THE CARLAT REPORT PSYCHIATRY

A CME Publication

AN UNBIASED MONTHLY COVERING ALL THINGS PSYCHIATRIC

Chris Aiken, MD
Editor-in-Chief

Volume 16, Issue 11 & 12
November/December 2018
www.thecarlatreport.com

IN THIS ISSUE

Focus of the Month:
Drug Metabolism

Learning Objectives

After reading these articles, you should be able to:

1. Identify the benefits and drawbacks of newer amphetamine and methylphenidate formulations.
2. Determine the potential for significant drug interactions with commonly used psychiatric medications.
3. Describe some of the drug combinations that can be used strategically to elicit beneficial drug interactions.
4. Summarize some of the current research on psychiatric treatment.

New Stimulants: From Remixed Amphetamines to Bedtime Ritalin

Special Double Issue! Worth 2 CME credits!

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

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

You may have noticed that a confusing array of new stimulants has been approved in the last few years. Since 2012, there have been five new amphetamines and two new methylphenidates. What are these preparations? Are any of them worth prescribing to your patients? To prepare you for the promotional downpour that's likely to accompany all this repackaging, we've pulled together a just-the-facts comparison.

In Summary

- There are many new stimulant formulations, but few that offer advantages over the generic ones.
- Mydayis has a 16-hour duration, which is unique among the newer long-acting versions of Adderall.
- A 2018 meta-analysis found children respond better to methylphenidate varieties of stimulants, while adults do better with amphetamine ones.

The three faces of amphetamine

For many years, amphetamine was only available in two preparations: Dexedrine and Adderall. Now there is a third, Evekeo, and to understand how these

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Q&A With the Expert

Effects of Drug Interactions
Neil Sandson, MD

Clinical Associate Professor, Department of Psychiatry at University of Maryland School of Medicine

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

TCPR: We're seeing a lot of computer alerts for drug interactions. Which ones should we pay attention to?

Dr. Sandson: The two issues to pay attention to are toxicity and loss of efficacy. Toxicity is the bigger concern, particularly if the drug has a "narrow therapeutic index," where modest differences in the level can have dangerous effects. Lithium, tricyclics, carbamazepine, and to a lesser extent valproate are some psychiatric examples where high levels can cause problems (see "Toxic Drug Interactions in Psychiatry" table on page 8). Drug interactions with inhibitors can cause high levels by blocking metabolism by P450 enzymes in the liver. The potency of the inhibitor also matters here. An inhibitor that raises a drug by only 20% is probably not going to cause much concern.

TCPR: What are some potent inhibitors we use?

Dr. Sandson: Fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), and duloxetine (Cymbalta). Fluoxetine and fluvoxamine are potent and hit a broad array of P450 enzymes, while paroxetine's effects are fairly

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New Stimulants: From Remixed Amphetamine to Bedtime Ritalin

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three differ, we'll need to review the amphetamine isomers.

Amphetamine comes in two isomeric forms: dextro- and levo-amphetamine. These two molecules are mirror images of one another. Of the two, dextro-amphetamine is more potent, with a higher abuse potential and greater appetite suppressant effects. Levo-amphetamine is longer-lasting and causes more cardiac side effects. Adderall mixes the dextro- and levo-isomers in a 3:1 ratio (with more dextro-), while Dexedrine and Vyvanse are pure dextro-. In Evekeo the ratio is even, 1:1.

Mailing Information

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

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

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

Evekeo

Isomer mix: 1:1 dextro-:levo-amphetamine

Duration: INSTANT RELEASE: Evekeo$ (9.25 hr)

($ indicates available as brand only)

Few people know that Evekeo is identical to an older drug, Benzedrine. Released in 1935, Benzedrine was the first stimulant to enter the U.S. market. Better known on the streets as "Bennie," Benzedrine developed a reputation as a drug of abuse that was memorialized in Elton John's song "Bennie and the Jets." It was a favorite of the Beat generation, whose founder, Jack Kerouac, reportedly wrote all of *On the Road* over the course of three Benzedrine-fueled days. Benzedrine's reputation for abuse was part of what led to its decline, but its actual abuse potential is less than Dexedrine's and more than Ritalin's.

The other reason Benzedrine fell out of use was efficacy. In 1976, a placebo-controlled crossover study concluded that Benzedrine was less effective for ADHD than the two other stimulants in use at the time: Ritalin and Dexedrine (Gross MD, *Dis Nerv Syst* 1976;37:14–16). However, a subset (15%) in that study actually fared better with Benzedrine, suggesting that Evekeo may have a role in a minority of patients with ADHD.

Evekeo is not the only stimulant to undergo this type of resurrection. Adderall had been available for years as the weight loss medication Obetrol. By the 1990s, amphetamines had fallen out of favor as anorexics, so Obetrol was renamed to the equally evocative "ADDerall" and repackaged for ADHD.

Adderall & co.

Isomer mix: 3:1 dextro-:levo-amphetamine

Duration: INSTANT RELEASE: Adderall IR (4–6 hr)

LONG-ACTING: Adderall XR (10–12 hr), Adzenys XR-ODT$ and ER liquid$ (10–12 hr), Dyanavel XR liquid$ (12 hr), Mydayis$ (16 hr)

Most of the new long-acting versions of Adderall offer little advantages over the original XR outside of an easier-to-swallow delivery. Mydayis is an exception. With a 16-hour duration, Mydayis offers a unique advantage for patients whose "day is" longer than the 12 hours of coverage that the other extended-release formulations provide (Markowitz JS et al, *J Child Adolesc Psychopharmacol* 2017;27(8):678–689). However, a generic equivalent of that effect can be achieved with Adderall XR in the morning and an additional IR in the late afternoon.

Dexedrine & co.

Isomer mix: 100% dextro-amphetamine

Duration: INSTANT RELEASE: Zenzedi$ (4–6 hr), ProCentra liquid$ (4–6 hr)

LONG-ACTING: Dexedrine ER spansules (6–10 hr), Vyvanse$ (9–14 hr)

The more potent of the two isomers, dextro-amphetamine, is available in instant- and extended-release versions. Zenzedi is a branded form of the instant-release version, and its main advantage is dose customization (it comes in 7 sizes: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, and 30 mg, while the generic instant-release version only comes in 5 mg and 10 mg). The original instant-release brand, Dexedrine, is no longer manufactured, but an ER form is available as Dexedrine spansules—a common cause for confusion at the pharmacy.

