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Chris Aiken, MD
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Learning Objectives

After reading these articles, you should be able to:

1. Identify the benefits and drawbacks of using esketamine for treatment-resistant depression.
2. Manage nausea, sweating, and dry mouth in patients on psychiatric medications.
3. Recognize differences between normal and pathological auditory hallucinations.
4. Summarize some of the current research on psychiatric treatment.

Esketamine Gets FDA Approval

Michael Posternak, MD. Psychiatrist in private practice, Boston, MA.

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

On March 5, 2019, the FDA approved esketamine (Spravato) nasal spray as add-on therapy to traditional antidepressant medications for treatment-resistant depression (TRD). In this article, I will describe the events that led to esketamine's development, review the data submitted to the FDA, and discuss what the future might hold for esketamine.

Background

Ketamine was first synthesized in 1962
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Highlights From This Issue

Three new CNS drugs were recently approved by the FDA. Two are fast-acting treatments for depression: esketamine for treatment-resistant depression and brexanolone for postpartum depression. The third, solriamfetol, is a noradrenergic and dopaminergic medication for excessive fatigue.

Auditory hallucinations occur in 1%–3% of adults with no evidence of mental illness, but these “healthy voices” have a different quality than pathological ones.

Nausea, dry mouth, and sweating are common side effects on psychotropics. Dr. Rajnish Mago shares practical strategies to manage them.

Medication Side Effects: Nausea, Sweating, and Dry Mouth

Rajnish Mago, MD

Editor-in-Chief of Simple and Practical Mental Health and author of Side Effects of Psychiatric Medications: Prevention, Assessment, and Management

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



TCPR: What's the best way to manage side effects: lower the dose of the current medication or use an antidote?

Dr. Mago: If the patient can stay well on a lower dose, that's usually my first approach. Most side effects are dose related.

TCPR: For the rest of this interview, we'll assume that lowering the dose or changing the medication was not feasible or effective for our patients. Let's cover a few common side effects. What can you tell us about nausea?

Nausea

Dr. Mago: Nausea is one of the top reasons that patients stop medications prematurely. That's unfortunate because nausea usually subsides in a little bit of time. We can also reduce the incidence of nausea greatly by starting at a low dose and titrating slowly, like after 1 week. In randomized trials, that strategy tends to cut the rate of nausea in half. When nausea does happen, we need to
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Esketamine Gets FDA Approval

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by Parke-Davis Pharmaceuticals with the goal of creating an alternative to the anesthetic agent phencyclidine (PCP), which had become a drug of abuse. Ketamine was approved by the FDA in 1970 for anesthesia, and it remains in use today, in part because it suppresses respiration less than most other anesthetics.

In 2000, Berman et al published the first study (n = 7) suggesting that intravenous ketamine can produce rapid antidepressant effects. Since then, nearly two dozen trials have for the most part replicated these results. Unlike current antidepressants that act primarily on monoamine neurotransmitters, ketamine appears to work by enhancing glutamate transmission through NMDA receptor antagonism.

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Although intravenous ketamine appears to be an effective rapid-acting antidepressant, its commercial prospects are limited by the fact that it is available generically and is unlikely to yield the kind of return on investment drug companies need in order to market new products. In order to get around this financial issue, Janssen was able to patent esketamine, which is the ketamine (S)-enantiomer. This is similar to the strategy Forest Pharmaceuticals used many years ago when it successfully marketed citalopram's (S)-enantiomer: escitalopram (Lexapro).

Esketamine trials

The first published study of esketamine used an intravenous version. It demonstrated rapid and robust antidepressant effects within 2 hours in a placebo-controlled trial of 30 subjects (Singh JB et al, *Biol Psychiatry* 2016;80(6):424-431). With these encouraging results, Janssen next focused on intranasal esketamine. Daly and colleagues randomized 67 TRD patients, who remained on their existing antidepressant, to twice-weekly adjunctive placebo or intranasal esketamine at fixed dosages of 28 mg, 56 mg, or 84 mg. After one week, placebo non-responders were then re-randomized to one of the same four treatment arms. By week 2, all three dosages separated from placebo with a significant dose-response effect (p < 0.001). These gains were maintained over 6 weeks of open-label follow-up treatment (Daly EJ et al, *JAMA Psychiatry* 2018;75(2):139-148).

Canuso and colleagues next evaluated the benefits of intranasal esketamine 84 mg as add-on therapy to oral antidepressants in hospitalized patients with active suicidal ideation (Canuso CM et al, *Am J Psychiatry* 2018;175(7):620-630). Here, esketamine showed acute benefits at 4 and 24 hours for both depression and suicidality, though these responses were not maintained through the duration of the 4-week study.

In addition to the studies above, Janssen submitted the results of four pivotal trials to the FDA, though they have not yet been published. These included three short-term, randomized, double-blind trials (a fixed-dose study, a flexible-dose study in adults, and a

flexible-dose study in geriatric subjects), and one long-term, double-blind maintenance study.

The findings were generally consistent with the previously published data. To keep things simple, I'll combine the results of the three short-term TRD trials. Overall response rates after 4 weeks of treatment were significantly higher for esketamine + antidepressant compared to placebo + antidepressant: 53% (199 of 373) vs 37% (102 of 268), respectively. Of the individual studies, however, only one separated statistically from placebo, though the geriatric trial fell just short (p = 0.06).

In the long-term maintenance trial, the median time to relapse in stable responders to esketamine + antidepressant was significantly longer (635 days) than for those randomized to placebo + antidepressant (88 days; p < 0.001).

Other potential uses

While esketamine has only been approved for TRD, pilot studies suggest that ketamine or esketamine could also be useful for bipolar depression, PTSD, OCD, generalized anxiety disorder, social anxiety disorder, and suicidal ideation (Zhang K and Hashimoto K, *Expert Rev Neurother* 2018;1-10).

Side effects and safety

Esketamine appears to be reasonably well tolerated, with only about 5% of patients discontinuing treatment due to side effects over the course of 1 year of treatment. The most common side effects include a bitter aftertaste, nausea, dizziness, and sedation. Esketamine increases blood pressure on average by 5-10 mm Hg, and this tends to peak about 40 minutes post-dose before gradually resolving. Dissociation (or a sense of feeling drugged) is also commonly reported, though this too tends to dissipate within 1-2 hours.

