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Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
ADHD

Learning Objectives
After reading these articles, you should be able to:

1. Trace the underlying factors that can impede patients' response to antidepressants.
2. Employ dosing strategies to ensure that psychiatric medications reach their peak efficacy.
3. Classify complementary therapies for core symptoms of ADHD.
4. Summarize some of the current research findings on psychiatric treatment.

What Gets in the Way of Antidepressants?

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Dr. Rossi and Dr. Aiken, authors for this educational activity, have no relevant financial relationship(s) with ineligible companies to disclose.

When patients don't respond to an antidepressant, it's a good idea to step back and look for anything that might be getting in the way. Major stress, substance use, medication nonadherence, anxiety, and medical and psychiatric comorbidities are high on that list, but recent research has added more possibilities that we'll review in this article.

Inflammation

Inflammation is the body's natural response to a wound or infection. It is a normal immunologic response, but when it becomes chronic and uncoupled from its original mission of fighting off microbes, depression can result. Chronic inflammation contributes to one in three cases of depression and one in two

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Highlights From This Issue

Feature article
CRP is a marker for inflammation, and elevated levels suggest the patient's depression is more likely to respond to nortriptyline or bupropion than to SSRIs.

Q&A
Dr. Richard Brown reviews evidence-based CAM therapies for ADHD, including ginseng for working memory, piracetam for dyslexia, and pycnogenol for core symptoms.

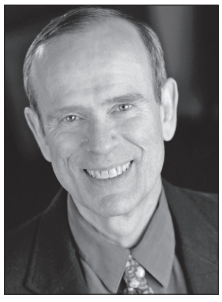
On page 5
Lithium is safer for the kidneys when dosed all at night.

Q&A With the Expert

Complementary Therapy in ADHD
Richard P. Brown, MD

Clinical Professor of Psychiatry at Columbia University. Author of over 80 articles and books on clinical psychiatry, including Non-Drug Treatments for ADHD *(WW Norton, 2012).*

Dr Brown, expert for this educational activity, has no relevant financial relationship(s) with ineligible companies to disclose.



TCPR: What's missing in how we treat ADHD?
Dr. Brown: Even with stimulant treatment, patients can still have a lot of executive dysfunction. Many have comorbid conditions like dyslexia or processing disorders that stimulants do not treat.
TCPR: How do you screen for those problems?
Dr. Brown: Neuropsychological testing is not necessary for diagnosing ADHD, but it can identify these co-occurring problems. If the patient can't afford testing, I'll refer them to a university with a good psychology program to get it done by a trainee. The biggest problems I see on these test results are dyslexia, slow processing speed (visual, verbal, or both), and decreased working memory.
TCPR: What do those problems look like in everyday life?
Dr. Brown: When patients ask what working memory is, I

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Expert Interview
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say, "Your brain has a 'clipboard' much like your computer does. It keeps important things in active play while you're working on solving a problem. People with ADHD have a harder time holding things in their clipboard." For simple information like numbers, most adults can hold five to nine items in their working memory, but that range goes down as the information gets more complicated.

TCPR: How does dyslexia present in ADHD?

Dr. Brown: People with dyslexia have difficulty reading or processing what they hear. Their mind reverses letters and numbers as they read (visual dyslexia) or doesn't accurately process sounds (verbal dyslexia). About one in three people with ADHD have dyslexia, and the rate is higher if we count all learning disorders like slow processing speed (Handler SM et al, *Pediatrics* 2011;127(3):e818–e856). To screen, I'll ask: "Do you have trouble reading or taking notes in class?" "Do you do better if you hear the material or see it?"

TCPR: Do medications help dyslexia?

Dr. Brown: In dyslexia, there is more evidence for complementary treatments than there is for medications, starting with piracetam. This is a synthetic compound that was discovered by a Belgian chemist in the 1950s, and it's considered the first "nootropic," which means "to learn better." In the 1980s, piracetam improved reading ability in students with dyslexia. I rarely use it, though, because it comes as a huge pill or bulky powder that's hard to swallow (dose 4.8 mg/day; Wilsher CR, *J Psychopharmacol* 1987;1(2):95–100). I've had success with similar "racetam" drugs that are descended from piracetam and are easier for patients to take. The two I use most often are aniracetam (800 mg BID) and pramiracetam (600 mg BID). They are affordable and well tolerated, and they don't carry any serious risks. Both are classified as pyrrolidinones and work via the NMDA and acetylcholine systems. At higher doses they have anticonvulsant activity, and they are structurally related to the anticonvulsant levetiracetam (Keppra).