One drawback of the dextro- form is its greater abuse liability. To get around that, Vyvanse was created in 2007 by tacking an amino acid (L-lysine) onto dextro-amphetamine to create lisdexamfetamine. The stimulant becomes activated as the amino acid is removed in the bloodstream. This activation process imparts a unique advantage to Vyvanse that patients who've never thought of snorting it will appreciate. Compared to Dexedrine, Vyvanse's metabolism is more steady and consistent, which translates to a longer duration of action and smoother effects throughout the day (Mattingly GW et al, *Postgrad Med* 2017;129:657–666). Vyvanse also capitalizes on the unique anorexic effects of the dextro- isomer and is the only stimulant with FDA approval for binge eating disorder, where it works best in the higher dose range (50–70 mg).

The new methylphenidates

Methylphenidate arrived in the 1960s as Ritalin, just as concern about stimulant

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Harnessing Beneficial Drug Interactions

Rehan Aziz, MD. Associate Professor of Psychiatry and Neurology at Rutgers Robert Wood Johnson School of Medicine. Chris Aiken, MD. Editor-in-Chief, The Carlat Psychiatry Report.

Drs. Aziz and Aiken have disclosed that they have no relevant financial or other interests in any commercial companies pertaining to this educational activity.

It's nice when we can get our patients better with a single medication, but that's not always possible. Sometimes the right combination of meds can do the trick, but studies of polypharmacy are scarce. In this article we dig through that research, small and limited as it is, to highlight a few useful combinations where the drug interaction can benefit your patient.

Stimulants with clonidine or guanfacine

Stimulants can raise blood pressure, which tends to be a problem as patients age. Adding an antihypertensive is a common solution, and two alpha-agonists, clonidine (Kapvay) and guanfacine (Intuniv), have FDA approval for both hypertension and ADHD. It sounds like a match made in heaven—but what do the data show?

This strategy was tested out in a randomized controlled trial in 207 children ages 7–14. It compared the combination of dex-methylphenidate XR (Focalin XR, 5–20 mg/day, average 15 mg/day) and guanfacine (1–3 mg/day, average 0.03 mg/kg/day) with each of those meds on their own. After 2 months, the combination strategy treated ADHD more effectively than either of the monotherapy arms. Side effects were also more favorable. The combined treatment had less blood pressure elevations than stimulant alone, and less fatigue than guanfacine monotherapy.

The combined treatment also had less QTc prolongation. That's important, as QTc prolongation is partly responsible for the rare cases of sudden cardiac arrest on stimulants. In contrast, other ADHD augmentation strategies—bupropion, atomoxetine, and modafinil—can further elevate both blood pressure and QTc.

There was no apparent downside to this strategy, but the benefits were not very large, and neither drug completely reversed the side effects of the other (McCracken JT et al, *J AACAP* 2016;55(8):657–666).

TCPR recommendation: Combining stimulants and guanfacine (and possibly clonidine) is a sensible strategy in ADHD, particularly when cardiac risks are present.

Dopamine agonists and SSRIs

The dopamine agonists pramipexole (Mirapex) and ropinirole (Requip) are FDA-approved for restless leg syndrome (RLS) and have antidepressant qualities in their own right. Of the two, pramipexole is better studied in depression and has worked in small, controlled trials of both bipolar and unipolar depression. Further, in one trial, patients with hard-to-treat MDD who received pramipexole combined with an SSRI/SNRI achieved better response than patients taking an SSRI/SNRI and placebo (Cusin C et al, *J Clin Psychiatry* 2013;74(7):e636–e641).

In terms of side effects, serotonergic medications can sometimes cause RLS (Debattista CB et al, *J Clin Psychopharm* 2000;20(2):274–275). Pramipexole can treat SSRI-induced RLS. That benefit, along with its ability to augment SSRIs in treatment-resistant depression, makes this an intriguing combination.

When using pramipexole, starting low (around 0.125–0.25 mg per day) and increasing the dose slowly (by 0.25 mg every week) helps reduce nausea and orthostasis, two common side effects with this drug. Sedation is also possible, and there have been rare reports of visual hallucinations and compulsive behaviors such as gambling (Aiken CB, *J Clin Psychiatry* 2007;68(8):1230–1236).

TCPR recommendation: When patients complain of restless legs on serotonergic antidepressants, try a low dose of pramipexole for RLS. The dose can be raised if depressive symptoms persist.

Lithium and carbamazepine

Lithium and carbamazepine might not be the first drugs you'd think about combining, given that they both have significant adverse reactions and potential toxicity. But there are reports that these drugs can cancel out some of each other's side effects. In particular, they have opposite effects on sodium and white blood count. Carbamazepine can lower sodium by raising SIADH, whereas lithium raises sodium by causing the opposite syndrome, diabetes insipidus. Small studies have concluded that lithium protects against hyponatremia on carbamazepine (Vieweg V et al, *Am J Psych* 1987;144(7):943–947).

In addition, carbamazepine can cause a potentially dangerous neutropenia, while lithium increases white blood cell production. In a placebo-controlled study, lithium successfully reversed the neutropenia that was induced by carbamazepine (Kramlinger KG and Post RM, *Am J Psych* 1990;147(5):615–620).

Beyond side effect neutralization, there may be an efficacy advantage with this combination. There are open-label studies of patients who did not respond to lithium or carbamazepine alone but who then responded to the two drugs together (Lipinski JF et al, *Am J Psych* 1982;139(7):948–949). The combination is particularly helpful in rapid-cycling bipolar disorder (Strömgren LS, *Comprehensive Psych* 1990;31(3):261–265).

This combination is not without its risks. Lithium and carbamazepine can have additive effects toward hypothyroidism, and there are rare reports of neurotoxicity even with normal plasma levels of each drug (Kim MD et al, *Jefferson J Psych* 1988;6(2):63–72).

TCPR recommendation: For patients with rapid-cycling or treatment-resistant bipolar disorder, the combination of carbamazepine and lithium can

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specific for CYP2D6. Sertraline (Zoloft) is also an inhibitor at CYP2D6, but it doesn't become potent until you reach the higher dosages, like 150 mg and above.