Risk Evaluation and Mitigation Strategy (REMS)

Esketamine is a Schedule III controlled substance; that's one level below the stimulants and one level above the benzos. It has regulations of its own, however. Providers must register with

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Esketamine Gets FDA Approval

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the REMS system, and the DEA needs to perform an in-person inspection of the provider's office (www.thecarlatreport.com/REMS). A health care provider needs to provide supervision while the patient self-administers the intranasal dose, and this supervision must continue for at least 2 hours afterward to monitor for hypertension, sedation, and dissociation. Patients are not allowed to drive on treatment days and cannot take the medication home.

TCPR'S TAKE

Esketamine is the first novel antidepressant introduced in over three decades. It offers a new alternative for TRD and rapid-acting relief for severe depression and suicidality.

So how good is the science? If we consider the entire body of ketamine and esketamine research, it seems impressive. The published trials have mostly yielded significant results, and these studies stand out by including patients with severe

depression and suicidal ideation. Another design feature worth noting is that esketamine was initiated at the onset of a new antidepressant trial, whereas most augmentation studies add agents to an ongoing, *failed* trial. Why should this matter? Because it's harder to demonstrate that a treatment works when there's therapeutic "noise" from a new antidepressant that may be offering some therapeutic benefit of its own. In other words, the design of the esketamine trials actually made it harder to demonstrate the drug's efficacy, so it's all the more impressive that the agent actually beat placebo.

With an 18% drug-placebo separation in relapse rates, esketamine's long-term benefits appear comparable to those seen with atypical antipsychotic augmentation (Borges S et al, *J Clin Psych* 2014;75(3):205–214), though these results need to be replicated.

If there is one drawback to the esketamine research that should temper our enthusiasm, it is the Achilles heel

of almost all drug research: side-effect unblinding. Esketamine produces predictable side effects of sedation, dissociation, and a bitter aftertaste. Many patients could probably guess whether they'd been randomized to esketamine and whether it had been withdrawn from them during the maintenance phase. Such unblinding artificially inflates drug-placebo differences (Moncrieff J et al, *Br J Psych* 1998;172:227–231).

The failure to reach statistical significance in two of the three esketamine studies may be due to their sample sizes, which were smaller than those in most trials submitted to the FDA. Esketamine's magnitude of effect is similar to or slightly lower than ketamine's, which implies a larger sample may have produced a positive result. On the other hand, it may be a weakness of the drug itself rather than the study design.

One factor that probably swayed the FDA was our dire need to offer something new for patients suffering from TRD. But caution is warranted. History reminds us that the enthusiasm accompanying novel treatments almost never stands the test of time.

TCPR VERDICT: Esketamine is a new, viable option for patients with severe TRD. It can provide almost immediate relief, and those benefits can be maintained with continued dosing every 1–2 weeks. It will be interesting to see how esketamine stacks up in head-to-head studies against other traditional TRD options such as combination medication strategies and ECT.

Esketamine: Quick Facts

Dose: 56–84 mg intranasally in conjunction with an oral antidepressant. Doses must be administered under medical supervision and cannot be taken home.

Recommended Dosing Schedule:

Weeks 1–4: twice a week

Weeks 5–8: once a week

After week 8: every 1–2 weeks

Eligible Patients: Moderate to severe major depressive disorder who have failed > 2 adequate trials of traditional antidepressants.

Cost: \$590 for each 56 mg dosage; \$885 for each 84 mg dosage. Monthly maintenance therapy is expected to cost between \$2,360 to \$3,540 depending on dose frequency (not including cost of clinical oversight).

Regulation: Schedule III. All health care settings and pharmacies must be certified under a Risk Evaluation and Mitigation Strategy (REMS) program (*insert Carlat web link*). Patients must be monitored for at least 2 hours post-treatment.

Expert Interview

Continued from page 1

step in energetically with solutions. I tell the patient, "Listen, I understand that this is bothersome. We are going to do something about it today, but I can reassure you the nausea is not harming your body."

TCPR: Then what do you tell the patient?

Dr. Mago: First, the patient needs to take the medicine after food. Not *with* food, but immediately after a meal. Taking ginger root is another strategy. This is not just an old wives' tale—there are several randomized placebo-controlled trials of ginger extract for nausea associated with chemotherapy or pregnancy (Bodagh et al, *Food Sci Nutr* 2019;7(1):96–108).

TCPR: What about ginger ale?

Dr. Mago: No, even if a brand says "contains real ginger" like Canada Dry now does, the amount of

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Expert Interview

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ginger in soft drinks is too low—about 50 times lower than what is used in clinical trials. I recommend ginger capsules, about 1 hour before eating. That gives the ginger time to absorb. Then patients should take their medication immediately after eating. Good brands include Vitamin Shoppe, Nature's Way, and Nature's Bounty. The standard dose for the 550 mg capsules is either 2 capsules once a day or 1 capsule 2–3 times a day. One can increase it, but we should not assume that ginger is completely benign. I usually don't exceed 3 capsules a day (1,650 mg).

TCPR: What's your second and third line for nausea?

Dr. Mago: Ondansetron (Zofran) works well and actually blocks the 5-HT₃ receptor, which is the cause of nausea with most serotonergic medications. It's a "clean" drug in terms of its receptor effects with limited side effects of its own, but constipation is possible. I use the orally disintegrating tablets, starting with 4 mg, and will raise the dose to 8 mg if needed. If that does not work, metoclopramide is another option for the treatment of nausea (10 mg po q8hr prn).

Sweating

TCPR: You've done a lot of research on sweating. What do you find useful?