TCPR: Do the racetams treat any other psychiatric conditions?

Dr. Brown: We have a few small, controlled trials for racetams in other disorders. In childhood autism, piracetam improved behavioral symptoms (800 mg/day), and in schizophrenia it improved positive and negative symptoms as well as tardive dyskinesia (3.2–4.8 g/day; Akhondzadeh S et al, *Child Psychiatry Hum Dev* 2008;39(3):237–245; Libov I et al, *J Clin Psychiatry* 2007;68(7):1031–1037).

TCPR: Do you have a preferred brand for these nootropics?

Dr. Brown: Currently I recommend Pure Nootropics, but let me clarify: I don't receive any funding from the industry or from any brands I recommend. My recommendations may change with time, especially as we see more shifts in manufacturing from Europe to less regulated countries in the East. Also, all of the therapies I'll discuss today can be safely combined with stimulants.

TCPR: Is there anything that improves working memory in ADHD?

Dr. Brown: The alpha-agonists have data there: clonidine and guanfacine. I think the benefit is real, but I have not been wowed by it in clinical practice. Both clonidine and guanfacine are FDA approved in ADHD, and they have more steady effects throughout the day than the stimulants do, so I've found them helpful to augment stimulants when patients have problems with their stimulant wearing off too early in the day. Some patients have that "crash," and they get irritable or have trouble going to bed at the end of the day, and these alpha-agonists have the benefit of improving sleep. Sedation is also their main drawback, though. On the complementary side, I've found American ginseng helpful for working memory.

TCPR: What is the evidence for American ginseng?

Dr. Brown: There are several types of ginseng: Korean (*Panax ginseng*), Chinese (*Panax notoginseng*), and American (*Panax quinquefolius*). All of them contain ginsenosides, which modulate acetylcholine and glutamate and have anti-inflammatory and neuroprotective effects in the CNS. They all have evidence to improve memory in various populations, and I've seen the best effect with American ginseng. It improved working memory in several controlled trials, and the benefits are measurable after just a few hours, but they also held up in studies lasting several months (Ossoukhova A et al, *Hum Psychopharmacol* 2015;30(2):108–122). Most of these studies were conducted in healthy adults, but ginseng also improved inattentive and hyperactive symptoms of ADHD in two placebo-controlled trials in children (Lee J and Lee SI, *J Atten Disord* 2021;25(14):1977–1987; Ko HJ et al, *J Child Adolesc Psychopharmacol* 2014;24(9):501–508).

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Expert Interview

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TCPR: How do you dose American ginseng?

Dr. Brown: A typical dose is 500–1000 mg BID of ginseng with 10% ginsenosides. I use the Hsu's American Gin-Max brand of American ginseng *(Editor's note: Cost is 50 cents per 500 mg tablet on Amazon).* People feel it working right away, whereas other brands have a slower onset. They solve problems more quickly. They process things a little bit better. One of my patients who switched said, "It's like I went from an old-fashioned TV to high definition." I've not seen many side effects with ginseng, but it can cause insomnia, anxiety, and headaches *(Editor's note: Ginseng doesn't have major medical risks but may increase bleeding time—exercise caution with patients who are undergoing surgery or taking anticoagulants).*

TCPR: You've talked about working memory and dyslexia. Do you also use complementary therapies for core symptoms of ADHD?

Dr. Brown: There are a lot of options out there with positive controlled trials, like B vitamins, omega-3 fatty acids, and zinc. What I do is try these out in practice and stick with the ones that are affordable, tolerable, and effective for my patients. I prescribe a lot of stimulants, and I recommend them first line, but sometimes patients have had problems with stimulants or want to start with natural things. Others get better on stimulants but not all the way, in which case I may augment with a complementary therapy.

TCPR: Which treatments do you find most helpful?

Dr. Brown: One overlooked treatment that I've found useful is pycnogenol, which is an extract of the French maritime pine bark tree. Pycnogenol is patented, which is a good thing in terms of ensuring quality, but you can find it in various brands because the company franchises the extract.

TCPR: What does pycnogenol do in the brain?

Dr. Brown: Pycnogenol is a polyphenol with neuroprotective properties, which puts it in the class of nutrients that have cognitive benefits, like those found in ginkgo, green tea, blueberries, and dark chocolate. Pycnogenol also seems to correct the low ratio of zinc to copper that we tend to see in people with ADHD.