TCPR: What about inducers?

Dr. Sandson: Inducers do the opposite. They lower drug levels, and potent ones can drop the affected drugs out of the therapeutic range. The inducers often tend to be among the anticonvulsants, and the most potent one we use in psychiatry is carbamazepine (Equetro, Tegretol). Induction is usually not as dangerous as inhibition, but there are exceptions.

TCPR: When is induction a serious problem?

Dr. Sandson: The main examples are oral contraceptives, warfarin, and immunosuppressants (cyclosporins, sirolimus, tacrolimus), all of which are significantly induced by carbamazepine at CYP3A4. Carbamazepine can render birth control ineffective. Lowering immunosuppressants can lead to organ rejection in people who've had a transplant, and lowering warfarin can result in ischemic events through coagulation. High levels of warfarin are also dangerous, causing bleeding and hemorrhage, and CYP2C9 inhibitors will raise it.

TCPR: What about other anticonvulsants? Can they induce 3A4 like carbamazepine does?

Dr. Sandson: Other psych meds that induce 3A4 include St. John's wort, modafinil (Provigil), armodafinil (Nuvigil), topiramate (Topamax), oxcarbazepine (Trileptal), and barbiturates. Several of these are less potent inducers, but you'd still want to avoid them when the risks of induction are serious. The actual interaction may vary by person, as well as by dose. Topiramate and oxcarbazepine's induction gets more potent as the dosage is increased.

TCPR: Does this 3A4 interaction affect all forms of birth control?

Dr. Sandson: Estrogen and progesterone-based contraceptives will be affected by 3A4 induction, which includes most of them. Ethinyl estradiol and progesterone are metabolized through 3A4, so inducers there are going to be a problem. The interaction is the same regardless of the route of delivery: oral, transdermal, vaginal ring, and implant. Now, many of these inducers will only reduce ethinyl estradiol/progesterone by 10%–20%, but the risk is nontrivial and the science inexact, so double protection is a wise strategy here.

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Ask the Editor

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

If you have a question you'd like Dr. Aiken to answer, please send an email to ***AskTheEditor@thecarlatreport.com.*** *Dr. Aiken won't be able to answer all questions received, but he will pick one each month that is of general interest.*

Which Antipsychotic Is Best When Patients Complain of Akathisia?

Akathisia is a sensation of inner restlessness so unpleasant that it independently elevates the risk of suicide. Among atypicals, quetiapine (Seroquel) has the lowest risk of akathisia, but that doesn't mean it's easy to take. Its other adverse effects, like sedation, weight gain, and hypotension, lead to more premature discontinuation and emergency room visits than with other antipsychotics (Hampton LM et al, *JAMA Psych* 2014;71:1006–1014; Zhou X et al, *Int J Neuropsychopharmacol* 2015;18:pyv060). So, it's helpful to know the runner-ups. Rates are also low for iloperidone, brexpiprazole, clozapine, and possibly ziprasidone[1] and olanzapine[1].

Newer is not always better. Cariprazine and lurasidone are among the worst offenders, but other new medications have lower rates of akathisia than the antipsychotics they were derived from (iloperidone and paliperidone < risperidone; brexpiprazole < aripiprazole). The highest rates are seen with high-potency conventional antipsychotics like haloperidol and fluphenazine.

The table at right lumps atypicals by their number needed to harm (NNH) for akathisia in schizophrenia. In mood disorders, the rates are higher but the pattern is similar. However, akathisia is difficult to measure reliably, and there are few head-to-head comparisons.

Akathisia is dose-dependent, so starting low and titrating slowly can help. Antidotes are numerous. Beta-blockers are first-line (propranolol 30–90 mg/day, betaxolol 10–20 mg/day). Treatments for restless leg syndrome can be helpful (rotigotine 2–8 mg/day, clonazepam 0.5–2.5 mg/day, gabapentin 300–1200 mg/day, amantadine 100–200 mg bid), and small studies support the use of 5-HT2A antagonists (trazodone 50–100 mg/night, mirtazapine ≤ 15 mg/night, cyproheptadine 16 mg/night) and vitamin B6 (600 mg bid).

[1] Studies are inconsistent, reporting both high and low rates.

Risk of Akathisia With Atypical Antipsychotics	
Low (NNH 100–200)	Quetiapine (Seroquel)
	Iloperidone (Fanapt)
	Brexpiprazole (Rexulti)
	Ziprasidone[1] (Geodon)
	Clozapine (Clozaril)
Medium (NNH 25–40)	Paliperidone (Invega)
	Asenapine (Saphris)
	Olanzapine[1] (Zyprexa)
	Aripiprazole (Abilify)
High (NNH 10–15)	Risperidone (Risperdal)
	Cariprazine (Vraylar)
	Lurasidone (Latuda)

Sources: Goldberg JF and Ernst CL, Ch 17 in *Managing the Side Effects of Psychotropic Medications,* APA Press, 2018; Gao K et al, *Neurosci Bull* 2015;31(5):572–588.

Expert Interview
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TCPR: Inhibitors and inducers are often described as "mild," "moderate," or "potent." What do those terms really mean?

Dr. Sandson: A mild inhibitor will increase blood levels somewhere in the 20%–50% range. Most patients can tolerate that difference, unless they are fragile or elderly. Moderate inhibitors raise levels 60%–100%, and potent inhibitors raise them over 100%, so they more than double it. Tobacco smoking can also be a potent inducer, especially with regard to antipsychotics and some antidepressants, and its effects vary depending on how much one is smoking.

TCPR: What about vaping and e-cigs?

Dr. Sandson: Those are different. It's actually the polycyclic aromatic hydrocarbons from smoking that induce the enzyme (CYP1A2), and we don't see that effect with nicotine itself, whether from e-cigs, patch, or gum. We do see some induction with marijuana smoking, which produces the same hydrocarbons. So when patients switch from smoking to e-cigs or quit marijuana, you'd expect to see increased levels of some antipsychotics and antidepressants (Anderson GD et al, *Clin Pharmacokinet* 2016;55:1353–1358). (See "Smoking Interactions" box on page 8.)