Dr. Mago: Sweating is something we see with almost all antidepressants, and it's very bothersome to the patient. Glycopyrrolate is my first choice and works very well (Mago R, *J Clin Psychopharmacol* 2013 33(2):279–280). It's an anticholinergic that does not cross the blood-brain barrier, so it won't impair cognition. That's a problem with centrally acting anticholinergics like oxybutynin and benztropine (Cogentin). Glycopyrrolate can have peripheral anticholinergic side effects, though, like constipation and dry mouth. Actually, that last one makes it useful for clozapine-induced drooling, and it's my first choice for that problem as well. Glycopyrrolate is dirt cheap, and you can take it prn. I dose it 1 mg, 1–2 po q6hr prn.

TCPR: What about terazosin, the alpha-1 antagonist?

Dr. Mago: Yes, there are two ways to treat sweating. You can block the effect of acetylcholine at the level of the sweat gland with an anticholinergic, or block the effect of norepinephrine at sympathetic ganglia with an alpha-1 antagonist. There's an interesting reason behind that. The sweat gland is the only gland in the body where the upper and lower motor neurons use different neurotransmitters: norepinephrine in the upper motor neuron, and acetylcholine in the lower motor neuron. Terazosin works very well, but has a couple of disadvantages. One is a small risk of hypotension, especially with the first dose, which means it cannot be taken on an as-needed basis.

TCPR: When do you use anticholinergics that do cross the blood-brain barrier, like benztropine (Cogentin)?

Dr. Mago: Not for sweating, because the cognitive side effects usually outweigh the benefits. But they are useful for antipsychotic-induced parkinsonism, because there you need a central mechanism for what you are trying to treat (parkinsonism). But still, the cognitive side effects are a bigger problem than is commonly realized (Lupu AM et al, *J Clin Psychiatry* 2017;78(9):e1270–e1275).

Dry mouth

TCPR: We see dry mouth with nearly all medications, particularly anticholinergics, antipsychotics, and tricyclics. Why is this important to address?

Dr. Mago: Dry mouth is not just uncomfortable. Saliva protects the teeth, so dry mouth can lead to significant problems like dental cavities. People with mental health problems are three times as likely to lose all their teeth than the general public, and dry mouth is one of the main reasons for that. Dry mouth can also be socially embarrassing. It causes bad breath. Also, others may notice patients with dry mouth licking their lips and sucking in their cheeks. Here's an important point: Other things being equal, anything that is socially embarrassing is more likely to affect adherence to medication. On the other hand, a lot of patients don't actively complain about dry mouth, but even mild cases can be problematic if they go on too long. So I'm proactive. I tell the patient, "Even though you don't think it's that important, it's worth addressing because otherwise you may get cavities."

TCPR: How do you address it?

Dr. Mago: First, protect the teeth. Ensure that the patient is getting frequent dental cleanings. A cleaning every 3 months would be ideal, but insurance won't cover that frequency, so the patient would have to pay for it out of pocket. Regular flossing and brushing the teeth at least twice a day are absolutely essential. Avoid mouthwashes that contain alcohol (like Listerine) because they may make dry mouth worse. I also recommend that patients take sips of water while eating. Doing so will enhance the taste of food and make it easier to swallow, both of which can be problems for people with dry mouth.

TCPR: What do you do after those basic steps?

“Nausea is one of the top reasons that patients stop medications prematurely. That's unfortunate because nausea usually subsides in a little bit of time. When nausea does happen, we need to step in energetically with solutions. I tell the patient, ‘Listen, I understand that this is bothersome. We are going to do something about it today, but I can reassure you the nausea is not harming your body.’ ”

Rajnish Mago, MD

Are Auditory Hallucinations Ever Normal?

Joseph M. Pierre, MD. Chief, Hospital Psychiatry Division at the VA West Los Angeles Healthcare Center. Clinical Professor in the Department of Psychiatry and Biobehavioral Sciences at UCLA.

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

When a patient presents with auditory hallucinations (AH), are you likely to diagnose a psychotic disorder? If no other symptoms are present, would you recommend an antipsychotic? If you answered yes to either question, there's some new research that may change your mind. Hearing voices may be a common experience for people without mental illness. Is it time to stop equating voice-hearing with psychosis?

How common is voice-hearing?

When people say they “hear voices,” they may be describing a wide range of experiences beyond the traditional definition of auditory verbal hallucinations.

When questionnaires are used to survey the general population about “hearing a voice as if someone had spoken when no one was there” or “hearing voices that other people said did not exist,” about 5%–15% report AH at some point in their lives. This isn't surprising, given that while AH are generally thought of as a hallmark of psychosis, they also occur in a wide range of non-psychotic disorders (Pierre JM, *Harv Rev Psychiatry* 2010;18(1):22–35).

But AH are also reported in adults without any other evidence of a psychiatric disorder. Just how common are these “normal voice-hearers”? That's open to debate. Some surveys have detected extraordinarily high rates, such as 60%–80% in some samples of college students or psychiatric nurses who otherwise had no evidence of mental illness (Beaven V et al, *J Ment Health* 2011;20(3):281–292). Those studies have

notable flaws, however, such as relying on written surveys with ambiguously phrased questions and failing to rule out drug-induced and sleep-related hallucinations. Hallucinations that occur while falling asleep (hypnagogic) or waking (hypnopompic) are not considered psychotic; they may be a sign of a sleep disorder or just a part of normal experience.

A more conservative estimate is that healthy voice-hearers make up 1%–3% of the population worldwide. That's the rate arrived at when using face-to-face structured interviews to ask about non-distressing AH and excluding those with psychotic disorders, drug-induced experiences, and sleep-related phenomena.

Normal vs pathological

How do healthy voices differ from pathological ones? The research on this is extensive, encompassing several thousand patients across 36 studies (Baumeister D et al, *Clin Psychol Rev* 2017;51:125–141). Key differences are that healthy voices are less distressing and more likely to involve positive comments, such as a guardian angel telling a person to keep pressing on. Notably, the two groups do not differ in the number of voices, their loudness, or their localization (eg, inside or outside of the head). Nor do they differ based on neuroimaging studies, which have found that fMRI activation during voice-hearing is indistinguishable between healthy and clinical voice-hearers.