TCPR: How good is the evidence?

Dr. Brown: Pycnogenol has two small, randomized, placebo-controlled trials in ADHD. One was positive, involving children at a dose of 0.5 mg/lb/day. The other was negative, involving adults at about twice the pediatric dose (1 mg/lb/day). The negative study is not very informative, though. It's a "failed" study because the active treatment arm—which was methylphenidate 45 mg/day—did not separate from placebo either. So the evidence is not definitive, but a larger trial is underway (Trebatická J et al, *Eur Child Adolesc Psychiatry* 2006;15(6):329–335).

"Ginsenosides (found in ginseng) have anti-inflammatory and neuroprotective effects in the CNS. I have seen the best effect with American ginseng, which improved working memory in several controlled trials. The benefits are measurable after just a few hours."

Richard P. Brown, MD

TCPR: Saffron is getting a lot of media attention in ADHD.

Dr. Brown: Yes, saffron has potential. Unfortunately, it has only one controlled trial in ADHD, but it did improve cognition in trials with other populations. In the ADHD trial—which was small, involving 54 children—saffron 30 mg/day worked as well as methylphenidate 30 mg/day (a lower dose, 20 mg/day for each drug, was used for children under 65 lbs). Although the result is encouraging, the study lacked a placebo arm, so we don't know if the improvements in both treatments were due to a robust placebo effect (Baziar S et al, *J Child Adolesc Psychopharmacol* 2019;29(3):205–212). In my experience, I've found saffron helpful for ADHD, depression, premenstrual dysphoric disorder, anxiety, and dementia *(Editor's note: Saffron has positive controlled trials in each of those conditions, as monotherapy and augmentation, at a dose of 30–60 mg/day, although most of the trials come from a single academic center; see Hausenblas HA et al,* J Integr Med *2015;13(4):231–240).*

TCPR: What else do you find helpful in ADHD?

Dr. Brown: I am seeing good results with *Rhodiola rosea*. It affects dopamine, as well as norepinephrine and serotonin, and it has a few small, positive controlled trials in depression (Gao L et al, *J Affect Disord* 2020;265:99–103). *Rhodiola rosea* is an herbal adaptogen—in other words, it helps people respond better to stress. Although it has not been studied in ADHD specifically, it did improve cognition and attention in controlled trials of other populations, like healthy adults who were under stress and people with nonspecific cognitive difficulties, including astronauts in spaceflight and men with brain injuries due to gunshot wounds (Lewis JE et al, *J Clin Transl Res* 2021;7(4):575–620). In my own practice, I have seen some turnarounds with it in ADHD.

TCPR: You also mentioned B vitamins, omega-3 fatty acids, and zinc, and I've seen positive trials involving vitamin D and l-carnosine in ADHD. Are any of those worth trying?

Dr. Brown: L-carnosine is often used to reduce inflammation in diabetes and improve exercise tolerance, and there are a few positive reports in autism and ADHD, but my experience with it was overwhelmingly unimpressive, so I stopped using it a few years ago. Vitamin D has largely been a "D" for disappointment. It may just be a marker for other factors that influence health, like how much time you spend outdoors. B vitamins, omega-3 fatty acids, and zinc have controlled trials in ADHD, but the effects are small—I don't see much difference in practice with them.

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

What Gets in the Way of Antidepressants?
Continued from page 1

cases of treatment-resistant depression (see *The Carlat Psychiatry Report* February 2020). Recent surgery, injury, or infection—including long COVID-19—are common causes, as are less obvious ones like poor diet, obesity, smoking, chronic stress, chronic medical illness, chemotherapy, insomnia, and lack of exercise.

If a patient has signs of inflammation and is not responding to an antidepressant, it may be worth checking their high-sensitivity C-reactive protein (hs-CRP). This inflammatory marker has been used in several studies to predict antidepressant response. Patients with an elevated hs-CRP tend to respond better to nortriptyline or bupropion than to SSRIs (Hashimoto K, *Int J Mol Sci* 2015;16(4):7796–7801; Jha MK et al, *Psychoneuroendocrinology* 2017;78:105–113). Elevated CRP also predicts response to a few complementary therapies: l-methylfolate (15 mg/day), n-acetylcysteine (2000 mg/day), and omega-3 fatty acids (1000–3000 mg/day, with an EPA:DHA ratio of at least 2:1; see *The Carlat Psychiatry Report* March 2022 for recommended products). Hs-CRP is a low-cost test ($20–$40), and the cutoff in most of these depression trials was >3 mg/dL for hs-CRP, although some used >2 or >1 mg/dL.