TCPR: Do drug interactions start as soon as the medicine is added, or is there a delay?

Dr. Sandson: For inhibitors, the effects typically build up over a few days. Inducers are slower. It takes 2 to 4 weeks for an inducer to rev up and reach full effect, and it's going to take about that long for reversal of induction. One exception is smoking. It only takes about 3 days for cigarette smoking to become a clinically meaningful inducer, and the reversal of that induction only takes about a week.

TCPR: Going back to inhibitors, are there any that can raise the seizure risk with bupropion?

Dr. Sandson: Possibly. Most antidepressants and antipsychotics can lower the seizure threshold, but bupropion is the biggest offender among the antidepressants available in the US, and the risk goes up with higher levels. Bupropion is metabolized by CYP2B6, and the major inhibitors to worry about adding to it are the "non-pram" SSRIs—that is, all of them except escitalopram and citalopram.

"Most antidepressants and antipsychotics can lower the seizure threshold, but bupropion is the biggest offender among the antidepressants. The major inhibitors to worry about adding to it are the 'non-pram' SSRIs—that is, all of them except escitalopram and citalopram—and the risk goes up with higher levels."

Neil Sandson, MD

TCPR: What happens when you add those SSRIs to bupropion?

Dr. Sandson: There it gets interesting, because most of bupropion's norepinephrine reuptake inhibition is accomplished through its metabolite: hydroxybupropion. Drugs that inhibit that conversion, like the non-pram SSRIs, will raise levels of the parent compound and lower levels of the active metabolite. This alters bupropion's metabolism in a way that effectively creates a new drug I call "Superbutrin."

TCPR: How does this Superbutrin compare to regular bupropion?

Dr. Sandson: Superbutrin has higher levels of the parent compound, bupropion, and lower levels of the metabolite, hydroxybupropion. In a test tube, the parent compound is twice as potent an inhibitor of norepinephrine reuptake as its metabolite. However, in the body, most of the actual norepinephrine reuptake results from the metabolite because its half-life is much longer than bupropion's. Everything we know about bupropion—from its seizure risks to its antidepressant effects—flies out the window with Superbutrin. It may be that Superbutrin has a lesser risk of seizures. One study suggests that's the case, but the data are pretty weak (Silverstone PH, *Ann Gen Psych* 2008;15(7):19). We really don't know as much about how this Superbutrin acts.

TCPR: What about drugs that are metabolized through multiple enzymes? Do we have to worry when an inhibitor blocks only one of those enzymes?

Dr. Sandson: Usually not, unless the single pathway that's inhibited is the major one. That's true for clozapine, which is predominantly metabolized at CYP1A2, though it has several auxiliary pathways. In general, drugs that are metabolized through only one pathway are more vulnerable to interactions.

TCPR: What are some one-pathway drugs?

Dr. Sandson: We have a few that are pretty exclusive for CYP3A4. Quetiapine (Seroquel), lurasidone (Latuda), and buspirone (Buspar); these are all going to be fairly exclusive at 3A4.

TCPR: Let's talk about trazodone. It seems like morning sedation is relatively common with that medication.

Dr. Sandson: Yeah, it certainly can be. Trazodone is also a 3A4 substrate, and so giving it with 3A4 inhibitors can heighten and prolong the sedation. But there's another interaction to worry about with trazodone. One of the metabolites of trazodone, and of nefazodone as well, is something called meta-chlorophenylpiperazine or mCPP, and abrupt increases in mCPP can be both dysphorogenic and anxiogenic, and even hallucinogenic. The body gets rid of mCPP through 2D6, so 2D6 inhibitors can cause it to rise. Potent 2D6 inhibitors include fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft) at dosages ≥ 150 mg, but many other antidepressants can inhibit it (see table on page 8).

TCPR: Seems like we combine trazodone with those meds a lot. How big a problem is this mCPP?

Dr. Sandson: We don't see it as often as you'd expect. This interaction tends to happen when trazodone is in the antidepressant dose range, like 300 mg and above. Also, it's abrupt increases in mCPP that are destabilizing.

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New Stimulants: From Remixed Amphetamines to Bedtime Ritalin
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abuse was rising. This was good timing, as methylphenidate's potential for abuse is lower than that of the amphetamines. Like the amphetamines, methylphenidate is also available in dex- and levo-isomeric forms, but in this case the levo- form is not just less effective, it is practically inert. There is no 3:1 mixture of these isomers, which are available as 1:1 methylphenidate (Ritalin, etc) or pure dex-methylphenidate (Focalin).

Methylphenidate & co.

Isomer mix: 1:1 dex:levo methylphenidate

Duration: INSTANT RELEASE: Ritalin, Methylin chewable, Ritalin liquid (3–5 hr) INTERMEDIATE-ACTING: Methylphenidate SR wax tabs (aka Ritalin SR, Metadate ER) (4–8 hr), Ritalin LA (6–9 hr), Metadate CD (8–10 hr), QuilliChew ER$^{\$}$ (8 hr) LONG-ACTING: Concerta (12 hr), Cotempla XR-ODT$^{\$}$ (12 hr), Daytrana transdermal patch$^{\$}$ (12 hr), Aptensio XR$^{\$}$ (12 hr), Quillivant/QuilliChew XR$^{\$}$ (12 hr), Jornay PM$^{\$}$ (8–11 hr)

Instant-release methylphenidate acts quickly and leaves just as fast. Its onset is 15–30 minutes, compared to 1 hour for Adderall, and its duration is 1–2 hours shorter than Adderall's. A series of formulations have appeared to extend its effects, beginning with wax-coated tablets in 1987. Today, there's little reason to use the wax tabs like Ritalin SR and Metadate ER, which are notorious for their inconsistent effects. For patients paying out of pocket, wax capsules (eg, Metadate CD) work better for a similar price ($60–$70/month, see: www.goodrx.com) (Elia J, *Psychiatry (Edgmont)* 2005;2(1):27–35).

