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Chris Aiken, MD
Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Deprescribing

Learning Objectives

After reading these articles, you should be able to:

1. Identify key principles and techniques for safely tapering psychiatric medications to minimize withdrawal symptoms.
2. Explain the pharmacologic properties and clinical applications of lisdexamfetamine, including its abuse potential.
3. Evaluate the risks and benefits of antipsychotics across mood disorders and other conditions, and explore alternative treatment strategies in psychiatric care.
4. Summarize some of the current research findings on psychiatric treatment.

Vyvanse Goes Generic: An Amphetamine Apart

David Liebers, MD. Psychiatry resident at NYU Langone, Department of Psychiatry.

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Dr. Liebers and Dr. Aiken have no financial relationships with companies related to this material.

Soon after Vyvanse's patent expired in 2023, applications for generic formulations of lisdexamfetamine dimesylate started flowing into the FDA. There are now 18 approved generic versions of the medication, a relief for patients facing the nationwide stimulant shortage. In this piece, I'll look at what sets lisdexamfetamine apart from other stimulants.

The prodrug

Lisdexamfetamine is an inactive prodrug of dextroamphetamine (Dexedrine), a

Highlights From This Issue

Feature article. Lisdexamfetamine (Vyvanse) moves up in our treatment algorithm for ADHD.

Q&A on page 1. Dr. Mark Horowitz shows us how to taper our patients off medications.

Q&A on page 7. Dr. Harish Kavirajan explains that antipsychotics offer limited benefits for depression and carry serious risks, urging caution in their use.

Research updates starting on page 9. Quetiapine vs esketamine in treatment resistant depression, renal risks with lithium, overdiagnosis of ADHD, and estrogen in schizophrenia.

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Q&A With the Expert

How to Stop a Psychiatric Med
Mark Horowitz, MBBS, PhD

Research and Development Department, Goodmayes Hospital, North East London NHS Foundation Trust, Essex, UK; Visiting Lecturer in Psychopharmcology, King's College London. Co-author of The Maudsley Deprescribing Guidelines *(Wiley-Blackwell; 2024).*

Dr. Horowitz is cofounder and consultant for Outro Health. Dr. Aiken has reviewed this educational activity and has determined that there is no commercial bias as a result of this financial relationship.

TCPR: How should we taper psychiatric meds?

Dr. Horowitz: I have three major principles. 1) Do it slowly, often months and sometimes more than a year for long-term users. 2) Do it at a rate that the patient can tolerate. Everyone's a bit different, so there's some trial and error here. 3) Go much slower at the end because small doses of psychiatric drugs have much larger effects than people would expect them to have.

TCPR: Slower toward the end. That's how we're taught to taper benzodiazepines.

Dr. Horowitz: Yes. It's called a hyperbolic or proportional taper, and I think it applies to most psychiatric medications. So, you might start by lowering escitalopram by 10%–20% of the most recent dose, like a 5 mg reduction from 20 mg. But once you get to 5 mg/day, lower by 1 mg reductions, and even smaller

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right at the very end. Some people will need to go as slowly as 5% of their last dose a month.

TCPR: What is the basis for the hyperbolic taper?

Dr. Horowitz: On a neurobiological level, small doses of psychiatric drugs have much larger effects than you'd think, which produces a hyperbolic curve. At low doses, the receptors for that drug are mostly unsaturated—"open for business." So every milligram of the drug has a large effect. At higher doses, the receptors are more saturated, and every milligram has less and less effect. For example, 2 mg of citalopram sounds like a homeopathic dose, but it has about half the effect of 20 mg on the serotonin transporter receptor (Horowitz MA and Taylor D, *Lancet Psychiatry* 2019;6(6):538–546).

TCPR: But 2 mg citalopram doesn't have much clinical effect.

Dr. Horowitz: I'm not sure that dose has been specifically looked at in studies. But if we look at dose-response curves, where the dose is plotted against clinical effects, it follows the same hyperbola as the neurobiology. There's a steep increase in the lower dose range, then it plateaus. That is true for most antidepressants, antipsychotics, and benzodiazepines (Leucht S et al, *Am J Psychiatry* 2020;177(4):342–353; Furukawa TA et al, *Lancet Psychiatry* 2019;6(7):601–609).

TCPR: Are there clinical studies of the hyperbolic taper?

Dr. Horowitz: A randomized trial is underway, but right now the taper is largely based on pharmacological principles and prospective cohort studies. The observational data are built on thousands of people who couldn't come off their antidepressant using a traditional linear approach over a few weeks. In one of those studies, 71% of respondents were unable to come off their antidepressant with a linear taper. When they switched to a much more gradual hyperbolic taper over months, 72% were able to stop successfully. When patients were asked how severe their withdrawal was, they rated it very severe (7/7) with the traditional method, but much milder (2/7) with the hyperbolic taper (Groot PC and van Os J, *Ther Adv Psychopharmacol* 2021;11:20451253211039327).

TCPR: How do patients get doses like 1 mg of escitalopram?

Dr. Horowitz: For some doses, you can use pill splitters, which are available at most pharmacies. For smaller doses, use liquid formulations. When those aren't available, compounding pharmacies can make specialized doses (eg, tapering strips). As a last resort—if professional compounding is not around—patients can liquefy their pills with a commercial product like Ora-Plus. Patients crush up their pills and emulsify them in this sugary liquid. A little math is required to make sure you dilute it in the right proportion, and the suspension should be carefully shaken before use. The NHS in the UK advises people who have trouble swallowing tablets on how to do this.

TCPR: Are there medications that can't be crushed?

Dr. Horowitz: If you crush extended-release meds, you'll often lose the extended-release effect but will still have the drug. Duloxetine won't work if it is crushed. It comes in beads that are covered with a gastro-resistant coating, and if that coat breaks the drug is neutralized in the stomach acid. Unfortunately, for people who have trouble coming off duloxetine, their only option is to open up the capsules and count or weigh the beads.

TCPR: Is there any logic to switching to another antidepressant for the taper?

Dr. Horowitz: People have looked at switching to a similar medication with a longer half-life for the taper, like diazepam or fluoxetine. For benzodiazepines, the studies are equivocal (Denis C et al, *Cochrane Database Syst Rev* 2006;3:CD005194). I judge it by the individual. In some ways, it's easier to stop a drug that they are accustomed to rather than introducing a new one. And fluoxetine is not "self-tapering" as advertised. It has a longer half-life than other drugs but not long enough for the months-or-longer taper that many longer-term users require, and about half of people experience withdrawal effects from it, which can be delayed in onset because of its half-life. When it comes to antidepressants, I generally don't recommend switching. I think the selective serotonin reuptake inhibitors (SSRIs) as a class are more dissimilar than benzodiazepines are as a class, although they are all SSRIs. The serotonin/norepinephrine reuptake inhibitors (SNRIs) are even more dissimilar to fluoxetine because of the noradrenergic effects.