Lifestyle changes are particularly important for inflammatory depression because—in addition to improving mood—they treat the underlying problem by lowering CRP and other inflammatory markers. That is important because inflammation worsens morbidity and mortality, and it won't necessarily go away by treating the depression. Exercise, Mediterranean-style diet, tai chi, mindfulness, and cognitive behavioral therapy for insomnia are treatments that both reduce inflammation and improve mood.

For the average patient with major depression, the optimal amount of exercise is 45 minutes of light aerobics three or four times a week. More intensive routines don't tend to improve mood any further unless the patient has an elevated hs-CRP, in which case more intensive exercise brings greater remission (Trivedi MH et al, *J Clin Psychiatry* 2011;72(5):677–684).

Cardiovascular health

About 60% of patients with depression respond to an SSRI, but that chance goes down to 40% in the presence of multiple medical comorbidities, particularly cardiovascular risk factors. Hypertension, hypercholesteremia (>200 mg/dL), smoking, and diabetes all dampen antidepressant response (Iosifescu DV et al, *Am J Psychiatry* 2003;160(12):2122–2127). Smoking cessation and good medical care are logical first steps, and some medical treatments may have antidepressant effects of their own. Metformin (1000 mg/day) and three of the statins (atorvastatin 20 mg/day, lovastatin 30 mg/day, and simvastatin 20 mg/day) augmented SSRIs in randomized controlled trials of patients with major depression without major medical illnesses, possibly because they have anti-inflammatory or neuroprotective effects (Abdallah MS et al, *Neurotherapeutics* 2020;17(4):1897–1906; Salagre E et al, *J Affect Disord* 2016;200:235–242).

Obesity

Obesity is also a strong predictor of non-response as well as slow response to antidepressants. These problems begin in the overweight range (BMI 25–30) and worsen in obesity (BMI 30–35), severe obesity (BMI 35–40), and morbid obesity (BMI >40). However, obesity is strongly correlated with inflammation, and it's difficult to disentangle that association. Two of the treatments that work better when inflammatory markers are high also work better when the patient's BMI is elevated: augmentation with bupropion or augmentation with l-methylfolate (Jha MK et al, *J Affect Disord* 2018;234:34–37).

Trauma and isolation

It's tempting to blame major stress when a patient doesn't respond to an antidepressant, but how strong is that connection? Certainly, many patients do respond in spite of stress, and baseline personality traits can raise those odds. Traits associated with resilience, like grit, spirituality, and a sense of self-efficacy, are associated with a more favorable antidepressant response (Laird KT et al, *Int J Geriatr Psychiatry* 2018;33(12):1596–1603). On the other hand, a few specific stressors are robustly associated with a poor antidepressant response: isolation, poor social supports, low income or education level, and a history of childhood abuse or neglect.

Some of these problems are modifiable. Patients may have friends they can call on, but they may have kept to themselves because of cognitions that lead to depressive avoidance ("I'm no good," "I'm a burden," "It's too stressful to be around people"). Those patterns may start to change when patients understand that they need at least a small daily dose of social interaction to give their antidepressant the best chance of working.

Antidepressants don't work in a vacuum, and a finding from animal research can illustrate that point for skeptical patients. When antidepressants were given to mice with depression, the medication worked as long as the mice were allowed some social time with other mice. Antidepressants did nothing for mice that were kept isolated in their cages. Animal studies also teach us that social isolation interferes with the antidepressant effects of exercise (Rief W et al, *Neurosci Biobehav Rev* 2016;60:51–64).

Childhood trauma is less modifiable, but it can inform the direction of treatment. Patients who don't respond to an antidepressant may do better with psychotherapy if they have a history of childhood trauma. When researchers compared psychotherapy, nefazodone, and the combination in 681 patients with chronic major depression, only the psychotherapy arms were effective for the 65% of subjects who had a history of early childhood abuse, neglect, or loss of a parent before age 15 (Nemeroff CB et al, *Proc Natl Acad Sci U S A* 2003;100(24):14293–14296). Biological reasons may explain why these patients do not respond well to antidepressants, as early trauma is associated with volumetric shrinkage in the limbic system.