Newer extended-release technologies started hitting the market in 2000, and two stand out among the ones that have gone generic: Ritalin LA and Concerta. Ritalin LA is preferred by patients who need a higher dose in the morning, as it contains more fast-acting instant-release methylphenidate within its beaded delivery system. Concerta's osmotic delivery has a slower onset (1–2 hrs) but a longer duration. It helps to specify the generic manufacturer "Activis" on Concerta scripts, as other generic substitutions are not considered bioequivalent by the FDA (an exception is the 72 mg capsule from Trigen, the only manufacturer of this dose, which is also bioequivalent and has coupons at: https://methylphenidateer72.com).

It's difficult to imagine how the new methylphenidates could improve on Concerta's 12 hours of smooth drug delivery, but bear with me. The new brands hope to ease the early mornings when kids are getting ready for school, through preparations that are quick to act or easy to swallow.

Quick to act. Aptensio XR's onset is 2–3 times faster than Concerta's and lasts about as long. Jornay PM, which is due out in 2019, offers a novel solution to the morning problem. Taken at night, it starts to work upon awakening 8–10 hours later. Jornay PM is a methylphenidate, and the company is working on an amphetamine version.

Easy to swallow. The remaining new methylphenidates have pharmacokinetics that are similar to Concerta but offer different routes of delivery (patch: Daytrana, liquid: Quillivant, chewable: QuilliChew, and orally disintegrating: Cotempla XR-ODT). Do these alternative routes have a role in adults? Swallowing problems do lead to nonadherence in 15% of adults, but the extra cost of these throat-friendly forms can lead to nonadherence as well (Mattingly GW et al, *Postgrad Med* 2017;129:657–666).

One form, the Daytrana transdermal patch, is probably worth avoiding—it can cause permanent loss of skin pigmentation, called leukoderma, around the application site. The patch is intended to allow easy on-off effects, but it is slow to start (1–2 hours) and lingers for 2–3 hours, or even up to 5 hours in some, after its removal. The patch is also prone to falling off, and can lead to mild overdoses with excess heat.

Focalin

Isomer mix: 100% dex-methylphenidate

Duration: INSTANT RELEASE: Focalin (3–5 hr) LONG-ACTING: Focalin XR (8–12 hr)

Although Focalin isolates the dex- isomer that's responsible for the beneficial effects of methylphenidate, there is little evidence that it is any better than methylphenidate. It's rumored to cause less insomnia and appetite suppression than methylphenidate, but head-to-head studies to prove that claim are lacking.

Selecting a stimulant

With so many versions available, it's hard to know where to start. Clinical lore is that children respond better to methylphenidate varieties while adults respond better to amphetamine varieties, and a new meta-analysis backs that up (Cortese S et al, *Lancet Psychiatry* 2018;5(9):727–738). However, it's hard to tell which will work best for any given patient, so a 1–2 month trial of each is a reasonable approach. I'll have both the patient and a family member complete a rating scale at the start and end of each trial; 50% improvement is considered a good response (see ASRS scale at: www.moodtreatmentcenter.com/measurement).

For the amphetamine trial, I'll generally start with Vyvanse or, if cost is an issue, Adderall XR. For methylphenidate, I tend to chose Concerta for its long, reliable duration. However, there's little reason to start with one over the other, so my preferences are more a product of habit than science. Another common strategy is to start with instant release and convert to a long-acting form once the dosage is established.

Once I know which class works better, I'll stick with the original agent that the patient improved on unless there are reasons to explore the different isomeric mixtures within that class. Those reasons are usually cost, efficacy, side effects, and duration. Side effects are the most difficult to predict, though cardiac issues would steer me away from Evekeo.

Converting the dose

Most of the methylphenidate versions have interchangeable dosing; exceptions are listed in the following conversion table.

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Converting Methylphenidate: A Precise Tool					
	Ritalin Daily	**Concerta**	**Cotempla XR**	**Jornay PM**	**Focalin**
Daily Dose	40 mg	48 mg	34.4 mg	52 mg	20 mg
Conversion Factor	n/a	Ritalin x1.2	Ritalin x0.86	Ritalin x1.35	Ritalin x0.5

Converting Amphetamines: An Approximate Tool					
	Adderall XR	**Adzenys***	**Evekeo**	**Dexedrine XR**	**Vyvanse**
Daily Dose	20 mg	12.5 mg	26 mg	16 mg	52 mg
Conversion Factor	n/a	Adderall x0.63	Adderall x1.3	Adderall x0.83	Adderall x2.6

**Adzenys conversion is exact. The others are approximate.*

Converting among the amphetamines is trickier because people differ in their sensitivities to each isomer. The conversion table gives some rough approximations, based on head-to-head comparisons and the potency of their dopaminergic effects (Biederman J et al, *Biol Psychiatry* 2007;62(9):970–976). Switching between Mydayis, Dyanavel, and Adderall does not require dose conversion.

What about changing from amphetamine to methylphenidate? A rule of thumb is that Adderall is about twice as potent as Ritalin (Adderall 10 mg ≈ Ritalin 20 mg). For more information, there is a useful conversion tool at: www.psychopharmacopeia.com/stimulant_conversion.php.

TCPR VERDICT: We have two stimulants, five isomeric mixtures, and 30 formulations, but are patients with ADHD really better off than they were 10 years ago? Probably not; however, some of the reliable long-acting agents like Adderall XR and Concerta have gone generic, adding a needed boost of accessibility to this highly priced and poorly covered line of medications.

Ed note: Additional sources for this article include *Physicians' Desk Reference* (71st ed. Montvale, NJ: Thomson PDR; 2017); *The Pharmacist's Letter* (https://pharmacist.therapeuticresearch.com/Home/PL), and *The Medical Letter* (https://secure.medicalletter.org).

Branded Stimulants Worth Considering		
Medication	**Compares To**	**Pros and Cons**
Vyvanse	Dexedrine ER spansules	Long duration of action and smooth delivery. Low abuse potential. FDA-approved in binge eating disorder. Patent expires 2023.
Mydayis	Adderall XR	Long duration of action (16 hr) but could cause more insomnia.
Evekeo	None (only 1:1 ratio of amphetamine salts)	May work in patients who did not respond well to other stimulants, but has more cardiac side effects.
Aptensio XR	Concerta	Faster onset than Concerta, with similar long duration.

Harnessing Beneficial Drug Interactions

Continued from page 3

be effective, even if neither of those meds worked on their own. Lithium can help reverse drops in white blood cells, neutrophils, and sodium caused by carbamazepine.