TCPR: For some, these withdrawal protocols require a lot of effort.

Dr. Horowitz: Yes, and I think it is worthwhile. Textbooks describe withdrawal effects as mild and self-limiting, and they are, for people who stopped a medication after taking it for eight to 12 weeks (which is what the industry-sponsored

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trials focused on). But the longer patients are on a medication, the more their brain adapts to it. In those cases, withdrawal effects are often severe and can be disabling: intense headaches, suicidality, panic attacks, and sometimes akathisia.

TCPR: Which meds cause akathisia during withdrawal?

Dr. Horowitz: It is well known during long-term antipsychotic use, but it can also happen when withdrawing from antidepressants, benzodiazepines, antipsychotics, and gabapentinoids. Patients are often pacing. They feel terrorized and restless. We did a survey of people who went to support groups for antidepressant withdrawal—so a very select group—and two in three experienced akathisia. It is often misdiagnosed as agitated depression or a manic state (Moncrieff J et al, *J Aff Dis Reports* 2024;16:100765).

TCPR: You've talked about antidepressants. How does the hyperbolic taper relate to other meds?

Dr. Horowitz: The basic principle is the same, where low doses have a proportionately larger effect than high doses. It's called the law of mass action. It's true for antipsychotics and their effect on D2 and 5HT2 receptors (Horowitz MA et al, *Schizophr Bul* 2021;47(4):1116–1129), and it's true with benzodiazepines. Prof. Heather Ashton noticed that people could lower diazepam from 20 mg to 19 mg, but not from 5 mg to 4 mg (Ashton CH. *Benzodiazepines: How They Work and How to Withdraw* [aka The Ashton Manual]. Newcastle-upon-Tyne, England: Newcastle University, 2002). There's a nonlinear relationship going on. Because it's a general pharmacological principle, it actually applies to all psychiatric drugs and all their targets.

"At higher doses, the receptors are more saturated, and every milligram has less and less effect. For example, 2 mg of citalopram sounds like a homeopathic dose, but it has about half the effect of 20 mg on the serotonin transporter receptor."

Mark Horowitz, MBBS, PhD

TCPR: How long do withdrawal effects tend to last?

Dr. Horowitz: Long-lasting withdrawal effects are possible. It's not the time it takes for the drug to leave the body, but rather the time it takes for the body to become used to the presence of less drug. That process takes longer: weeks, months, or even years. One effect of SSRI antidepressants is reduced sensitivity of serotonin receptors, and we still see that change for up to four years after stopping the antidepressant in neuroimaging studies of people who've been exposed to long-term antidepressants (Horowitz MA et al, *CNS Drugs* 2023;37(2):143–157).

TCPR: Some have argued that these syndromes are not withdrawal but relapse, a return of the original condition.

Dr. Horowitz: Relapse is certainly possible after stopping treatment, but we know that withdrawal is also involved because we see these problems in people who were prescribed antidepressants for reasons other than mental health, like pain, menopause, and healthy volunteers. Among patients with psychiatric disorders, the withdrawal symptoms are often different from the symptoms they originally presented with (Moncrieff et al, 2024). Also, controlled studies find that the faster the med is stopped, the more likely a patient will experience problems (Baldessarini RJ et al, *Am J Psychiatry* 2010;167(8):934–941). Relapse, by contrast, should not depend on the rate that the med is stopped. Fast or slow, the underlying condition is going to reveal itself when the treatment is taken away. When we see a difference between abrupt and gradual withdrawal, it is due to withdrawal effects, not relapse.

TCPR: How do you tell the difference between withdrawal effects and return of the condition?

Sidebar: A Basic Hyperbolic Taper

We developed this SSRI taper with Dr. Horowitz for patients who are at low risk for withdrawal effects. Longer tapers may be needed for patients who have been on an SSRI for more than a year, are taking a higher-risk medication (like paroxetine), or have a history of withdrawal problems. The best guide is the patient's experience of withdrawal symptoms. Tapering too quickly can trigger protracted withdrawal syndromes that don't respond to restarting the med. See *The Maudsley Deprescribing Guidelines* for details on slower schedules.

1. **Lower to the minimum dose more quickly**

Reduce the dose to the minimum suggested in the table "Tapering Doses and Liquid Conversions for Common SSRIs" on page 4 if not already there (eg, citalopram 20 mg). The dose can be reduced linearly (eg, by 5–10 mg) at this stage because the main risk is depressive relapse, not serotonin withdrawal. When determining the rate of the taper, consider the patient's history in terms of previous withdrawal experiences, duration of use, type of drug, and dose. Lowering every two to four weeks is reasonable for most patients.

2. **Assess baseline symptoms**

Check if the patient is having any symptoms that correspond to SSRI withdrawal symptoms at baseline (www.tinyurl.com/y3wtyzu5).

3. **Lower for one month and reassess**

Now move to the first tapering dose in the table (eg, citalopram 10 mg). Monitor for withdrawal symptoms throughout the taper—between daily and weekly monitoring is most helpful. Adjust the rate of taper based on 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 progress through each step depends on how sensitive the patient is to withdrawal. Your assessment of their symptoms at baseline and one month later will give you a sense of that. At a minimum, allow two weeks between each step, and four weeks is a rough average. Patients who experience withdrawal effects will benefit more from making smaller reductions at each step rather than spacing out the time between dose reductions. Some patients will require much slower schedules than the table lays out, which can mean years for long-term users and/or users of high-risk antidepressants.

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Dr. Horowitz: The first thing is to ask if the symptoms are different from the patient's original symptoms. If they started an antidepressant for fatigue and depression and now—after stopping it—they're having shooting pains, panic, insomnia, then it's more likely a withdrawal effect. So I think that is a very big misunderstanding about how long these effects can last for and how severe they can be.

TCPR: If it is withdrawal, do you restart the medication?

Dr. Horowitz: For acute withdrawal, like if the patient forgot their meds at the beach, restarting will quickly take care of the problem. But for people with protracted withdrawal (months of withdrawal), things are more difficult to predict. Restarting may work, but it may take a couple months for things to settle down. Then there are some who actually get worse on reinstatement.