CARLAT VERDICT

When patients don't fully respond to an antidepressant, look for modifiable factors that might be getting in the way. Addressing these is just as critical as the next step in the psychopharmacologic algorithm.

Six Tips From *Prescribing Psychotropics*

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

Dr. Aiken, author for this educational activity, has no relevant financial relationship(s) with ineligible companies to disclose.

Every day we are faced with prescribing dilemmas that don't have ready answers. Instant or extended release? Brand or generic? With food or without? How should we adjust dosing to account for drug interactions, age, gender, ethnicity, or genetic testing results? Our new textbook *Prescribing Psychotropics: From Drug Interactions to Pharmacogenetics* is packed with answers to questions like these, and in this issue, we've reprinted some of our favorites.

Bupropion SR, XL, or Aplenzin?

When bupropion first came out in 1985, it caused a big problem. The drug creates a risk of seizures that is dose dependent, and it was launched with a liberal maximum dosage of 600 mg/day. Patients could push that dose even higher by accidentally doubling up on their pills, an easy mistake to make with bupropion's immediate-release formulation that required TID dosing. The result was an alarming 3% risk of seizures, and the drug was withdrawn after less than a year on the market.

Bupropion was re-released in 1989 with a more cautious maximum daily dose of 450 mg. At this dose, the seizure risk fell to 0.4%, and at 300 mg it was 0.1%, about the same as the risk with SSRIs and close to the rate of new-onset seizures in the general population (0.08%). Later, extended-release formulations reduced those rates even further by smoothing over the peak plasma levels and lowering the chance of accidental double dosing. With those improvements, bupropion now has one of the lowest epileptogenic potentials of all antidepressants. In a 2018 meta-analysis, clomipramine had the highest seizure risk, followed by amitriptyline, venlafaxine, citalopram, sertraline, trazodone, mirtazapine, paroxetine, bupropion, escitalopram, fluoxetine, and duloxetine (Steinert T and Fröscher W, *Pharmacopsychiatry* 2018;51(4):121–135).

While the extended-release formulation is a safer option, there are now three versions to choose from: sustained release (SR), extended release (XL), or Aplenzin—which is a new, branded version of bupropion. Aplenzin has similar pharmacokinetics to bupropion XL, but it uses a different binding agent: hydrobromide instead of hydrochloride. Both bupropion XL and Aplenzin can be dosed once a day, but XL is generally less expensive than Aplenzin because it is generic—and for this reason, we recommend prescribing XL over the newer product.

Bupropion also has a reputation for causing anxiety and mild agitation, and this is where the immediate-release formulation still has a role. Those problems improve with slow titration, and immediate-release bupropion allows that with its low 75 mg dose. Starting there and raising by 75 mg every week is useful in sensitive populations, like the young, the old, and those with anxiety or bipolar disorders.

CARLAT TAKE

Bupropion is probably safer and better tolerated in its extended-release forms, although the immediate release is useful for slow titrations. Most of the time, bupropion XL is preferred.

Better lithium dosing

Most patients prefer extended-release lithium over the immediate-release lithium carbonate, and for good reason. The extended-release versions cut the rate of many side effects in half, including nausea, tremor, and possibly cognitive dulling and urinary frequency. However, if your patient complains of diarrhea as a side effect, consider switching to immediate-release lithium, which is less likely to cause this problem.

There are two versions of extended-release lithium—lithium ER (Lithobid) and CR (Eskalith)—and they have slightly different pharmacokinetics. Lithium CR releases slower and has a smoother peak than lithium ER. In theory, that might improve tolerability, and some patients appreciate that CR allows them to take their dose with fewer pills (it comes as 450 mg, while ER is 300 mg). The kidneys also appreciate the smoother peaks of these formulations, as renal impairment is linked to high serum levels of lithium. It may be possible to avoid renal problems altogether by keeping the serum level within the recommended maintenance range of 0.6–0.8 mmol/L (0.6–0.8 mEq/L). In a 12-year cohort study, every level above that range raised the risk of renal impairment, but the kidneys were spared when the levels stayed within those limits (Clos S et al, *Lancet Psychiatry* 2015;2:1075–1083).

Another way to reduce lithium's renal risks is to give the entire dose at night. That strategy worked better than BID dosing in a few controlled studies, and it makes sense with lithium's half-life of 18–24 hours (Girardi P et al, *Drugs R D* 2016;16(4):293–302). But wait. Didn't we just say that the kidneys do better when lithium's levels are spread out? The kidneys are finicky organs. They like their lithium levels low, and they also like to get a break from lithium for part of each day. Dosing in the evening with an extended-release formulation satisfies both ends.