Clozapine and fluvoxamine

Clozapine is one of the less friendly atypicals when it comes to weight gain, diabetes, and triglycerides. Most of those metabolic side effects are not due to clozapine itself but to its metabolite, norclozapine. Fluvoxamine (Luvox) blocks the conversion of clozapine into norclozapine by inhibiting the CYP1A2 enzyme. In theory, combining these drugs creates a more tolerable version of clozapine.

This strategy has been used since the 1990s, but it wasn't tested in a randomized controlled trial until this year. In that study, 85 patients with schizophrenia were given clozapine either as monotherapy (300 mg/day) or in combination (clozapine 100 mg/day with fluvoxamine 50 mg/day). After 3 months, the combination group had significantly less weight gain, insulin resistance, glucose, and triglycerides compared to clozapine monotherapy. The combined group also had greater improvement on the PANSS psychopathology scores.

Serum levels of clozapine were similar in both groups, but as predicted, the norclozapine metabolite was lower in the combination group (Lu ML et al, *Schizophrenia Research* 2018;193:126–133).

TCPR recommendation: For patients who need to stay on clozapine but have significant side effects with the medication, you could consider carefully adding fluvoxamine. However, drug interactions are difficult to predict, so check a clozapine level before and after adding fluvoxamine, and follow it regularly while using them together.

TCPR VERDICT: When polypharmacy is needed, look for combinations that reduce the side effect burden instead of raising it.

Expert Interview
Continued from page 5

When chronically administered and slowly titrated, mCPP is actually protective and works as a partial serotonin agonist. So if you start trazodone when a 2D6 inhibitor is already in place, you'll gradually titrate up the mCPP with the trazodone and there's no problem. On the other hand, if the patient has been on high-dosage trazodone for a while and a 2D6 inhibitor is suddenly added, then you might expect some adverse psychological effects.

TCPR: What are some of the interactions we should be aware of with the newer antidepressants?

Dr. Sandson: Vortioxetine (Trintellix) is mainly metabolized at CYP2D6, so it's going to be susceptible to potent inhibitors. For example, bupropion will reliably increase vortioxetine levels about 2-fold. Vilazodone (Viibryd) is a 3A4 substrate, but it's metabolized by many other enzymes, so it's actually kind of hard to derange vilazodone levels through inhibition, but 3A4 inducers will drop blood levels. Desvenlafaxine (Pristiq), levomilnacipran (Fetzima), and milnacipran (Savella) are not very susceptible to CYP interactions.

TCPR: You mentioned that drug interactions vary by individual. Can genetic testing clarify that?

Dr. Sandson: Genetic testing tells us about a patient's enzyme function before any drug interactions. Most people are extensive metabolizers—meaning normal—but at any given enzymatic pathway they can also be "poor," "intermediate," or "ultra-rapid."

TCPR: Do those genetic variations slow or speed up the enzymes like drug interactions do?

Dr. Sandson: The effect is similar, where "poor" would be like having a potent inhibitor on board, "intermediate" a mild-moderate inhibitor, and "ultra-rapid" a potent inducer. But the actual biology is not about fast and slow. An ultra-rapid metabolizer at CYP2D6 doesn't have faster enzymes, just more of them. Intermediate metabolizers are "slow" because they have fewer enzymes. With poor metabolizers, on the other hand, the issue is one of quality, not quantity: They have a nonfunctional form of the enzyme. A rule of thumb is to cut the dosage in half when dealing with an intermediate metabolizer or a mild-moderate drug interaction, but dosing is difficult and unpredictable with poor or ultra-rapid metabolizers.

TCPR: Another common interaction is lithium and NSAIDs. How strong is that effect?

Dr. Sandson: On average, NSAIDs like ibuprofen and naproxen raise lithium levels 20%–50%, but there's a wide bell curve here, and it can range from 20% to 200% in practice. Clearly, most cases are going to be in the 20%–50% range. What I do when patients on lithium start an NSAID—other than aspirin or sulindac (Clinoril)—is reduce their lithium level in advance by 30% and recheck a level in a week. Lithium interactions are exceedingly rare with aspirin and sulindac, so I don't lower the dosage there, but I'll still check a level after starting them.

TCPR: What's in the future with drug interactions?

Dr. Sandson: Interactions can happen at many levels: gut absorption, liver metabolism, protein binding, renal excretion, and even the blood-brain barrier. There's a family of transporters called P-glycoprotein that act like gatekeepers at both the gut lumen and blood-brain barrier, regulating how drugs get into and out of the systemic vasculature and the brain, respectively. When you put it all together it gets rather complicated, and I think what is really needed is better computer software to sort through all this in a meaningful way. We're not there yet.

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

Smoking Interactions

Cigarettes and marijuana can lower:

Antipsychotics
Olanzapine (Zyprexa), clozapine, haloperidol

Antidepressants
Duloxetine (Cymbalta), fluvoxamine (Luvox), mirtazapine (Remeron)

Other
Caffeine, propranolol, ramelteon (Rozerem)

Source: Anderson GD, Chan LN, *Clin Pharmacokinet* 2016;55(11):1353–1368

Toxic Drug Interactions in Psychiatry

Medication	Potentially Raised By[1]	Toxic Effects
Benzos	**CYP3A4 inhibitors** (see below) raise alprazolam and triazolam. **Valproate** can raise diazepam and lorazepam. Fluoxetine, amiodarone, and cimetidine inhibit multiple enzymes and can raise some benzos.	Falls, cognitive problems, respiratory depression.
Carbamazepine	**CYP3A4 inhibitors** **Azole antifungals, anti-retrovirals,** pimozide, diltiazem, verapamil, cimetidine, grapefruit juice, and cipro-/norfloxacin.	Coma, respiratory depression, seizures, arrhythmia, anticholinergic effects.
Lithium	**Thiazide diuretics** (HCTZ), **ACE inhibitors** (-prils), **angiotensin receptor blockers** (-sartans), NSAIDs, antibiotics (eg, tetracyclines, levofloxacin).	Renal failure, cerebellar damage, arrhythmias, coma, seizures. Past toxicity is not a contraindication for future lithium trials.
Trazodone	**CYP3A4 and 2D6 inhibitors** **Azole antifungals, fluoxetine, paroxetine, pimozide,** diltiazam, verapamil, cimetidine, grapefruit juice, **anti-retrovirals,** and **antibiotics** (cipro- and norfloxacin).	Sedation with CYP3A4 inhibitors. CYP2D6 inhibitors may raise levels of mCPP, a metabolite that can cause depression, anxiety, and hallucinations.
Tricyclics	**CYP2D6 inhibitors** **Fluoxetine, paroxetine,** sertraline at ≥ 150 mg, bupropion, **duloxetine,** phenothiazines (chlorpromazine, perphenazine, thioridazine), **pimozide, quinidine, ritonavir.**	Cardiac arrest, arrhythmias, respiratory depression, seizures, hallucinations, hyperthermia.