TCPR: So the longer the withdrawal symptoms have gone on, the harder they are to treat.

Dr. Horowitz: Yes. We don't understand protracted withdrawal well, but it's as if there is some injury from coming off too quickly. The best approach is to prevent the problem, which is why I advocate for a long, hyperbolic taper. Otherwise, it's very difficult to put the toothpaste back in the tube.

TCPR: Withdrawal from benzos peaks, on average, one to two weeks after stopping them. What about antidepressants?

Dr. Horowitz: Often the symptoms are worse after a week or two, but there is a lot of variability. I have also seen people whose symptoms peak months after stopping. It may be that these kinds of protracted or delayed withdrawals are more common in people who have been on the drug for many years. In neuroimaging studies, antidepressants linger longer in the central nervous system than in the serum. It can take several weeks for the med to dissociate from the serotonin transporter (Sørensen A et al, *Mol Psychiatry* 2022;27(1):192–201). I wonder if that slower dissociation may explain delayed withdrawal effects. Or perhaps it is simply downstream effects that take time to accumulate (like the game Mouse Trap).

TCPR: With antidepressants, we worry most about withdrawal from SSRIs and SNRIs, but what about the other classes?

Dr. Horowitz: Withdrawal effects have been described for every antidepressant, from mirtazapine to monoamine oxidase inhibitors. Any drug that causes changes in the brain, adaptations that take longer to resolve than the drug takes to be removed from the body, will cause withdrawal effects (Reidenberg MM, *J Pharmacol Exp Ther* 2011;339:324–348). It's driven by the law of homeostasis and persisting changes. When you are attending a loud concert, your eardrums become less sensitive to sound. When you walk out in the quiet street, your friends' voices sound muffled for a few minutes—the time taken for your eardrums to relax. Likewise, if you increase levels of a neurotransmitter, the brain will become less sensitive to it. Then, when you remove the drug, the brain can take months or longer to go back to its "predrug" sensitivity ("factory settings")—and the person experiences withdrawal for that period.

TCPR: What do we worry about with antipsychotic withdrawal?

Dr. Horowitz: There's insomnia, headache, dizziness, but the big thing is withdrawal psychosis. Stopping antipsychotics can lead to a relapse of psychotic symptoms. This can sometimes be more than just a return of an underlying condition. There are cases of people with no psychiatric conditions who were prescribed dopamine antagonists like domperidone for nausea or for trouble lactating after giving birth (because antipsychotics can raise prolactin), and frank psychosis developed in some patients when they stopped abruptly: Capgras delusions, paranoid delusions, command hallucinations. The most common explanation is dopamine supersensitivity, which has been described since the 1970s (Moncrieff J, *Acta Psychiatr Scand* 2006;114(1):3–13). But antipsychotic withdrawal also causes insomnia, and insomnia can trigger psychosis.

TCPR: I understand tardive dyskinesia can also worsen when an antipsychotic is stopped.

Dr. Horowitz: Yes, and that is another example of dopamine supersensitivity. The dopamine receptor becomes more sensitive when it is blocked by an antipsychotic. When that medication is taken away, the receptor gets exposed to more dopamine, which can cause withdrawal dyskinesias.

TCPR: What do we worry about with anticonvulsive withdrawal?

Dr. Horowitz: Here the research is thinner. In my experience, people have less trouble coming off anticonvulsants than antidepressants, benzodiazepines and antipsychotics, but I have still seen people with trouble.

Tapering Doses and Liquid Conversions for Common SSRIs

Medication	Minimum Daily Dose[1]	Tapering Doses (mg/day)	Liquid Conversions (mL/day)
Citalopram	20 mg	10 mg → 5 → 3.4 → 2.3 → 1.5 → 0.8 → 0.4 → stop	2 mg/mL: 5 mL → 2.5 → 1.7 → 1.2 → 0.8 → 0.4 → 0.2 → stop
Escitalopram	10 mg	5 mg → 2.7 → 1.7 → 1.2 → 0.7 → 0.4 → 0.2 → stop	1 mg/mL: 5 mL → 2.7 → 1.7 → 1.2 → 0.7 → 0.4 → 0.2 → stop
Fluoxetine	20 mg	8.5 mg → 4.5 → 2.7 → 1.7 → 1.0 → 0.6 → 0.3 → stop	4 mg/mL: 2.1 mL → 1.1 → 0.7 → 0.4 → 0.3 → 0.2 → 0.1 → stop
Fluvoxamine	50 mg	25 mg → 15 → 10 → 8 → 5 → 2 → 1 → stop	No liquid (use 25 mg tabs or compounding pharmacy)
Paroxetine	20 mg	11.4 mg → 7.4 → 5.0 → 3.4 → 2.2 → 1.3 → 0.6 → stop	2 mg/mL: 5.7 mL → 3.7 → 2.5 → 1.7 → 1.1 → 0.7 → 0.3 → stop
Sertraline	50 mg	25 mg → 14 → 9.1 → 5.9 → 3.8 → 2.2 → 0.9 → stop	20 mg/mL: 1.3 mL → 0.7 → 0.5 → 0.3 → 0.2 → 0.1 → 0.05 → stop

[1]*The dose where 80% occupancy of the serotonin receptor is achieved. It corresponds roughly with the minimum effective dose for depression with each SSRI.*
Sources: Horowitz MA and Taylor D, Lancet Psych *2019;6(6):538–546; Subara T et al,* Arch Gen Psych *2003;60:386–391; Meyer JH et al,* Am J Psych *2004;161:826–835.*
Scale available at www.tinyurl.com/y3wtyzu5.

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TCPR: And with lithium?

Dr. Horowitz: With lithium, we have very good evidence of strong withdrawal effects. People who come off lithium have a seven-fold increased risk of mania or depression compared to their predrug baseline (Suppes T et al, *Arch Gen Psychiatry* 1991;48:1082–1088). In other words, before the drug was stopped, they had an episode every year, and now they have an episode within seven weeks. People need to come off very slowly. In controlled trials, patients did much better stopping it over four weeks instead of abruptly, but I think four weeks is still too fast. For long-term users, I would taper off over at least a year, with a hyperbolic pattern.

TCPR: When should we consider deprescribing?

Dr. Horowitz: There are a lot of situations where you need to know how to stop a medication. 1) The harms, like sexual side effects, emotional numbing, and weight gain, may outweigh the benefits. 2) Patients may be on the medication longer than guidelines recommend. Most antidepressant guidelines recommend six to 12 months of treatment for a single episode of anxiety or depression. A lot of people start a medication in the context of an acute stressor and may be able to come off after the stressor has resolved. 3) Polypharmacy is another reason to consider stopping, especially as people get older where the additive side effects can become problematic.