Healthy voice-hearers are more likely than clinical voice-hearers to attribute their voices to an external source, often within a spiritual framework. This finding matches an illustrative case found in one of the first published studies of healthy voice-hearers. It described a 42-year-old woman living in the Netherlands who had no mental illness but had heard voices dating back to childhood. She was “in private practice as a psychic healer”

and described communicating with her voices and consulting with them “for the benefit of herself or her clients.” She found her voices comforting and helpful, characterizing them as “protective ghosts” (Honig A et al, *J Nerv Ment Dis* 1998;186(10):646–651).

This example mirrors a recent study that concluded that self-identified “clairaudient psychics,” who believe that they “receive auditory messages from spirits” but are otherwise free of mental illness, may represent a typical example of healthy voice-hearers who interpret their voices within a sanctioned, and perhaps even adaptive, cultural context (Powers AR et al, *Schizophr Bull* 2017;43(1):84–98). Such cases are reminiscent of Carl Jung's writings, where he described his conversations with a “spirit guide” called Philemon. Stanford anthropologist Tanya Luhrmann described normal voice-hearers as “people who lose themselves in nature, become captivated by books, or pray ardently—in other words, people who get caught up in their inner worlds” (<https://tinyurl.com/ycush83h>).

Just how “healthy” are healthy voice-hearers?

In the research reviewed above, healthy voice-hearers were recruited from the general population and had no history of mental illness or psychiatric treatment, either by self-report or diagnostic interview. However, several studies comparing healthy voice-hearers to healthy controls who did not hear voices found evidence of schizotypal traits such as delusion-like beliefs, magical thinking, and formal thought disorder (but the voice-hearers did not meet full criteria for schizotypal personality disorder). On cognitive tests, healthy voice-hearers tend to perform at the lower end of the normal range. This suggests that while they may not have mental illness per se, they lie somewhere on a psychotic spectrum.

Another enduring finding is that a history of childhood sexual abuse is overrepresented among both healthy voice-hearers and clinical voice-hearers. While a causal relationship has not been established, childhood abuse may be an important risk

Voice Characteristics	Healthy Voice-Hearers	Clinical Voice-Hearers
Content	Often positive, non-distressing	More often negative and distressing
Onset	Late childhood	Adult or late adolescence
Duration	Less frequent, shorter duration	More frequent, longer duration
Functional impairment	Rare	Common

Are Auditory Hallucinations Ever Normal?

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factor for voice-hearing. Hallucinations could be a distressing consequence of childhood trauma in clinical cases, but also a potentially adaptive coping mechanism in healthy voice-hearers.

Although AH in people without mental disorders can be normal, there's reason to think they warrant clinical monitoring. A recent prospective study followed healthy voice-hearers who had no mental illness and didn't need mental health treatment at baseline. After 5 years, 40% of the sample went on to require care and were eventually diagnosed with a range of mental disorders, including not only psychotic disorders but also bipolar disorder, depression, PTSD, ADHD, and autism (Daalman K et al, *Psychol Med* 2016;46(9):1897–1907). While voice-hearing can occur without evidence of mental illness, it may also be an early sign of a developing psychiatric disorder.

Clinical recommendations

When asking patients about voice-hearing, you should first distinguish between AH and other non-hallucinatory experiences. "Voices" may represent one's conscience

or inner voice, depressive ruminations, metaphorical expressions, idioms of distress, or malingering. Those kinds of experiences shouldn't be mistaken for psychosis and can respond to supportive psychotherapy and pharmacotherapy without antipsychotics (Pierre JM et al, *Biol Psychiatr* 2010;68(7):e33–e34).

When voices sound like genuine hallucinations, but are non-distressing and occur without other psychiatric symptoms, no intervention may be necessary. However, for patients in their teens or early twenties with a family history of psychosis or personal history of drug use (including cannabis), careful monitoring is in order. These patients are at risk for progression to psychosis. Finally, when patients with psychotic disorders like schizophrenia report distressing AH, an antipsychotic trial is clearly indicated. In this population, AH often respond well to pharmacotherapy, though this is certainly not always the case. Other interventions like cognitive behavioral therapy may help relieve distress.

Self-help groups have emerged for healthy voice-hearers that provide support in a non-judgmental

environment. These groups encourage a de-stigmatized (and often de-medicalized) understanding of voice-hearing experiences (eg, www.hearing-voices.org). For voice-hearers at the healthier end of the continuum, they offer much-welcomed reassurance and acceptance. I view these groups much like I do Alcoholics Anonymous—complementary treatments that can be a vital source of psychosocial support and sometimes psychotherapy, but can also be harmful if they encourage the rejection of psychiatric care for voice-hearers with clear mental illness.

TCPR VERDICT: Hallucinations are like coughs. They range in severity from normal and insignificant to a pathological symptom of a life-threatening disease like schizophrenia. Like a cough, hallucinations might warrant no intervention, cautious monitoring, or specific treatment, depending on your full assessment.

For more on this subject, listen to our podcast, "Ginger Ale and Normal Hallucinations" at www.thecarlatreport.com/podcast5

Expert Interview

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Dr. Mago: One thing that really helps—both with dental hygiene and halitosis (bad breath)—is xylitol. This is a natural sugar that bacteria consume and cannot metabolize. It lowers the bacterial count in the mouth. Xylitol is available in chewing gums, lozenges, and sprays. The chewing gum also mechanically cleans the teeth. One important detail is that xylitol products must be used no less than 4 times a day to have a significant effect on the bacterial count in the mouth (Villa A et al, *Ther Clin Risk Manag* 2014;11:45–51).

TCPR: What are some specific products?

Dr. Mago: Spry and Epic are brands that I recommend, but there are others. Xylitol-containing products are relatively cheap. You'll find them in almost all pharmacies and grocery stores next to the toothpaste and mouthwashes.

TCPR: What about Biotene products?

Dr. Mago: Biotene is a saliva substitute that moisturizes the mouth. It provides symptom relief, but it doesn't kill bacteria. I usually recommend the mouthwash or the gel. The mouthwash can be used at night, which might make sleeping a bit more comfortable; using a humidifier in the bedroom can also help with that. The Biotene gel has the advantage of being easy to carry around and use at any time of day. You squeeze a small amount out on your tongue and move your tongue to spread it around.