CARLAT TAKE

Extended-release lithium is better tolerated than immediate-release lithium, unless the side effect in question is diarrhea. To protect the kidneys, give lithium all at night and avoid levels above 0.8 mmol/L.

Olanzapine: Swallowed or dissolved?

Orally disintegrating medications are usually prescribed when patients have difficulty swallowing, but olanzapine ODT (Zyprexa Zydis) has two other purported advantages. In emergency settings, the ODT is thought to provide rapid relief of agitation by dissolving quickly in the mouth. In theory, this route also lowers the risk of weight gain because the medication is absorbed in the oral mucosa and goes directly into the systemic circulation, allowing it to bypass the appetite-regulating serotonin receptors in the gut. Sounds plausible, but how well do these ideas hold up?

To determine if the ODT form of olanzapine works faster than the standard oral version, researchers compared them in 11 healthy people. Each subject received three versions of olanzapine 5 mg, about two weeks apart: regular olanzapine tablets, olanzapine ODT swallowed, and olanzapine ODT delivered sublingually.

After 10 minutes, both ODT forms were detectable in subjects' serum, whereas it took 30 minutes for the tablet form to

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Six Tips From *Prescribing Psychotropics*
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be detectable. There was no statistically significant difference between swallowing the ODT and allowing it to dissolve sublingually (Markowitz JS et al, *J Clin Pharmacol* 2006;46(2):164–171). The bottom line is that olanzapine ODT is a good choice for rapid control of agitation when patients are willing to take a pill, and it has the advantage of being very difficult to cheek because it dissolves almost instantaneously.

Turning to weight gain, the picture gets murkier. In the 2000s, there was hope that olanzapine might cause less weight gain in its ODT form, as nine open-label studies and case reports documented weight loss (half a pound a week, on average) after switching from standard olanzapine to ODT. Those hopes were dashed, however, when three randomized, placebo-controlled trials failed to find any difference in weight gain between the two formulations (Kusumi I et al, *Prog Neuropsychopharmacol Biol Psychiatry* 2012;36(2):313–317).

CARLAT TAKE
Olanzapine ODT is useful for acute control of agitation and psychosis, but it is no less likely to cause weight gain than regular olanzapine.

Dosing by half-life

When a manufacturer releases a medication, they usually base the dosing schedule on its half-life. A medication with a 24-hour half-life is dosed once a day (QD), a med with a 12-hour half-life is dosed twice a day (BID), and a drug with an eight-hour half-life is dosed three times a day (TID). However, as years go by, clinicians often end up ignoring recommended dosing intervals and simplifying the schedules to once a day. That makes dosing easier for patients to follow, but does it compromise the drugs' efficacy?

A few studies have tested this out, comparing QD to BID dosing for antipsychotics and antidepressants with short half-lives (eg, trazodone, clozapine, quetiapine, and ziprasidone). In all cases we're aware of, the two dosing strategies had the same clinical outcomes. Most likely, the drugs' therapeutic benefits depend on downstream effects like neurotropic factors and receptor adaptation, and the brain doesn't require constant steady-state exposure to the drug to achieve those effects (Yýldýz A and Sachs GS, *J Affect Disord* 2001;66(2–3):199–206).

However, changing the dosing interval does significantly impact side effects. Sedation improves with evening dosing, a strategy that has been successfully employed with antidepressant doses of trazodone, which can be given entirely at night. Other side effects may improve with divided dosing, particularly the side effects that worsen as a medication's level peaks: nausea, dizziness, fatigue, orthostasis, and QTc prolongation.

CARLAT TAKE
Psychiatric medications with delayed benefits can usually be given once a day without loss of efficacy. This strategy improves some side effects like sedation. Other side effects, though, are alleviated by spreading out the dose and lowering the drug's peak levels.

Do drugs with long half-lives take longer to work?

There's a myth that drugs with long half-lives take longer to work than drugs with short half-lives. Apparently, this comes from misinterpreting the meaning of steady state. It's true that meds with long half-lives take longer to reach steady state. For example, fluoxetine, in concert with its metabolite norfluoxetine, has a half-life of about two weeks and takes two and a half months to reach steady state. Nonetheless, fluoxetine works just as quickly as antidepressants with short half-lives (Gelenberg AJ and Chesen CL, *J Clin Psychiatry* 2000;61(10):712–721). Evidently, serotonin receptors aren't waiting around for fluoxetine to reach steady state.