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

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Vyvanse Goes Generic: An Amphetamine Apart

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stimulant with a long history of use in children and adults with ADHD or narcolepsy. It remains inactive until the lysine is cleaved off, converting the prodrug to active dextroamphetamine. Originally, this was assumed to occur in the GI tract, but we now know the cleavage takes place in red blood cells. The delay in activation means that snorting or injecting the medication results in much less of a high compared to other amphetamine formulations (Carton L et al, *Expert Rev Clin Pharmacol* 2022;15(8):921–925). Abuse rates of lisdexamfetamine are lower than those for short-acting stimulants, and people with amphetamine use disorder tend to "like" the euphoria with lisdexamfetamine less than they do with short-acting mixed amphetamine salts like Adderall.

The D-isomer

Amphetamine comes as two mirror-image isomers, dextro- (D-) amphetamine and levo- (L-) amphetamine, each with different biological effects. Of the two, D-amphetamine has more potent effects on the central nervous system (two to four times more powerful). L-amphetamine has a longer half-life and causes more side effects like motor tics and cardiovascular effects. Of the pure D-amphetamine medications, lisdexamfetamine is preferred because of its lower abuse potential and longer duration of action.

The clinical difference

Many patients report a "smoother" experience taking lisdexamfetamine compared to mixed amphetamine salts, which may also relate to the prodrug mechanism. Activation in the red blood cells is much more consistent than absorption in the GI tract, which means that lisdexamfetamine's levels are less affected by food, gut pH, or bariatric surgery (Auiler JF et al, *Curr Med Res Opin* 2002;18(5):311–316). Extended-release beads of mixed amphetamine salts (Adderall XR), for example, are delayed more by a heavy meal (around two and a half hours) than lisdexamfetamine (around one hour).

A network meta-analysis of ADHD treatments identified amphetamines as the most effective treatments for ADHD in adults. In this class, lisdexamfetamine was among the most effective amphetamines (it had the highest difference from placebo), but there was no statistically significant evidence of it being superior to other long-acting amphetamines (Cortese S et al, *Lancet Psychiatry* 2018;5(9):727–738).

Binge eating disorder

In 2015, the FDA approved lisdexamfetamine for binge eating disorder (BED) as part of its priority review program, given limited treatment options. It remains the only approved medication for BED. Amphetamines have long been known to decrease appetite, sometimes causing weight loss (more so than methylphenidates), and lisdexamfetamine's use in BED is an example of leveraging a side effect as a therapeutic. The number needed to treat for achieving remission (four weeks of no binging) was 4 in the pivotal trials (McElroy SL et al, *Neuropsychopharmacology* 2016;41(5):1251–1260).

Vyvanse's manufacturer sought FDA approval in depression augmentation, where it showed early promise in Phase II trials (Trivedi MH et al, *J Clin*

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Lisdexamfetamine Overview

FDA Indications	ADHD in children and adults, binge eating disorder (BED) in adults.
Dosage	Start at 30 mg every morning and titrate by 10–20 mg each week to target of 30–70 mg for ADHD, 50–70 mg for BED.
Side Effects	Common: Decreased appetite, weight loss, anxiety, diarrhea, dry mouth, insomnia. Rare but serious: Psychosis, mania, growth suppression in children, and sudden cardiac death in those with underlying cardiovascular disease.
Interactions	Avoid within 14 days of a monoamine oxidase inhibitor (hypertensive crisis). In theory, CYP2D6 inhibitors (eg, bupropion, duloxetine, fluoxetine, and paroxetine) can raise dextroamphetamine levels, but this is rarely of clinical significance.
Cost	$75–$150 per month (GoodRx.com).

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Psychiatry 2013;74(8):802–809; Madhoo M et al, *Neuropsychopharmacology* 2014;39(6):1388–1398). When it advanced to larger Phase III trials and an additional dose-ranging study, it didn't work and thus was not granted the indication (Richards C et al, *J Psychopharmacol* 2017;31(9):1190–1203; Richards C et al, *J Affect Disord* 2016;206:151–160).

A single trial in bipolar depression augmentation found no difference in the main depressive scale compared to placebo (McElroy SL et al, *Int Clin Psychopharmacol* 2015;30(1):6–13).

Conversion from Adderall to Vyvanse

If you are converting from amphetamine/D-amphetamine mixed salts (Adderall), where there is a 3:1 ratio of D-amphetamine to L-amphetamine, to lisdexamfetamine, you need to adjust for isomers. That's because D-amphetamine is more potent than L-amphetamine. Ordinarily this would mean a reduction in dose (which is true when converting to pure D-amphetamine), but lisdexamfetamine's dosing is inflated by the lysine weighing down the active form of the drug. Thus, when converting from Adderall to Vyvanse, the conversion factor is 2.6. If the amphetamine/D-amphetamine mixed salts dose is 20 mg, this would translate to about 50 mg of lisdexamfetamine, and 30 mg would translate to 70 mg (see the table "Lisdexamfetamine Overview" on page 5).

CARLAT VERDICT

While methylphenidates remain the first choice for ADHD given the favorable side effect profile, we recommend considering generic lisdexamfetamine alongside or even before other long-acting amphetamines as a next step.

News of Note

Azstarys: Vyvanse's Dexmethylphenidate Cousin

As Vyvanse goes generic, the first abuse-deterrent methylphenidate has entered the market. Azstarys is the brainchild of Travis Mickle, PhD, who also brought us Vyvanse, and the two share much in common. While Vyvanse locks the prodrug with L-lysine, Azstarys uses a combination lock with the B3 vitamin niacin and the amino acid L-serine. The resulting prodrug is serdexmethylphenidate. Like Vyvanse, it is the more potent dex- version of the stimulant. Beyond that, the similarities end.

For Vyvanse, drug activation takes place in the red blood cells. For serdexmethylphenidate (Azstarys), it occurs in the lower GI tract. Most importantly, activation is much slower with serdexmethylphenidate, with at least a three-hour wait. To overcome this therapeutic delay, Azstarys is front-loaded with 30% instant-release (IR) dexmethylphenidate, allowing onset within 30 minutes. The manufacturer estimates its therapeutic duration at 13 hours, though Azstarys stopped separating from placebo after 10 hours in its singular controlled trial (Kollins SH et al, *J Child Adolesc Psychopharmacol* 2021;31(9):597–609).

