannabidiol (CBD), which is one of the two main active components of marijuana (the other being THC), for the treatment of schizophrenia.

In this 6-week, double-blind, randomized controlled trial, adult patients diagnosed with schizophrenia or a related psychotic disorder were recruited from multiple sites across Europe. All patients were actively psychotic, though they could not be entirely treatment-resistant (ie, patients had to have displayed at least a partial response to antipsychotic medications). Patients entered the study only after they had been on a stable dosage of antipsychotic medication for at least 4 weeks, and this medication was continued throughout the course of the study. CBD was dosed at 1,000 mg/day in the form of an oral solution. Active substance use was *not* grounds for exclusion. The primary efficacy measure used was the Positive and Negative Syndrome Scale (PANSS), while cognition was measured using the Brief Assessment of Cognition in Schizophrenia (BACS) scale.

43 patients were randomized to CBD and 45 to placebo. Positive symptoms (eg, delusions or hallucinations) were significantly reduced at endpoint

for patients receiving CBD compared to placebo. Improvement in negative symptoms (eg, flat affect) favored CBD, but this difference did not reach statistical significance. Patients receiving CBD also fared better on global assessment of functioning, clinicians' global assessment of improvement, and cognitive measures, though this latter difference fell just short of statistical significance ($p = 0.07$). No major adverse events occurred that were attributed to CBD, and the participants were not able to tell if they were taking CBD or placebo.

TCPR'S TAKE

CBD's therapeutic potential has received a lot of attention lately and is covered elsewhere in this issue. This is the most rigorous study of CBD in schizophrenia to date, and its intriguing findings warrant replication with a larger sample and longer duration. Given the many limitations and pitfalls associated with traditional antipsychotic medications, a novel compound that might be devoid of those pitfalls is a most welcome development.

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

PSYCHOPHARMACOLOGY

Is Ketamine Just Another Opiate?

REVIEW OF: Williams NR et al, *Am J Psychiatry* 2018;175:1-11

TYPE OF STUDY: Double-blind, placebo-controlled, crossover study

Ketamine's rapid antidepressant effects have now been demonstrated in over two dozen double-blind, placebo-controlled trials, but how it works is less clear. For many years, NMDA receptor antagonism was thought responsible, but other NMDA antagonists have not worked well in depression. Another possibility is the endogenous opioid system, which is responsible for ketamine's analgesic effects. If that system is also involved in ketamine's antidepressant effects, then the opioid antagonist

naltrexone ought to interfere with those benefits. This study sought to determine whether naltrexone would in fact dampen ketamine's benefits in depression.

Thirty subjects with chronic, highly refractory depression were enrolled (with a mean of 9.8 unsuccessful antidepressant trials). Each participant received, in random order, 2 separate IV infusions of ketamine 0.5 mg/kg—one preceded by naltrexone 50 mg and the other preceded by placebo. The primary outcome was reduction in depressive symptoms at postinfusion day 1. The dissociative effects of ketamine were examined as well.

When ketamine was given with a placebo, the response (58%) and remission (42%) rates for depression were high, but coadministration with naltrexone brought those rates to zero. In contrast, naltrexone did not have any discernible impact on ketamine's dissociative effects. Data collected on blinding suggested that participants were unable to discern when they were receiving naltrexone vs placebo.

The results were dramatic enough that the study was halted midway through for ethical reasons, so only 12 of the 30 subjects completed both arms.

TCPR'S TAKE

Could ketamine be nothing more than an opiate masquerading as an NMDA receptor antagonist? While the opioid system appears critical to ketamine's antidepressant effects, that doesn't mean ketamine directly affects opioid receptors in the way that morphine or codeine does. Endogenous opioids have well-known mood elevating properties, and exercise and even placebo stimulate endogenous opioids. Given the public health crises stemming from both treatment-refractory depression and opioid abuse, this study will no doubt stimulate a flurry of research into the exact role that the opioid system plays. Perhaps ketamine will unlock some of the mysteries behind the mechanisms of antidepressants.

—*Michael Posternak, MD.*

CME Post-Test

To earn CME or CE credit, you must read the articles and log on to www.TheCarlatReport.com to take the post-test. You must answer 75% of the questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be completed within a year from each issue's publication date. As a subscriber to *TCPR*, you already have a username and password to log onto www.TheCarlatReport.com. To obtain your username and password, please email info@thecarlatreport.com or call 978-499-0583.

The Carlat CME Institute is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. Carlat CME Institute is also approved by the American Psychological Association to sponsor continuing education for psychologists. Carlat CME Institute maintains responsibility for this program and its content. Carlat CME Institute designates this enduring material educational activity for a maximum of one (1) *AMA PRA Category 1 Credit*[™] or 1 CE credit for psychologists. Physicians or psychologists should claim credit commensurate only with the extent of their participation in the activity.

For those seeking ABPN Self-Assessment (MOC) credit, a pre- and post-test must be taken online at <http://thecarlatcmeinstitute.com/self-assessment/>

Below are the questions for this month's CME/CE post-test. This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Note: Learning Objectives (LO) are listed on page 1.