[1] *Potent inhibitors are in bold*

Research Updates IN PSYCHIATRY

BIPOLAR

Probiotics for Bipolar Disorder

REVIEW OF: Dickerson F et al, *Bipolar Disord* 2018. doi:10.1111/bdi.12652 [Epub ahead of print]

TYPE OF STUDY: Randomized double-blind placebo-controlled trial

Probiotics, the so-called "good" bacteria in the gut flora, have become popular as a natural treatment for various disorders. They are taken as capsules or through food sources like yogurt, vinegar, and fermented foods. Of relevance to psychiatry, some have theorized the existence of a "gut-brain axis," in which probiotics influence mood and behavior through the vagus nerve and the endocrine and immune systems. Probiotics have shown promise in small studies of anxiety, depression, cognition, and weight loss, and this trial tested whether a daily probiotic could lower the rate of rehospitalization after a manic episode.

The authors randomized 66 patients to receive either a probiotic or placebo as an adjunct to their usual medications after discharge from a hospital stay for mania. The probiotic capsule contained two bacterial strains that are found in breast milk and thought to modulate immune function: *Bifidobacterium lactis bb-12* and *Lactobacillus rhamnosus GG*.

After 6 months, the rate of rehospitalization was 3 times lower in patients who took probiotics (8 of 33, 24%) compared to those taking placebo (24 of 33, 73%). However, probiotics had no effect on manic and depressive symptoms (measured monthly using the YMRS, BPRS, and MADRS scales). No significant side effects were reported in this study.

TCPR'S TAKE

The study is small and needs replication, and while probiotics apparently reduced rehospitalization, the lack of benefit for actual mood symptoms reduces our confidence in the results.

Probiotics have potential benefits for medical conditions that often accompany bipolar disorder, like metabolic and irritable bowel syndromes. On the other hand, they may not be safe for everyone. While we await further confirmation of their risks and benefits, these "healthy bacteria" should be avoided in people who are pregnant, immunocompromised, or at high risk of infection, where probiotics pose known risks. The specific strains used in this study have a good safety record in humans, and they are available on Amazon as USANA-108 probiotic sticks and Culturelle Baby Grow and Thrive liquid.

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

DEPRESSION

Does TMS Really Work in Depression?

REVIEW OF: Yesavage et al, *JAMA Psychiatry* 2018;75(9):884–893

TYPE OF STUDY: Randomized, sham-controlled trial

Repetitive transcranial magnetic stimulation (rTMS) has been FDA-approved for treatment-resistant depression (TRD) since 2008. This non-invasive therapy uses an electromagnetic coil to stimulate electrical activity in the frontal cortex. The present study tested its efficacy in a VA population of TRD patients with complex comorbidities.

This was a double-blind, sham-controlled, randomized trial conducted across 9 VA medical centers. In total, 164 subjects were enrolled; the average age was 55, and 81% were men. Treatment resistance was defined as 2 or more failed adequate antidepressant trials. Subjects had high rates of comorbidity, including PTSD (49%), medical comorbidity (49%), and a history of substance abuse (54%). Most were poorly functioning: Only 24% were working, and only 38% were married.

rTMS and sham rTMS were delivered for up to 30 sessions. Both groups came for treatment 5 days a week. Importantly, the sessions included supportive elements such as daily queries of mood and medication adherence and weekly screening for substance use. The primary outcome was remission of depression (≤ 10 on the Hamilton Depression Rating Scale).

rTMS displayed no advantage over sham treatment on the primary measure. Specifically, 41% achieved remission with active treatment, compared to 37% with sham treatment (p = .67). A sub-analysis suggested that rTMS might be more effective for depressed patients without comorbid PTSD (49% vs 43% remission rates), though this difference did not reach statistical significance either (p = .09). rTMS was very well-tolerated.

TCPR'S TAKE

Does this mean rTMS does not work? Not exactly, but it offered little benefit in this population of predominantly low-functioning men with complex comorbidities in the VA system. Remission rates were unusually high in both groups, and the fact that 40% recovered with the sham speaks to the therapeutic value of behavioral activation, structure, and social interaction in overcoming even the most seemingly refractory depressions. When all the studies are considered, ECT is more effective than rTMS and should be first-line when depression has not responded to traditional pharmacotherapy (Chen JJ, *Behav Brain Res* 2017;320:30–36).

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

SCHIZOPHRENIA

Is Clozapine the Next Step After a Single Failed Antipsychotic Trial?

REVIEW OF: Khan RS et al, *Lancet Psychiatry*, published online 8/13/2018

TYPE OF STUDY: Sequential trial with open-label and randomized, double-blind comparison phases

Clozapine is often used as a last resort in schizophrenia, even though practice guidelines recommend a trial of this medication after failing 2 antipsychotics. The current study set out to test a treatment algorithm based on those guidelines in patients with first-episode psychosis.

Continued on page 10

Research Updates IN PSYCHIATRY

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Researchers recruited a total of 446 patients from 27 clinics in various European countries. All patients were in their first psychotic episode and had diagnoses of schizophrenia (51%), schizophreniform disorder (43%), or schizoaffective disorder (6%). To refresh your memory, schizophreniform disorder means that symptoms of schizophrenia have been present for more than a month but less than 6 months. The average age was 26; most were male (70%) and Caucasian (87%). The primary outcome was symptomatic remission on the Positive and Negative Syndrome Scale (PANSS). The trial was funded by the European Commission.