Antipsychotic-carbamazepine pairings

Many of the medications that are commonly paired with an antipsychotic will change the antipsychotic's blood levels. Bupropion, duloxetine, valproate, and most SSRIs (except citalopram and escitalopram) raise some antipsychotic levels, while carbamazepine lowers nearly all of them. That's a problem when you need to augment carbamazepine with an antipsychotic due to breakthrough mania. The worst choice in those cases is quetiapine. Carbamazepine not only lowers quetiapine levels by 80%, it speeds quetiapine's conversion into norquetiapine, a compound with antidepressant properties that has been linked to manic switching (Rovera C et al, *Drug Saf Case Rep* 2017;4(1):13). Instead, choose asenapine, the only atypical antipsychotic with no significant carbamazepine interactions.

Asenapine has a catch, however. It may not waver in the face of carbamazepine, but it can raise levels of other psychotropics through CYP2D6 inhibition. Most other antipsychotics do not inhibit or induce the major metabolic enzymes, so don't worry about upsetting other drug levels when adding them to a patient's regimen.

CARLAT TAKE
Asenapine is a good choice for carbamazepine augmentation, but it may increase the levels of other psychotropics.

Research Updates IN PSYCHIATRY

ADHD

Vyvanse for Sluggish Cognitive Tempo in ADHD

Thomas Jordan, MD. Dr. Jordan, author for this educational activity, has no relevant financial relationship(s) with ineligible companies to disclose.

REVIEW OF: Adler LA et al, *J Clin Psychiatry* 2021;82(4):20m13687
STUDY TYPE: Randomized placebo-controlled trial

Patients with ADHD often also struggle with sluggish cognitive tempo (SCT). Characteristics of SCT include being prone to daydreaming, being easily bored, feeling "spacey" or lethargic, and not processing information quickly or accurately. This diagnosis—which is not found in the DSM—is controversial, and it has the most support when it occurs as a comorbidity of ADHD.

Studies of methylphenidate and atomoxetine have shown some improvement in SCT among youth with ADHD.

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CME Post-Test

To earn CME or CE credit, log on to www.TheCarlatReport.com to take the post-test. You will be given two attempts to pass the test. You must answer 75% of the questions correctly to earn credit. Tests must be completed within a year from each issue's publication date. The Carlat CME Institute is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. Carlat CME Institute maintains responsibility for this program and its content. Carlat CME Institute designates this enduring material educational activity for a maximum of one (1) *AMA PRA Category 1 Credit*™. Physicians or psychologists should claim credit commensurate only with the extent of their participation in the activity. This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Learning Objectives are listed on page 1.

1. What is the optimal amount of exercise for an average patient with major depression (LO #1)?
   [ ] a. One hour of light aerobics with resistance training seven days a week
   [ ] b. 25 minutes of resistance training five to six days a week
   [ ] c. 30 minutes of light aerobics two times a week
   [ ] d. 45 minutes of light aerobics three to four times a week
2. In a 2019 meta-analysis, which medication had the highest seizure risk (LO #2)?
   [ ] a. Duloxetine [ ] b. Venlafaxine [ ] c. Trazodone [ ] d. Clomipramine
3. According to Dr. Brown, which type of ginseng has the best effect in improving working memory and contains benefits that are measurable after a few hours (LO #3)?
   [ ] a. Korean ginseng (*Panax ginseng*)
   [ ] b. Chinese ginseng (*Panax notoginseng*)
   [ ] c. American ginseng (*Panax quinquefolius*)
   [ ] d. Brazilian ginseng (*Pfaffia glomerata*)
4. A 2021 study of postpartum depression (PPD) concluded that vitamin B6 is safe for pregnancy and may reduce the risk of PPD. What was this study's main limitation (LO #4)?
   [ ] a. It lacked blinding in the raters
   [ ] b. It did not control the exact duration of B6 therapy
   [ ] c. It did not control for physical activity
   [ ] d. It did not control for blood levels of the active metabolite of B6
5. Which of the following is a true statement about high-sensitivity C-reactive protein (hs-CRP) (LO #1)?
   [ ] a. Hs-CRP is an expensive test ($100–$200), and its cutoff in most depression trials was >6 mg/dL
   [ ] b. Patients with hs-CRP respond better to SSRIs than to nortriptyline
   [ ] c. Elevated hs-CRP predicts response to therapies such as l-methylfolate and nortriptyline
   [ ] d. Lower-intensity workouts result in greater remission among major depressive patients with elevated hs-CRP

Research Updates

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This industry-sponsored study, which used lisdexamfetamine (Vyvanse), is the first stimulant trial for SCT in adults.