TCPR: Do you ever use medications for dry mouth?

Dr. Mago: There are two FDA-approved medications for dry mouth: cevimeline and pilocarpine. I never prescribe them because they have significant cholinergic side effects like diarrhea, but they are useful for medical conditions like Sjögren's syndrome, which can cause severe dry mouth. I use a different strategy with these to avoid systemic side effects. I'll prescribe pilocarpine in the eye drop formulation at the highest strength (4%) rather than the tablets. Add a few of those drops to half a teaspoon of water and swish it around in the mouth. Next, and this is important, I tell the patient to spit it out to avoid systemic side effects. It's a good localized treatment for dry mouth and can be used as needed. Pilocarpine is generic and very affordable.

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

Editor's note: We'll continue this interview in our August issue, addressing hair loss, weight gain, akathisia, and orthostasis. Practical tips on a wide variety of topics in psychopharmacology from Dr. Mago are available on his website at www.simplendpractical.com.

Brexanolone (Zulresso) for Postpartum Depression

On March 19, 2019, the FDA approved brexanolone (Zulresso), the first medication for postpartum depression (PPD). Delivered by intravenous injection, brexanolone is an analogue of the hormone allopregnanolone. Allopregnanolone levels fall abruptly after childbirth, which is thought to contribute to PPD by destabilizing GABA_A receptors.

We covered brexanolone's mechanism in our January 2019 issue and have some practical updates for readers who want to start using it.

How is it delivered?

As a one-time, 60-hour IV infusion at 60–90 µg/kg/hour.

How effective is it?

To achieve remission, the number needed to treat with brexanolone is 5–8. The efficacy is based on three positive randomized, double-blind, placebo-controlled trials involving 267 women with moderate or severe PPD (Meltzer-Brody S et al, *Lancet* 2018;392:1058–1070).

Are the effects long lasting?

We only have data up to 30 days, and 94% of patients who responded maintained their response at that point.

Are there side effects?

The main risk is excessive sedation (2%–4%) and loss of consciousness. Otherwise, side effects were similar in the placebo and brexanolone groups and included dry mouth, loss of consciousness, and flushing.

Can women breastfeed during the infusion?

Possibly. We have data on only 12 women, and brexanolone had a low rate of transfer to the infant in that group (1%–2% of maternal weight-adjusted dosage).

Who can administer it?

Brexanolone is a schedule IV controlled substance and requires both the patient and health care provider to

enroll in a REMS program (see www.thecarlatreport.com/REMS). Because of the risk of excessive sedation, brexanolone must be administered with continuous pulse oximetry during the 60-hour infusion. If hypoxia occurs, the infusion should be stopped and not restarted. Patients can engage with their children during the infusion, but they are required to be accompanied by another adult because of the risk of sedation.

What is the cost?

\$34,000 for the drug without insurance, plus costs associated with administration and monitoring. Insurers have not developed their coverage policies yet, but it's likely they will require failure of antidepressant trials before authorizing it.

How can I find a brexanolone center for my patient?

Sage Therapeutics keeps a list of certified providers at 844-472-4379.

TCPR'S TAKE

Brexanolone's main advantage is speed. Each month of depression takes a toll on infant development and maternal attachment, so a medication that works within a few days is worth considering. The main drawback is the cost and lengthy infusion period. While the one-time treatment will be appealing to some patients, we need more research to know if these recoveries can last beyond 30 days.

—*Talia Puzantian, PharmD, BCPP, and Chris Aiken, MD.* Drs. Puzantian and Aiken have disclosed that they have no relevant financial or other interests in any commercial companies pertaining to this educational activity.

A New Dopamine and Norepinephrine Reuptake Inhibitor for Excessive Sleepiness

Solriamfetol (Sunosi), a new dopamine and norepinephrine reuptake inhibitor (DNRI), has been approved by the FDA “to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea.” The

medication has never been studied in psychiatry, but is likely to have important psychiatric effects.

How effective is it?

Approval was based on four studies of over 900 adults. In a randomized double-blind controlled trial of 239 adults with narcolepsy, 150 mg/day of Sunosi (but not 75 mg/day) showed statistically significant improvements in both objective (the Maintenance of Wakefulness Test) and subjective (the Epworth Sleepiness Scale) measures of sleepiness. In a similar study of 476 adults with sleep apnea, patients showed significant improvement on measures of sleepiness at 3 doses: 37.5 mg/day, 75 mg/day, and 150 mg/day. Both studies lasted 12 weeks, and the gains held up in two open-label maintenance studies that lasted up to 50 weeks.

What are the side effects?

About 1 in 25 people had at least one psychiatric side effect: anxiety, irritability, or insomnia. Based on its mechanism of action, psychosis and mania are potential risks, but we don't know how serious those problems are since solriamfetol has not been studied in psychiatric populations. The most common physical side effects were headache, nausea, and low appetite. Solriamfetol also raises blood pressure and pulse in a dose-dependent manner. It should be avoided with monoamine oxidase inhibitors (MAOIs) because taking them together can raise the risk of hypertensive crisis.

Does solriamfetol have an abuse potential?

Solriamfetol has an abuse potential that was documented in a study of people with a history of recreational stimulant and polydrug abuse. Compared to phenteramine, it produced similar elevations of mood, relaxation, and “drug liking.” However, this only appeared to be a problem at doses higher than recommended (300–1200 mg). At lower doses, subjects found that solriamfetol's aversive effects outweighed its reinforcing effects.

Continued on page 12

Research Updates IN PSYCHIATRY

ANTIDEPRESSANTS

A New Proposal for SSRI Withdrawal

REVIEW OF: Horowitz MA and Taylor D, *Lancet Psychiatry*, March 2019, published online

TYPE OF STUDY: Literature review and clinical guideline

Withdrawal problems rank among patients' top concerns with antidepressants. They include insomnia, flu-like symptoms, irritability, distractibility, and unusual sensory experiences such as "brain zaps." To avoid

The Hyperbolic Taper for SSRIs

1. Lower to the minimum dose

Reduce the dose to the minimum suggested in the table on this page if not already there (eg, citalopram 20 mg). The dose can be reduced linearly at this stage because the main risk is depressive relapse, not serotonin withdrawal. Consider the patient's history, including risk of relapse and prior response to lower doses, in determining the rate of the taper. Lowering every 1–2 weeks is reasonable for most patients.