- Recent studies have shown CBD to be helpful for which of the following? (LO #1)
 - a. Mania
 - b. Psychosis
 - c. Weight loss
 - d. Cognition
- Your 68-year-old patient with well-managed anxiety has been taking lorazepam as a sleep aid for 5 years. According to Dr. Farrell, what is the general recommendation to follow for deprescribing benzodiazepines? (LO #2)
 - a. Lower by 5% every 2 weeks, and then by 2.5% near the end of the taper
 - b. Lower by 10% every 2 weeks, and then by 5% near the end of the taper
 - c. Lower by 25% every 2 weeks, and then by 12.5% near the end of the taper
 - d. Lower by 50% every 2 weeks, and then by 25% near the end of the taper
- Because the FDA maintains strict controls over the sale of CBD oil, over 75% of products contain the amount of CBD listed on the label. (LO #1)
 - a. True
 - b. False
- Due to risks such as stroke or cardiac arrest, patients taking antipsychotics for the behavioral and psychological symptoms of dementia (BPSD) should begin a gradual withdrawal once their symptoms have stabilized for _____. (LO #2)
 - a. 2 weeks
 - b. 1 month
 - c. At least 3 months
 - d. At least 6 months
- One drawback in a recent study on CBD in schizophrenia was that participants were able to tell if they were taking CBD as opposed to placebo. (LO #3)
 - a. True
 - b. False

News of Note

Brexanolone: A New Treatment for Postpartum Depression

There is a need for rapid treatment in postpartum depression, as each month of this potentially severe condition can take a toll on infant development. That is why brexanolone (Zulresso), which was recently fast-tracked for approval by the FDA, is causing such a splash.

Brexanolone is a neurosteroid that activates GABA_A receptors. It was originally developed as an anticonvulsant before its antidepressant properties were discovered. The pending approval is based on three randomized, double-blind, placebo-controlled trials involving 267 women with moderate or severe postpartum depression (Meltzer-Brody S et al, *Lancet* 2018;392:1058–1070). Most

were not taking antidepressants. Patients randomized to brexanolone surpassed those on placebo by 2–5 points on the Hamilton Depression Rating Scale. Furthermore, most of the responders (94%) maintained their improvement for 30 days after administration of the medication, which is given as an injection. Women with severe depression saw the greatest improvements. Longer follow-up data are not available, but an oral version of the drug is being developed that could play a role in prevention. The treatment was well-tolerated, with mild increases in headache, dizziness, and somnolence.

Is it just for postpartum depression?

Brexanolone's mechanism is particularly relevant to the postpartum period, but it plays a role in other psychiatric disorders

as well. It is actually a prescription form of allopregnanolone, a neuroactive steroid with known effects in anxiety, depression, aggression, and negative symptoms of schizophrenia in both women and men (Schüle C et al, *Prog Neurobio* 2014;113:79–87). Basically, brexanolone is to allopregnanolone as levothyroxine is to thyroxine (T₄).

Allopregnanolone activates GABA_A receptors, the same ones responsible for the anxiolytic effects of benzodiazepines. Its levels rise during pregnancy and then fall abruptly after childbirth. Some women are particularly sensitive to that fall, and the state of GABAergic withdrawal it creates is thought to be one of the pathways to postpartum depression. Allopregnanolone levels also rise and

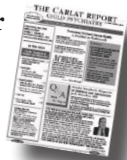
Continued on page 8

Hone your child psychiatry skills with...

The Carlat Child Psychiatry Report



This newsletter offers all of the same great features as *The Carlat Psychiatry Report* with a focus on child psychiatry.



One year: \$129
Two years: \$229

To subscribe, visit
www.thecarlatchildreport.com

THE CARLAT REPORT: PSYCHIATRY

P.O. Box 626
Newburyport, MA 01950

This Month's Focus:
Deprescribing

**Next month in *The Carlat Psychiatry Report*:
Dark and Light Therapy**

News of Note

Continued from page 7

fall during the menstrual cycle, though to a lesser degree, and those fluctuations are thought to contribute to premenstrual dysphoric disorder (PMDD).

In other psychiatric disorders, it is low levels of allopregnanolone rather than fluctuations that appear to play a role. Allopregnanolone is persistently low in major depression, post-traumatic stress disorder, and chronic stress. Several antidepressants raise allopregnanolone levels (SSRIs, tricyclics, and mirtazapine). However, as with most hormones, balance is the issue. Too much allopregnanolone can cause anxiety, depression, and irritability (Bäckström T et al, *Prog Neurobiol* 2014;113:88-94).

What's next?

The FDA is expected to make a final decision on brexanolone in early 2019. If approved, there will still be hurdles to overcome because brexanolone must be delivered as an IV infusion over 60 hours. Unless overnight clinics step in to supervise the treatment, hospitalization will be required.

An oral version is expected in the future, and that may broaden its indications. Oral brexanolone (SAGE-217) has a positive randomized controlled trial in major depression and is currently undergoing phase III clinical trials for that condition.

—Chris Aiken, MD.

- Yes! I would like to try *The Carlat Psychiatry Report* for one year. I may cancel my subscription at any time for a full refund if not completely satisfied.
Regular subscriptions – \$129
International – Add \$20 to above rates
- Please send me the *TCPR Binder* – \$14.99

Enclosed is my check for

Please charge my

- Visa
- MasterCard
- Amex

Card # Exp. Date

Signature

Name

Address

City State Zip

Phone E-mail

Please make checks payable to Carlat Publishing, LLC
Send to *The Carlat Psychiatry Report*,
P.O. Box 626, Newburyport, MA 01950
Or call toll-free 866-348-9279 or fax to 978-499-2278
Or subscribe online at www.TheCarlatReport.com