The investigators recruited 39 adults with comorbid ADHD and SCT. This was a "clean" cohort, meaning that no one had another active psychiatric disorder and no one had a lifetime history of bipolar disorder. The trial used a crossover design, in which all patients received either stimulant or placebo over a four-week treatment block, then everyone underwent a two-week washout period before switching to the other group in a second four-week treatment block. Lisdexamfetamine was started at 30 mg daily and titrated up to 70 mg daily.

The dual primary outcomes were changes in the ADHD Rating Scale and the Barkley Sluggish Cognitive Tempo Scale. In the first treatment block, lisdexamfetamine had a medium effect size (0.68) for SCT, but the stimulant had only a nonsignificant effect during the second block, possibly due to a carryover effect. When the subjects on lisdexamfetamine were switched to placebo for the second block, their average ratings for SCT did not revert to baseline, suggesting that lisdexamfetamine's benefits may have carried over after the switch. Alternatively, the findings in the first block may have been a false positive.

Unlike the changes in SCT, subjects' ADHD ratings showed improvements in both four-week treatment periods with lisdexamfetamine (all $p = <0.05$), including measures of executive functioning and functional impairment.

Side effects were what we would expect from lisdexamfetamine: decreased appetite (11%), headache (10%), and anxiety (4%). There were no serious adverse events, and only one participant withdrew due to side effects (anxiety).

CARLAT TAKE

Patients with SCT and ADHD can expect to see improvement with amphetamine-based stimulants like lisdexamfetamine. SCT by itself is not an accepted diagnosis, and we should take caution to avoid overdiagnosis.

DEPRESSION

Does Vitamin B6 Prevent Postpartum Depression?

Brian Miller, MD, PhD, MPH. Dr. Miller, author for this educational activity, has no relevant financial relationship(s) with ineligible companies to disclose.

REVIEW OF: Khodadad M et al, *Int J Prev Med* 2021;12:136
STUDY TYPE: Single-blind placebo-controlled trial

Postpartum depression (PPD) is common, occurring in about one in eight women and adversely affecting children and families. Treatments are limited, but some lines of evidence hint at a potential role for vitamin B6. For example, vitamin B6 levels naturally decrease during the second and third trimesters of pregnancy, and vitamin B6 has shown potential in the treatment of premenstrual dysphoric disorder. This study tested the treatment in the third trimester for women at risk of PPD.

This randomized, single-blind trial tested vitamin B6 versus placebo in 86 pregnant women in Iran in their third trimester. The women had at least one risk factor for PPD (including history of a psychiatric disorder, antenatal anxiety or depression, unplanned pregnancy, lack of social support, marital stress, and recent stressful life events), but did not have a level of depression or anxiety that required treatment. Patients were evenly randomized to either B6 (80 mg/day) or placebo from the 28th week until delivery, and then a lower dose of B6 (40 mg/

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Research Updates

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day) or placebo for one month after delivery. Depression was assessed at baseline and one and a half months after delivery with the Edinburgh Postnatal Depression Scale (EPDS). The majority of participants (94%) completed the trial. The patients did not know whether they were receiving placebo or B6, but the researchers and symptom raters were aware of treatment assignment.

The B6 and placebo groups were well matched with respect to participant's age, husband's age, BMI, education, employment, pregnancy and mental health histories, and baseline EPDS score. The mean EPDS score decreased significantly in the B6 group (from 10.1 to 4.2, where ≥13 is the cutoff for depression), whereas there was a nonsignificant increase in mean EPDS scores in the placebo group (from 9.3 to 10.4).

Limitations include the lack of significant anxiety or depression in the subjects and the lack of blinding in the raters. Also, the study did not control for the exact duration of B6 therapy (based on delivery date), dietary B6 intake, blood levels of the active metabolite of B6, and physical activity. Vitamin B6 is considered safe in pregnancy and has an FDA rating of category A.

CARLAT TAKE

While vitamin B6 is safe in pregnancy and may reduce the risk of PPD, the limitations of this study call for further research.

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