2. Assess baseline symptoms

Check if the patient is having any SSRI withdrawal symptoms at baseline (see www.thecarlatreport.com/serotonin).

3. Lower for one month and reassess

Now move to the first tapering dose in the table (eg, citalopram 10 mg). After a month, reassess for SSRI withdrawal symptoms.

4. Start the long-tail taper

The doses for each step of the final taper are listed in the table (eg, citalopram 5 mg, then 3.4 mg). How quickly you go down at each step depends on how sensitive the patient is to withdrawal; your assessment of symptoms at baseline and one month later will give you a sense of this. At a minimum, allow 1 week between each step; 2 weeks is a rough average, and sensitive patients may require 6 weeks between each step.

this syndrome, most clinicians taper antidepressants *linearly*, lowering the dose by a fixed amount at a regular rate. For example, a typical linear taper of citalopram 30 mg daily might proceed like this: citalopram 20 mg daily for 1 week, 10 mg daily for 1 week, then stop. A new study suggests we might need to rethink that practice.

The authors examined clinical and biological research on tapers of serotonergic antidepressants. Their review included six major clinical trials examining SSRI and SNRI tapers, covering a total of 1,687 patients. The clinical outcomes on linear tapers were problematic. In one study, 60% of patients required 4 months or more to taper. In another, patients had particular difficulty at the final tail of the taper. They stalled when the taper reached half of the minimum therapeutic dose for depression (eg, when citalopram reached 10 mg daily). Only 37% were able to complete the taper beyond that point.

To better understand these problems, the authors looked at PET scan data. In line with the clinical findings, there was a dramatic fall in serotonin transporter inhibition when linear tapers reached half of the minimum therapeutic dose for depression. Inhibition of the serotonin transporter is the principal mechanism of SSRIs, and changes in that inhibition are thought to contribute to serotonergic withdrawal symptoms.

The authors proposed a new tapering strategy to prevent this dramatic fall: the "hyperbolic taper." In this taper, the SSRI is lowered with a long tail of incrementally smaller dose reductions (see sidebar). With this strategy, the serotonin inhibition would fall linearly as the SSRI is tapered at an increasingly slower rate. Theoretically, this "hyperbolic taper" could prevent serotonin withdrawal symptoms. The authors recommend the same strategy with fluoxetine, although the risk of withdrawal problems is lower with this SSRI because of its long half-life.

TCPR'S TAKE

Tapers with a long tail have been used successfully with benzodiazepines, and the clinical and biological data presented here suggest they may be preferable with serotonergic antidepressants as well. Although the idea lacks clinical proof, so does current practice, and a "hyperbolic taper" is worth trying in patients who have trouble with serotonin withdrawal.

—Greg Sazima, MD, and Chris Aiken, MD. Drs. Sazima and Aiken have disclosed that they have no relevant financial or other interests in any commercial companies pertaining to this educational activity.



For more on this subject, listen to our podcast, "A New Strategy for SSRI Withdrawal" at www.thecarlatreport.com/podcast8

Medication	Minimum Daily Dose ¹	Tapering Doses (mg/day)	Liquid Conversion (mL/day)
Citalopram	20 mg	10→ 5.0→ 3.4→ 2.3→ 1.5→ 0.8→ 0.4→ stop	2 mg/mL: 5.0→ 2.5→ 1.7→ 1.2→ 0.8→ 0.4→ 0.2→ stop
Escitalopram	10 mg	5→ 2.7→ 1.7→ 1.2→ 0.7→ 0.4→ 0.2→ stop	1 mg/mL: 5.0→ 2.7→ 1.7→ 1.2→ 0.7→ 0.4→ 0.2→ stop
Fluoxetine	20 mg	8.5→ 4.5→ 2.7→ 1.7→ 1.0→ 0.6→ 0.3→ stop	4 mg/mL: 2.1→ 1.1→ 0.7→ 0.4→ 0.3→ 0.2→ 0.1→ stop
Fluvoxamine	50 mg	25→ 15→ 10→ 8→ 5→ 2→ 1→ stop	No liquid (use 25 mg tabs or compounding pharmacy)
Paroxetine	20 mg	11.4→ 7.4→ 5.0→ 3.4→ 2.2→ 1.3→ 0.6→ stop	No liquid (use 10 mg scored tabs, 7.5 mg caps, or compounding pharmacy)
Sertraline	50 mg	25→ 14→ 9.1→ 5.9→ 3.8→ 2.2→ 0.9→ stop	20 mg/mL: 1.3→ 0.7→ 0.5→ 0.3→ 0.2→ 0.1→ 0.05→ stop

¹The dose where 80% occupancy of the serotonin receptor is achieved. It corresponds roughly with the minimum effective dose for depression with each SSRI. (Source: Suhara T et al, *Arch Gen Psych* 2003;60:386–391; Meyer JH et al, *Am J Psych* 2004;161:826–835.)

BIPOLAR DISORDER

Mood Stabilizers and Stroke Risk in Bipolar Disorder

REVIEW OF: Chen PH et al, *Br J Psychiatry* 2018;1-6. doi:10.1192/bjp.2018.203

STUDY TYPE: Case-crossover study

People living with bipolar disorder already have a decreased life expectancy of 10+ years compared to the general population (Crump C et al, *JAMA Psychiatry* 2013;70:931-939). Most of these years of lost life have been attributed to cardiovascular and cerebrovascular causes. Bipolar disorder itself affects the vascular system, as do some of the medications that treat it. A new study parses out which of the mood stabilizers are the worst offenders when it comes to the risk of stroke.