That trial was a three-week classroom study of 149 children aged 6–12 years with ADHD, followed by a larger one-year open-label trial. That is usually not enough for FDA approval, but the agency approved Azstarys in part based on its serum levels, which were close to those of once-a-day dexmethylphenidate IR, at least for the first five hours. Dexmethylphenidate extended release (XR) would provide a more useful comparison.

The manufacturer suggests that the three dose levels of Azstarys (26.1/5.2, 39.2/7.8, and 52.3/10.4 mg, where the lower number represents IR) are equivalent to dexmethylphenidate XR 20, 30, and 40 mg, respectively. This equivalence is not suggested by the pharmacokinetic data, where dexmethylphenidate XR hovers at serum levels approximately double those of Azstarys over the first eight hours. Head-to-head clinical studies are needed.

What about Azstarys' misuse potential? Generally, methylphenidates are less rewarding than amphetamines, but this difference is offset by Azstarys' inclusion of an IR stimulant. Under oral ingestion, Azstarys is about as "liked" as placebo. Unfortunately, those "likes" rise with intranasal insufflation. This is why Azstarys is classified as a Schedule II narcotic even though its prodrug serdexmethylphenidate (which cannot be prescribed alone) falls under the less restrictive Schedule IV classification (along with benzodiazepines). Vyvanse is also a Schedule II drug, although some have suggested it deserves a looser restriction because its rewarding qualities are not changed by intranasal or intravenous delivery and are significantly lower than those of D-amphetamine (Heal DJ et al, *Adv Pharmacol* 2024;99:251–286).

CARLAT TAKE

Azstarys dampens the potential of stimulant misuse some of the way, but not as much as Vyvanse. Azstarys may not perform as well as dexmethylphenidate XR, particularly in the later half of the day, but head-to-head studies are lacking.

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

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

Q&A With the Expert

Antipsychotics Reconsidered

Harish Kavirajan, MD

Psychiatrist in private practice. Associate Professor of Clinical Psychiatry, University of California Irvine, Irvine, CA.

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

TCPR: You've been skeptical of antipsychotics in mood disorders. What led to that?

Dr. Kavirajan: It's mainly their adverse effects. The thing I'm most fearful of is tardive dyskinesia (TD) since it can be irreversible. Typically, I do not even consider using an antipsychotic until I have tried at least one antidepressant from each class of the modern, easier-to-use ones that have emerged since the 1980s. If the person is still significantly depressed, I will consider augmentation, but lithium is usually first on my list. If that does not work, I will often consider a monoamine oxidase inhibitor (MAOI), transcranial magnetic stimulation, ECT, or the ketamines before an antipsychotic (Kavirajan H, *N Engl J Med* 2023;388(21):2012–2013).

TCPR: What is the risk of tardive dyskinesia?

Dr. Kavirajan: It's 3.9% per year with second-generation antipsychotics, which is a little less than the rate with first-generation drugs: 5.5%. But that difference starts to collapse in older patients, where the risk is 5% per year with both generations (Correll CU and Schenk EM, *Curr Opin Psychiatry* 2008;21(2):151–156). Older patients are more at risk, so this is particularly salient for me as geriatric psychiatry is my subspecialty. *(Editor's note: For more information, see the table "Risk Factors for Tardive Dyskinesia" on page 8.)*

> **"Antipsychotics have only a small effect size, around 0.3, for augmenting antidepressants. When a drug has a small benefit and serious risks, I'm cautious."**
>
> Harish Kavirajan, MD

TCPR: Some depression guidelines consider antipsychotics to have favorable tolerability.

Dr. Kavirajan: Some of these meds do look favorable in short-term trials, but their major risks, like TD and metabolic problems, are delayed. Even if those risks are rare, I give them more weight, as they are quite serious and debilitating.

TCPR: One reason that antipsychotics rank so high in treatment guidelines is that the studies are large and numerous.

Dr. Kavirajan: Yes, but in my opinion the efficacy has been exaggerated. The main issue is the magnitude of the effect. Across the board, antipsychotics have only a small effect size, around 0.3, for augmenting antidepressants. That's equal to three or four points of difference from placebo on the Montgomery-Åsberg Depression Rating Scale, which is like 6% of this 60-point scale (Wang J et al, *Medicine (Baltimore)* 2023;102(38):e34670). When a drug has a small benefit and serious risks, I'm cautious.

TCPR: That's a small effect size. Are any of them more effective than the rest?

Dr. Kavirajan: Not really. Aripiprazole has a larger effect size in some meta-analyses, and it also has more studies supporting its efficacy than the others. Quetiapine also stands out as it is the only one with good evidence as monotherapy in major depressive disorder.

TCPR: Monotherapy? But it's not indicated for that, right?

Dr. Kavirajan: No, it's not. The manufacturers tried to get approval as a monotherapy for major depression, and they had the efficacy trials to support it. The number needed to treat was 7 for doses of 150–300 mg QHS as a first-line "antidepressant" (Maneeton N et al, *BMC Psychiatry* 2012;12:160). But the FDA had concerns about exposing 5% of the population to an antipsychotic, so they declined it as monotherapy. My concern with the FDA's decision to approve quetiapine in cases of one failed antidepressant was that the decision would still permit mass exposure to antipsychotics. It only requires failure of one antidepressant trial, which captures about 70% of people with depression.

TCPR: Quetiapine does form a metabolite (norquetiapine) with properties that resemble a serotonin/norepinephrine reuptake inhibitor (SNRI), so it may still contain an antidepressant even as monotherapy.

Dr. Kavirajan: Yes, that's true. Quetiapine also has good data as monotherapy in generalized anxiety disorder, and here the effective dose range was lower, 50–150 mg QHS (Maneeton N et al, *Drug Des Devel Ther* 2016;10:259–276). It came close to approval there, but again the FDA had concerns about exposing a large population to those risks.

TCPR: You mentioned aripiprazole has the best evidence of efficacy. What about others?

Dr. Kavirajan: It pretty much goes downhill from there. Brexpiprazole had two pivotal studies that were used to justify the approval by the FDA, but only one was positive, and even then, there was no statistically significant difference between drug and placebo on remission. Cariprazine had a very small effect size (0.12) across five trials (Xie M et al, *J Psychiatr Res* 2024;172:71–80). Olanzapine-fluoxetine combination (OFC) looks less effective in some analyses, but that's not a fair comparison. OFC is the only one that is approved in treatment-resistant depression (TRD), defined as lack of meaningful response to two adequate antidepressant trials.

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Expert Interview – Antipsychotics Reconsidered
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TCPR: What about other risks with antipsychotics?