The patients were entered into a three-phase study:

- Phase 1: All 446 patients were prescribed open-label amisulpride, an antipsychotic used outside the US, for 4 weeks at ≤ 800 mg/day.
- Phase 2: Those patients who did not achieve remission on amisulpride were randomly assigned to a double-blind trial of either continuing amisulpride or switching to olanzapine (≤ 20 mg/day, mean 16 mg/day) for 6 weeks.
- Phase 3: Patients who did not respond to either amisulpride or olanzapine were treated with open-label clozapine (≤ 900 mg/day, mean 490 mg/day) for 12 weeks.

Amisulpride and olanzapine were selected for this algorithm because their effect sizes are second only to clozapine's in schizophrenia.

Just over half (56%) of the patients remitted during the first phase of antipsychotic treatment with amisulpride. Of the 93 patients who started the second phase, about 32% remitted with either amisulpride continuation or olanzapine switch, with no significant differences between these drugs. Finally, 40 patients were left to assign to clozapine; 18 of those completed the 12-week trial, and 5 (28%) achieved remission.

Because switching to olanzapine did not yield better outcomes than continuing the first antipsychotic, the authors suggested that this second-line switch could be skipped and that patients who don't respond to their first antipsychotic might be better served by going straight to clozapine.

TCPR'S TAKE

Moving clozapine up to a second-line treatment in schizophrenia is a bold suggestion. We'd like to see that tested out in a more controlled manner before changing practice guidelines. What these results do tell us is that schizophrenia recovery can take time. If patients haven't recovered after 10 weeks, whether with one antipsychotic or two, a trial of clozapine is not unreasonable, but it's not clearly the best option either.

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

News of Note

New Approvals for TMS

We know that transcranial magnetic stimulation (TMS) works for treatment-resistant depression (TRD) (see *TCPR* July/August 2017 for our most recent coverage), but one disadvantage is the length of the treatment sessions. We also don't know if TMS works for other disorders.

Recently, the FDA granted new approvals that address both these issues. One approval was for "Express TMS," a rapid form of TMS for depression that reduces the treatment time from 20–38 minutes to 3 minutes. The other approval was for using TMS in OCD.

The approval for Express TMS was based on a randomized non-inferiority study that showed its efficacy was similar to traditional TMS. Express TMS works faster because it uses a high-intensity magnet that produces something called "intermittent theta burst stimulation (iTBS)." It sounds a little scary, but the treatment was generally well-tolerated, though it did cause a bit more scalp pain than the lower-intensity magnet. The main risk with TMS is seizures, and we don't yet know if this risk will be greater or lower with Express TMS because the frequency of these events is too rare to capture in a single study. Like standard TMS, Express TMS requires treatment sessions every weekday for 6 weeks.

The OCD indication was based on a randomized, sham-controlled multicenter trial of 100 adults with OCD. Response rates were 38% with TMS vs 11% in the sham group, and the number needed to treat to see response (NNT) was 4. Responses were maintained 1 month after treatment ended. Patients continued their usual medications during TMS. Side effects were limited to headaches.

Each of these approvals is tied to a specific manufacturer. Express TMS is available through an upgrade to the MagVita device, made by MagVenture. TMS for OCD requires a modification to Brainsway's Deep TMS machine, which has been approved for TRD since 2013. To modify the machine for OCD, a magnetic coil is attached to aim the magnet at the anterior cingulate cortex—the brain region thought to be involved in OCD. Patients are directed to conjure their obsessive thoughts prior to each 20-minute treatment, which activates that brain region and improves response.

The diagnostic reach of TMS is expected to grow in the future. It is being investigated for schizophrenia, PTSD, anxiety, addictions, autism, migraines, chronic pain, dementia, and Parkinson's disease.

—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.

CME Post-Test

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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.

1. Which of the following statements about Vyvanse and Dexedrine ER is true? (LO #1)

   [ ] a. Vyvanse has a higher abuse potential than Dexedrine ER
   [ ] b. Dexedrine ER is FDA-approved for binge eating disorder while Vyvanse is not
   [ ] c. Both Vyvanse and Dexedrine ER in low dosages are effective for binge eating disorder
   [ ] d. Vyvanse's metabolism is more steady and consistent compared to Dexedrine ER

2. A moderate drug inhibitor will increase blood levels in the _____ range. (LO #2)

   [ ] a. 20%–50% [ ] b. 60%–100% [ ] c. 100%–140% [ ] d. over 150%

3. In a 2018 study on transcranial magnetic stimulation for OCD, patients were able to continue their usual medications during treatment and side effects were limited to headaches. (LO #4)

   [ ] a. True [ ] b. False

4. Your 35-year-old patient on escitalopram has been experiencing restless leg syndrome, which is impacting her sleep quality. Which medication in combination with the SSRI may be beneficial? (LO #3)

   [ ] a. Trazodone [ ] b. Aripiprazole [ ] c. Zolpidem [ ] d. Pramipexole

5. The main advantage of Zenzedi, a branded form of the instant-release (IR) version of dextro-amphetamine, over the generic IR formulation is dose customization. (LO #1)

   [ ] a. True [ ] b. False

6. According to Dr. Sandson, drug interactions with inducers can cause loss of efficacy, and potent ones can drop affected drugs out of therapeutic range. _____ is an example of a potent inducing drug. (LO #2)

   [ ] a. Paroxetine [ ] b. Valproate [ ] c. Carbamazepine [ ] d. Fluvoxamine

7. Which of the following medications, in combination with a stimulant, has the potential to reduce cardiac risks such as QTc prolongation in patients being treated for ADHD? (LO #3)

   [ ] a. Bupropion [ ] b. Guanfacine [ ] c. Modafinil [ ] d. Atomoxetine

8. Your 40-year-old patient, who is taking clozapine, has switched from cigarettes to vaped nicotine in the past month. What effect can you expect to see in his medication levels when you run his labs? (LO #2)

   [ ] a. No effect on clozapine levels until after 3 months of quitting marijuana
   [ ] b. Increased clozapine levels
   [ ] c. Decreased clozapine levels
   [ ] d. No effect on clozapine levels

THE CARLAT REPORT: PSYCHIATRY

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This Month's Focus:
Drug Metabolism

Next month in *The Carlat Psychiatry Report:*
Deprescribing