The authors examined medical records of the Taiwan National Health Insurance Research Database to identify people between ages 15 and 65 who had been diagnosed with bipolar disorder and then later had their first stroke. Among the 19,433 cases of bipolar disorder, 609 had a stroke during the study period and were included in the analysis. Both ischemic and hemorrhagic strokes were included. This was a case-crossover design, in which the study subjects served as their own controls. In this case, the medications they took in the 2 weeks before the stroke were compared to four other 2-week periods in the year preceding the stroke. The particular medications examined were carbamazepine, valproic acid, lithium, and lamotrigine.

Only two of those mood stabilizers increased the risk of stroke. The worst offender was carbamazepine, which increased the risk of any kind of stroke (adjusted risk ratio [ARR] 1.68; $p = 0.018$). Valproic acid only increased the risk of hemorrhagic stroke (ARR 1.76; $p = 0.022$). Lithium and lamotrigine had no significant effect on the occurrence of stroke in this analysis.

One weakness of the study was that it only examined the acute effects

of treatment, and not the risks of long-term exposure to mood stabilizers. The study also did not examine severity of illness and what burden that may have on stroke risk; presumably, less severe patients may have been prescribed lithium or lamotrigine. A strength was that the study controlled for concomitant use of other medications that might influence the risk of stroke, such as antipsychotics, cardiovascular drugs, and diabetic medications.

TCPR'S TAKE

This study should make us think a little more when choosing a mood stabilizer. The risk of stroke with carbamazepine has previously been reported in epilepsy (Chuang YC et al, *Epilepsia* 2012;53:120-128). Although atypical antipsychotics were not included in this study, their well-known metabolic risks would give us pause. If people already have risk factors for stroke, consider treatment with lithium or lamotrigine as first-line agents. Although not generally thought of as heart-friendly, lithium has numerous cardioprotective effects and lowers the risk of myocardial infarctions (Chen PH et al, *Prog N Biol Psych* 2019;88:208-214).

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



For more on this subject, listen to our podcast, "Lithium's Health Benefits" at: www.thecarlatreport.com/podcast10

OCD

New Augmentation Strategies in OCD

REVIEW OF: Naderi S, *Psychiatry Clin Neurosci* 2019;73(4):169-174 and Zheng H et al, *Eur Neuropsychopharmacol* 2019;29(3):397-404

STUDY TYPES: Positive RCTs

Serotonergic agents—both SSRIs and clomipramine—have historically been the

cornerstone of pharmacotherapy for OCD. However, response rates are notoriously low, and few patients achieve full remission. Atypical antipsychotics have so far failed to distinguish themselves as viable augmentation agents. Two novel augmentation strategies—amantadine and methylphenidate—recently underwent placebo-controlled trials in OCD, and we'll review those results here.

Amantadine

Amantadine is a glutamatergic and dopaminergic agent that was originally approved in 1966 for the influenza virus and, more recently, in an extended-release form for Parkinson's disease. Several other glutamatergic agents have demonstrated benefits for OCD in small (sample sizes of 15-50), double-blind, placebo-controlled augmentation trials: memantine, riluzole, N-acetylcysteine, and ketamine. Amantadine has also been found to enhance energy and cognition in Alzheimer's dementia, multiple sclerosis, depression, and ADHD; and reduce irritability in autism and traumatic brain injury.

The most recent amantadine study randomized 100 subjects with moderate to severe OCD in a double-blind manner to receive fluvoxamine (Luvox; titrated up to 200 mg/day by week 4) plus either amantadine 100 mg/day or placebo over 12 weeks. Improvement was assessed at weeks, 4, 10, and 12 using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). Y-BOCS scores were significantly lower in the subjects receiving amantadine augmentation compared to those receiving placebo augmentation at week 4 (reduction of 8.4 vs 5.6; $p < 0.01$) and at the 12-week endpoint (reduction of 12.4 vs 9.7; $p < 0.05$), though the difference fell just short of significance at week 10 (reduction of 11.9 vs 9.4; $p = 0.08$). The number needed to treat to see response was 2.5. As has historically been the case, amantadine was very well tolerated, with no side effects that were reported at a statistically significant higher rate than placebo.

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Research Updates IN PSYCHIATRY

Continued from page 9

Methylphenidate

Stimulants have been used to augment SSRIs in OCD since the early 1980s, but they can also induce compulsive behaviors. As the first placebo-controlled trial of a stimulant in OCD, this new study brings needed clarity.

The methylphenidate trial enrolled 44 patients with significant OCD who failed to respond to an effective dose of fluvoxamine. They were randomized for 8 weeks to 250 mg fluvoxamine and placebo, or 250 mg of fluvoxamine and extended-release methylphenidate. Subjects in the treatment arm blindly received 18 mg of methylphenidate for the first 4 weeks and 36 mg for the remainder of the study. The primary outcome was the total score on the Y-BOCS.

Patients given methylphenidate in combination with fluvoxamine showed robust improvement compared to those who received fluvoxamine alone. The treatment group had a significant reduction in their total OCD symptoms as measured by the Y-BOCS (reduction of 6.7 vs 1.9). Additionally, the treatment group showed a reduction in the obsessive subscale of the Y-BOCS (reduction of 5.5 vs -0.2). The number needed to treat to see response was 1.8. Secondary measures of depression and anxiety also showed significant improvement. Side effects were minimal (palpitations and headache). Dropout rates were similar in the treatment and placebo arms, and no subjects dropped out due to adverse effects.

Notably, the two studies differed in the types of patients enrolled. In the stimulant study, the patients had failed a trial of fluvoxamine; in the amantadine study, the patients began fluvoxamine along with amantadine.

TCPR'S TAKE

These studies were well designed and build on previous findings as well as plausible biological pathways in OCD. The number needed to treat translates to an impressive 50% response rate, but with the small sample sizes, that estimate is very rough. Amantadine and

methylphenidate have been used for a long time, so we have a good sense of their risks. Both are reasonable options when OCD persists after standard treatments.

—*Michael Posternak, MD, and Edmund S. Higgins, MD.* Drs. Posternak and Higgins have disclosed that they have no relevant financial or other interests in any commercial companies pertaining to this educational activity.