Dr. Kavirajan: Their metabolic risks are concerning. That risk is greater in children but is similar for adults and geriatric patients. Falls are another risk that is more of a problem in older adults, but this is also a risk with antidepressants in general, and two head-to-head studies suggest antipsychotics may have an advantage there, at least with aripiprazole. These were two trials that compared bupropion and aripiprazole as augmentation agents in TRD. One, the PROSPECT trial, was strictly geriatric, and the other, the VAST-D, was from the VA. In these studies, bupropion and aripiprazole had similar benefits, but there was a higher rate of falls with bupropion compared to aripiprazole (Ji M et al, *PLoS One* 2024;19(4):e0299020). That is consistent with early trials showing a fall risk with bupropion as well as the SSRIs, SNRIs, and trazodone.

TCPR: Antipsychotics were commonly used for depression in the 1970s. What can we learn from that history?

Dr. Kavirajan: Yes, this actually goes back to 1961 when an MAOI-antipsychotic combo pill was released: tranylcypromine/trifluoperazine (Parstelin). More popular was amitriptyline-perphenazine (Triavil, Etrafon), which is still available. These had support from controlled trials where they were compared to placebo, benzodiazepine augmentation, or antidepressants. There was some effort to identify ideal subtypes for these combos, and patients with anxiety and agitation seemed more responsive. These combinations fell out of favor as we became aware of the risk of TD.

TCPR: So 40 years ago psychiatry dropped antipsychotic-antidepressant combos, and now they are back. Why is that?

Dr. Kavirajan: Guidelines and meta-analyses tend to limit their view to high-quality, double-blind, placebo-controlled trials. Those are expensive to run, which means they are usually industry sponsored and—importantly—short term, so they will miss longer-term adverse effects like TD and metabolic syndrome. The adverse effects associated with long-term treatment are especially important in major depression, where maintenance treatment usually extends for several months if not years.

TCPR: None of the antipsychotics are approved for long-term prevention in major depression.

Dr. Kavirajan: Yes, but that is how they tend to get used. In terms of evidence, we don't have much to guide us there. It's reasonable to attempt to taper off after a stable recovery, like if the patient has been well for six to 12 months and doesn't have a lot of stress going on or other factors that would increase their risk of relapse. But even then, the tapers are not always successful, and there is some evidence the risk of TD is greater for patients who come on and off antipsychotics than it is with continuous use.

TCPR: Do you see a lot of industry bias in the guidelines?

Dr. Kavirajan: I did notice a pattern there and published on that recently. Treatment guidelines that had better protocols to reduce industry influence did a better job of warning about adverse effects on antipsychotics. An earlier study had put forth criteria for treatment guidelines, and I looked at the 11 guidelines that met their criteria for quality. Of those 11, only four even mentioned TD, and only about two-thirds of them mentioned the need to monitor for metabolic adverse effects (Kavirajan H, *Am J Psychiatry* 2024;181(4):342–345).

TCPR: How do you talk to patients who request an antipsychotic after seeing an advertisement or hearing about a friend's recovery on one?

Dr. Kavirajan: I tell them, "These are very dirty drugs. I do use them in selected patients if I think the risks outweigh the benefits, but what troubles me is their risk of weight gain, diabetes, and a potentially irreversible movement disorder called TD." I will demonstrate what some of the oral movements in TD look like. Usually, when I educate patients about these risks, they no longer want to try antipsychotics.

TCPR: You mentioned lithium is high on your list for augmentation, but lithium is also risky for older patients.

Dr. Kavirajan: Yes, but we can test for kidney and thyroid function on lithium. With antipsychotics, we can monitor for TD, but by the time you see it, it may have reached a point where it's irreversible. I've found lithium reasonably well tolerated in the elderly, but you have to aim for a lower serum level. As people age, more lithium passes into the brain, so you can get the same efficacy—and fewer side effects—with serum levels 20%–30% below the typical targets of 0.6–0.8 for depression. Lithium also lacks metabolic risks. In recent meta-analyses, there was no statistically detectable weight gain with lithium. That was surprising. I'd guess that some patients gain weight, but on the whole, it is a lot less than we've assumed (Gomes-da-Costa S et al, *Neurosci Biobehav Rev* 2022;134:104266).

TCPR: You also mentioned using MAOIs in TRD. Which one do you start with?

Dr. Kavirajan: I tend to use tranylcypromine (Parnate), which is a little more favorable in terms of side effects, particularly weight gain and fatigue. If the patient is very anxious, I will choose phenelzine (Nardil), which has better evidence in anxiety and GABAergic effects. One downside to MAOIs is that the titration is slow—you need to do that to avoid orthostatic hypotension. I check blood pressure in the office and have the patient check while at home (sitting and then standing after two to three minutes, recording blood pressure and heart rate). Depending on the risk for that, I will start low and raise every two weeks toward the target, typically 30–100 mg/day for tranylcypromine and 45–60 mg/day for phenelzine.

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Risk Factors for Tardive Dyskinesia

- Longer duration, higher dose of antipsychotic treatment
- First-generation > second-generation antipsychotic
- High-potency > low-potency antipsychotic
- Intermittent antipsychotic dosing
- Early extrapyramidal adverse effects
- Older age (>50)
- Dementia
- Female gender
- African descent
- Possibly affective disorder

Expert Interview – Antipsychotics Reconsidered
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TCPR: What about isocarboxazid and selegiline (Emsam)?
Dr. Kavirajan: Isocarboxazid is the least studied of the MAOIs. Emsam—unlike oral MAOIs—does not have studies in TRD. Estimates from studies of oral selegiline suggest that a high dose—such as 18+ mg/day—would be needed to achieve efficacy in TRD. This dose is not achievable with the patch and would require the same dietary restrictions as oral MAOIs anyway.
TCPR: What about dietary restrictions?
Dr. Kavirajan: The impact on diet is actually quite small, but the person needs to be aware of them. And then, of course, there's the drug-drug interactions.
TCPR: What else do you use for augmentation in older patients?
Dr. Kavirajan: I tend to use low-dose stimulants, usually methylphenidate but sometimes dextroamphetamine. The doses for both would be in the 10–20 mg/day range. Sometimes I use thyroid augmentation with T3. *(Editor's note: See our interview with Dr. Tammas Kelly, "Thyroid Augmentation in Bipolar Disorder," in the April 2022* TCPR*.)*
TCPR: Dextroamphetamine (as Vyvanse) failed as antidepressant augmentation for adults in a large, industry-sponsored trial. Do the data look different in geriatrics?
Dr. Kavirajan: Yes, there was at least one good placebo-controlled augmentation study of citalopram with methylphenidate (mean dose 16 mg/day), and then there are smaller studies (Lavretsky H et al, *Am J Psychiatry* 2015;172(6):561–569). One reason it may work better in older adults is that the phenomenology of depression looks a little bit different in some patients. I tend to use stimulants in patients who seem very flat. They are lethargic, apathetic, and may even look a bit parkinsonian. Some of these patients may have "vascular depression," which refers to a subgroup where depression may be related to subcortical vascular disease (Taylor WD et al, *Am J Psychiatry* 2018;175(12):1169–1175).
TCPR: Thank you for your time, Dr. Kavirajan.