For more on this subject,
listen to our podcast,
"How to Use Amantadine" at:
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DEPRESSION

Lithium in Geriatric Depression

REVIEW OF: Buspavanich P et al, *J Affect Disord* 2019;251:136–140

TYPE OF STUDY: Prospective, non-randomized controlled trial

Augmentation with lithium has long been established as an effective strategy for refractory depression, but how does it fare in geriatric patients? There is a dearth of evidence on lithium in the geriatric population, which may explain why it is rarely used in older patients. In this multicenter, prospective, non-randomized controlled trial, investigators evaluated the effectiveness of lithium augmentation in geriatric vs non-geriatric patients with major depressive disorder.

The study enrolled 226 patients with moderate to severe major depression (non-bipolar) who had failed at least one antidepressant trial. Lithium was added to their current antidepressant, and those who received at least 4 weeks of lithium were analyzed for response (n = 167), which was defined as ≥ 50% reduction on the Hamilton Depression Rating Scale. These patients were followed for 7–8 weeks. Responses were compared in geriatric (age ≥ 65) and adult patients.

Of the 167 patients analyzed, 22 were geriatric and 145 non-geriatric. The proportion of patients who completed the study was similar in both groups, as were other variables except age of onset, which

was higher in the geriatric group. Most patients were female and had been in their current episode for 3 to 12 months. Both groups had similar mean lithium levels at the end of the study (0.61 for geriatric patients and 0.69 for non-geriatric).

Interestingly, geriatric patients had a significantly greater and more rapid response to lithium augmentation than those under age 65 (p = 0.04). Clinical response was 68.2% for geriatric patients and 46.9% for non-geriatric. The authors proposed these differences could be explained by age-related changes in pharmacokinetics and pharmacodynamics. For instance, decline in integrity of the blood-brain barrier with age may allow for quick and sufficient lithium levels. Additionally, lithium has neuroprotective effects, and neurodegenerative processes may play more of a role in the pathophysiology of depression in geriatrics.

While the authors claimed safety and tolerability were implied by the number of patients completing the study, the lack of data on adverse outcomes was a weakness. Plus, the sample size of geriatric patients was small, at least relative to non-geriatric patients. Another weakness was the lack of a non-lithium control group, making it difficult to establish whether these outcomes were unique to lithium.

TCPR'S TAKE

Geriatric patients are usually less responsive to antidepressant therapies than younger cohorts, so these results are a surprise. They lend further support to lithium augmentation in refractory depression. However, older patients are more at risk for adverse effects, drug interactions, and medical problems with lithium. Those risks need to be weighed against the risk of continued depression, which takes a toll on physical as well as mental health.

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



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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.

- Which of the following statements about auditory hallucinations is true? (LO #3)
 - a. Voices that sound like hallucinations and occur without other psychiatric symptoms indicate psychosis
 - b. Healthy voice-hearing occurs in about 15% of the population
 - c. Hallucinations that occur while falling asleep are mainly seen during a psychotic disorder
 - d. Healthy voices do not differ from pathological ones in terms of number or volume of voices
- According to Dr. Mago, which medication is a first-line choice for patients experiencing sweating as a side effect of medication? (LO #2)
 - a. Glycopyrrolate
 - b. Gabapentin
 - c. Metoclopramide
 - d. Clonidine
- Esketamine has a high side effect profile, with at least 25% of patients discontinuing treatment after 1 week due to weight loss, headaches, and fatigue. (LO #1)
 - a. True
 - b. False
- According to a 2018 study, patients with bipolar disorder had the greatest risk of stroke when taking which of the following mood stabilizers? (LO #4)
 - a. Lamotrigine
 - b. Lithium
 - c. Valproic acid
 - d. Carbamazepine
- Your patient is experiencing nausea as a side effect and would like to try a non-medication antidote. According to Dr. Mago, what should you advise for daily use of ginger? (LO #2)
 - a. Drink 8 ounces of ginger ale 30 minutes before two or three meals
 - b. Consume one 550 mg ginger capsule 1 hour before a meal
 - c. Consume two 550 mg ginger capsules 1 hour after a meal
 - d. Drink 8 ounces of ginger ale 30 minutes after a meal
- According to a 2019 study, patients with OCD taking methylphenidate in combination with fluvoxamine showed more improvement compared to those taking fluvoxamine alone. (LO #4)
 - a. True
 - b. False
- Clinical voices differ from healthy ones in which of the following ways? (LO #3)
 - a. They rarely cause a person to be functionally impaired
 - b. They are more likely to begin in early to late childhood
 - c. They occur more frequently and are longer in duration
 - d. They are more likely to be attributed to an external source
- The FDA currently requires that patients self-administering esketamine be supervised in a healthcare setting and monitored by a healthcare professional for at least how long after treatment? (LO #1)
 - a. 20 minutes
 - b. 2 hours
 - c. 4 hours
 - d. 6 hours

This Issue:
Side Effects Part I
June/July 2019

Next Issue:
Side Effects Part II
August 2019

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News of Note

Continued from page 7

The FDA plans to classify solriamfetol as a controlled substance but has not released the exact schedule yet (Carter LP, *J Psychopharmacol* 2018;32:1351-1361).

How will it be prescribed?

Sunosi will be available as scored 75 mg tablets and 150 mg tablets. Starting dose is 75 mg QAM for patients with narcolepsy and 37.5 mg QAM for patients with sleep apnea. Dose may be increased at intervals of at least 3 days; maximum dose is 150 mg/day. The half-life of Sunosi is approximately 7 hours. Sunosi is metabolized renally rather than hepatically; dose adjustments are recommended in renal impairment.

What is the cost?

Sunosi pricing is not available, and the drug is not yet available in pharmacies.

TCPR'S TAKE

Solriamfetol joins modafinil (Provigil) and armodafinil (Nuvigil) as the only wakefulness-promoting agents with approval in both narcolepsy and obstructive sleep apnea. As a DNRI, its mechanism shares some overlap with other psychotropics, including modafinil, traditional stimulants, and bupropion. However, its profile is unique, and we'll need to watch carefully when psychiatric patients start solriamfetol for narcolepsy or sleep apnea.

—Talia Puzantian, PharmD, BCPP, and Chris Aiken, MD.

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