❖ ❖ ❖

Research Updates IN PSYCHIATRY

DEPRESSION

Esketamine vs Quetiapine in Treatment-Resistant Depression

Ivy Song, MD. Dr. Song has no financial relationships with companies related to this material.

REVIEW OF: Reif A et al, *N Engl J Med* 2023;389:1298–1309

STUDY TYPE: Randomized, single-blind controlled trial

In treatment-resistant depression (TRD), should you augment a selective serotonin reuptake inhibitor (SSRI) or serotonin/norepinephrine reuptake inhibitor (SNRI) with quetiapine or esketamine? Quetiapine, an oral medication, poses potential metabolic side effects. Esketamine requires in-office monitoring but is FDA approved for TRD after at least two antidepressant failures—a criterion not met by all studies on quetiapine. A recent head-to-head study compared these medications.

A total of 676 adults with major depressive disorder were drawn from 171 sites across 24 countries. Their average age was about 45. All participants had TRD, defined as an insignificant response to two to six treatments from at least two antidepressant classes, including their current SSRI or SNRI. Upon entering the trial, participants continued their current medication, but all augmenting agents were discontinued. Those on low-dose quetiapine underwent a seven-day washout period before the researchers randomized them to receive adjunctive open-label esketamine (n=336) or extended-release quetiapine (n=340), with doses adjusted to 50–300 mg over three weeks. The study's primary goal was remission at week eight, defined as a Montgomery-Åsberg Depression Rating Scale (MADRS) score of 10 or less. A secondary endpoint was ongoing remission up to week 32. Janssen, the maker of esketamine, funded the study.

At week eight, the esketamine group was 1.5 times more likely to achieve remission than the quetiapine group (27.1% vs 17.6%, p=0.003). Approximately 50% of the esketamine group reached remission by week 32, compared to 30% in the quetiapine group. However, the difference in MADRS scores between the groups was marginal: 2.8 points out of 60 at week eight and 2.2 points at week 32, bringing the clinical significance of these findings into question.

Adverse effects led to higher discontinuation rates in the quetiapine group compared to the esketamine group (11% vs 4.2%), with both groups experiencing high rates of side effects (93% vs 78%). One patient in the esketamine group developed acute coronary syndrome and one developed dizziness, both attributed to the medication. No serious adverse events were linked to quetiapine.

CARLAT TAKE
This study suggests esketamine may be somewhat more effective than quetiapine for augmentation in TRD. However, the study's funding source, Janssen, raises concern for potential biases, particularly in study design. Notably, all participants in the esketamine group were naive to this treatment, unlike some in the quetiapine group, who may have previously tried and not responded to atypical antipsychotics. This discrepancy could disadvantage the quetiapine arm. Despite these concerns, the direct comparison offered by this clinical trial is valuable.

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SIDE EFFECTS

Lithium, Valproate Have Low (and Similar) Risk of Kidney Injury

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

REVIEW OF: Bosi A et al, *JAMA Netw Open* 2023;6(7):e2322056

STUDY TYPE: Retrospective cohort study

Studies have had mixed results regarding the relationship between lithium and kidney injury. A 2012 meta-analysis of lithium and kidney injury was inconclusive, and studies since then have suffered from limitations and conflicting results. In an effort to clarify this issue, researchers once again looked at the risk of kidney injury in patients taking lithium—this time comparing it to those taking valproate.

This retrospective cohort study analyzed data from about 11,000 Stockholm residents who began lithium or valproate between 2007 and 2018 and had no prior history of kidney transplant or maintenance dialysis. Using data from Stockholm's Creatinine Measurements database, the study tracked these patients for up to 10 years, covering roughly 5,300 individuals per medication group, with a median follow-up duration of 4.5 years. The primary outcome was progression of chronic kidney disease (CKD), incidence of acute kidney injury (AKI), changes in estimated glomerular filtration rate (eGFR), and the onset of new albuminuria. Researchers measured both lithium and valproate levels, specifically looking at outcomes at lithium levels above and below 1.0 mmol/L.

The study found no significant difference in CKD progression between patients starting on lithium or valproate, with about 3.5% of individuals in each group developing CKD. There were also no significant differences in non-CKD eGFR reduction, AKI risk, or albuminuria between the two groups. Surprisingly, the overall risk of AKI over the 10-year study period was actually 3.2% lower for lithium than valproate (95% confidence interval [CI] -5.6 to -1.1).

However, there was some concerning news about lithium. For the subgroup of lithium-treated patients with blood levels higher than 1.0 mmol/L, the risk of CKD was almost triple that of patients with levels below 1.0. Even a level of more than 0.8 mmol/L significantly increased the risk of AKI (hazard ratio 2.56, 95% CI 1.67–3.92).

CARLAT TAKE

Despite its reputation, lithium does not increase the risk of acute or chronic kidney injury any more than valproate. The overall risk of kidney injury in both groups was low, and keeping lithium below 0.8 mmol/L (when clinically feasible) is safest renally. In this study, valproate was more likely to cause AKI than lithium, and there are case reports of kidney injury in patients starting valproate (Anguissola G et al, *Pediatr Nephrol* 2023;38(6):1725–1731). No guidelines call for checking kidney function any time a patient starts valproate—but we should be aware of the rare possibility of AKI.

ADHD

Overdiagnosis of ADHD

Alvin Marquez, MD. Dr. Marquez has no financial relationships with companies related to this material.

REVIEW OF: Harrison et al, *J Atten Disord* 2023;27(12):1343–1359

STUDY TYPE: Systematic review

When a patient presents with a positive score on an ADHD screener, how much weight should we give the test? Overreliance on self-report may lead to overdiagnosis of adult ADHD. This study aimed to describe the psychometric properties of commonly used ADHD screening tools to help clinicians interpret results.

The authors conducted a systematic review, including 20 studies of several self-report measures, such as the Adult ADHD Self-Report Scale. They looked at sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) to see how well the tests separated ADHD from both healthy adults and symptomatic non-ADHD adults. False positives are expected with screening tools, which are designed to be more sensitive (that is, catching those who need further evaluation) than specific (that is, identifying those who don't).

Surprisingly, none of the studies used a comprehensive "gold standard" evaluation to verify the diagnosis. Many instead relied on other self-reports, often with high false positive rates. PPV scores were poor, particularly in clinical settings, where most tests had scores below 30%. In other words, a positive result for most tests had less than a coin flip's chance of correctly identifying ADHD. Conversely, nearly every measure exhibited an NPV score of 95% or more, meaning a negative result rarely missed true ADHD, even in the presence of comorbid psychiatric conditions. This held true for most tests, except for two that focused on patients undergoing substance use treatment. Because the DSM criteria for ADHD include domains not captured by most self-reports (such as childhood onset and functional impairment), it is perhaps unsurprising that diagnosing by self-report alone is not reliable.

CARLAT TAKE

While a negative result on an ADHD screener helps rule out the diagnosis, a positive result doesn't tell us that the patient has ADHD. To diagnose adult ADHD, first rule out other causes. Seek third-party input and look for symptoms that date back to childhood (before age 12), are stable through time, and cause specific problems in multiple areas of life.

SCHIZOPHRENIA

Estrogen in Schizophrenia

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

REVIEW OF: Li Z et al, *Act Psychiatrica Scandinavica* 2023;147(4):360–372

STUDY TYPE: Meta-analysis of randomized, double-blind, placebo-controlled trials

Estrogen has long been thought to play a protective role in schizophrenia. The onset of the illness is delayed in women,

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1. What is the recommended approach for tapering psychiatric medications (LO #1)?
   - [ ] a. Taper at a consistent rate throughout
   - [ ] b. Taper more slowly at the end
   - [ ] c. Taper quickly to avoid prolonged treatment
   - [ ] d. Gear the taper to the patient's preference

2. Which statement applies to lisdexamfetamine (LO #2)?
   - [ ] a. It is activated primarily in the gastrointestinal tract
   - [ ] b. It is a direct-acting stimulant that does not require metabolic activation
   - [ ] c. It is an inactive prodrug that is converted to dextroamphetamine in red blood cells
   - [ ] d. It has a higher potential for abuse compared to other stimulant medications

3. Which strategy does Dr. Kavirajan prioritize before considering antipsychotics for augmentation in mood disorders (LO #3)?
   - [ ] a. Increasing the dose of existing antidepressants
   - [ ] b. Using ketamine as a first-line treatment
   - [ ] c. Trying lithium and other nonantipsychotic options
   - [ ] d. Referring the patient for psychotherapy

4. In a study by Reif et al, which adjunctive medication demonstrated a higher likelihood of achieving remission in treatment-resistant depression (LO #4)?
   - [ ] a. Quetiapine
   - [ ] b. Escitalopram
   - [ ] c. Esketamine
   - [ ] d. Bupropion

5. What percentage of patients were able to stop taking an antidepressant when they were switched to a hyperbolic taper (LO #1)?
   - [ ] a. 28%
   - [ ] b. 47%
   - [ ] c. 72%
   - [ ] d. 81%

6. What clinical application of lisdexamfetamine is notable aside from its use in ADHD (LO #2)?
   - [ ] a. Treatment of narcolepsy with a focus on immediate symptom relief
   - [ ] b. Approved treatment for binge eating disorder
   - [ ] c. Primary treatment for generalized anxiety disorder
   - [ ] d. First-line medication for depression augmentation

7. What is the primary concern associated with the long-term use of antipsychotics in mood disorders, as discussed by Dr. Kavirajan (LO #3)?
   - [ ] a. Low efficacy in treating depression
   - [ ] b. Tardive dyskinesia and metabolic risks
   - [ ] c. Difficulty in tapering off the medication
   - [ ] d. High cost of treatment

8. Findings from a cohort study of the effects of lithium vs valproate on kidney health suggest which of the following (LO #4)?
   - [ ] a. Lithium was associated with a higher incidence of chronic kidney disease compared with valproate at therapeutic levels
   - [ ] b. Compared with valproate, lithium had a lower overall risk for acute kidney injury
   - [ ] c. Both medications significantly increased the risk for new albuminuria
   - [ ] d. Lithium was found to be safe at levels higher than 1.0 mmol/L

Research Updates

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and psychotic symptoms tend to worsen in women when estrogen wanes, such as during premenstruation, postpartum, and menopause. The estrogen hypothesis, which suggests that estrogen has neuroprotective properties and regulates dopamine activity while preserving cognitive function, has prompted investigations into estrogen therapy as a potential adjunctive treatment for schizophrenia in women.

In this meta-analysis, the authors examined 13 randomized, placebo-controlled, double-blind trials that evaluated the efficacy of adjunctive hormonal treatments in women with schizophrenia. The hormonal options considered were estradiol and raloxifene, a selective estrogen receptor modulator used for the treatment of osteoporosis and menopausal symptoms. Six trials focused on estradiol versus placebo in women of childbearing age (n=724, average age 36.6 years), while seven studies compared raloxifene to placebo in menopausal women (n=419, average age 57.4). All participants continued their current psychotropic regimen, which included antipsychotics. The duration and dosage of adjunctive treatments

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varied across studies. The primary outcome measured was the change in severity of psychotic symptoms, assessed using the Positive and Negative Syndrome Scale (PANSS).

Adjunctive treatment with estradiol demonstrated superior outcomes compared to placebo, as indicated by a significant improvement in PANSS scores (mean difference -7.29, 95% confidence interval [CI] -10.67 to -3.91, p<0.001). Similarly, adjunctive treatment with raloxifene also outperformed placebo, resulting in a significant reduction in PANSS scores (mean difference -6.83, 95% CI -11.69 to -1.97, p=0.006). Estradiol studies also showed significant improvements in the positive and negative symptom subscales. Menstrual irregularities were the most frequently reported adverse event.

Factors such as baseline estradiol levels, menstrual cycle stage, and concurrent therapies (eg, oral contraceptives) were not considered in this study but may influence treatment outcomes.

CARLAT TAKE

Estrogen is worth considering in women with schizophrenia, although it is best to defer to OB-GYN for the decision as the treatment carries cardiac and cancer risks. In postmenopausal women with schizophrenia and osteoporosis, raloxifene may offer dual benefits.

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