THE CARLAT REPORT PSYCHIATRY

A CME Publication

Subscribe today! Call 866-348-9279

AN UNBIASED MONTHLY COVERING ALL THINGS PSYCHIATRIC

Chris Aiken, MD
Editor-in-Chief

Volume 19, Issue 3
March 2021
www.thecarlatreport.com

IN THIS ISSUE

Focus of the Month:
Stopping Psych Meds Part 2

Learning Objectives

After reading these articles, you should be able to:

1. Identify the advantages and disadvantages of TMS vs ECT for depression.
2. Evaluate the potential role of alpha-2 agonists for ADHD.
3. Describe best practices for tapering off of medications for mood and anxiety disorders.
4. Summarize some of the current research findings on psychiatric treatment.

TMS Treatment for Depression: An Update

Adam Strassberg, MD. Psychiatrist, private practice.

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

Highlights From This Issue

TMS is one of the more effective strategies for treatment-resistant depression, but ECT works 1.5 times better, particularly in psychotic depression.

The hyperbolic taper may reduce withdrawal problems when coming off a serotonergic antidepressant.

The ADHD medications guanfacine ER (Intuniv) and clonidine ER (Kapvay) are now generic, and we describe how to choose between them and when to use the ER, IR, or skin patch.

With six FDA approvals and several devices on the market, transcranial magnetic stimulation (TMS) has changed a lot in the past decade. No longer just for depression, it's now FDA approved for OCD, nicotine cessation, and migraines. Efforts are underway to gain approval in bipolar depression, and the device has promising studies in PTSD, anxiety, schizophrenia, autism, and dementia. In this article, I'll review these updates and see how TMS compares to other options for treatment-resistant depression (TRD).

TMS vs ECT

TMS treats depression, but not as well as ECT. Whether comparing effect size, response, or remission rates, ECT is consistently about 1.5 times as effective as TMS (Micallef-Trigona B, *Depress Res Treat* 2014;2014:135049). ECT is particularly

Continued on page 2

Q&A With the Expert

How to Come Off a Psych Med Part 2: Antidepressants, Stimulants, and Benzos

Swapnil Gupta, MD

Associate professor at Icahn School of Medicine at Mount Sinai. Co-author of Deprescribing in Psychiatry *(Oxford, 2019).*

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

TCPR: Before we talk about your experience with tapering medications, tell us about the population you work with.

Dr. Gupta: In the past, I worked at the Connecticut Mental Health Center for Yale University. There I saw patients with pretty serious mental illness: mainly psychotic disorders, severe trauma, addictions, and serious psychosocial stressors like homelessness. In 2020 I moved to Mount Sinai St. Luke's, and now I see a more varied outpatient mix: milder cases of panic disorder or depression along with bipolar disorder and schizophrenia.

TCPR: Let's start with antidepressants. How long should we continue them in unipolar depression?

Dr. Gupta: At a minimum, we should continue them for 6 months after remission. We know from dozens of studies that tapering before

Continued on page 3

TMS Treatment for Depression: An Update
Continued from page 1

effective for psychotic depression, while psychotic features predict a worse response to TMS.

Although TMS was first approved for depression that failed to respond to 1 (but not 2) antidepressant trials, we now know that it can work after multiple antidepressant failures. In the most recent meta-analysis, which included two dozen trials, TMS had an overall response rate of 25% (vs 11% for sham) and remission rate of 17% (vs 6% for sham). Most of those trials (80%) included only patients with true TRD, meaning more than 2 antidepressant failures (Sehatzadeh S et al, *J Psychiatry Neurosci* 2019;44(3):151–163). When it comes to TRD, both TMS and ECT have diminishing benefits as the number of failed antidepressant trials goes up.

The main advantage of TMS over ECT is tolerability, particularly when it comes to cognition. While cognition can worsen during ECT, it generally improves with TMS, including in patients with post-stroke depression (Wang Y, *Psychiatry Res* 2019;276:186–190). ECT also has the downside of requiring anesthesia, which adds to the inconvenience because patients cannot drive after the treatment. However, ECT is a little faster than TMS (kicking in at 2 vs 4 weeks) and can be administered 3 days a week instead of 5 days a week for TMS.

TMS vs medication augmentation

We don't know how TMS compares to other augmentation strategies like the atypical antipsychotics, lithium, or the ketamines (IV ketamine and intranasal esketamine), as head-to-head trials are lacking. Judging by their effect sizes in TRD, however, TMS and IV ketamine fall in the large range (0.8–1.3), while other medication strategies (including intranasal esketamine) fall in the small range (0.3–0.4). The ketamines have the advantage of working quickly (within hours), but it's not clear how well they work in the long term. IV ketamine was mainly studied as a short-term therapy, and the FDA-approved intranasal esketamine (Spravato) was practically indistinguishable from placebo by the 4-week mark in the majority of trials (Hung YY et al, *Prog Neuropsychopharmacol Biol Psychiatry* 2020;99:109850; Papakostas GI et al, *J Clin Psychiatry* 2020;81(4):19r12889).

Durability of response

The durability of TMS seems very similar to the durability of ECT, with 40%–50% of patients relapsing after about 6 months. A recent meta-analysis (Senova S et al, *Brain Stimul* 2019;12(1):119–128) showed that among initial responders, 66.5% sustained this response by 3 months, 52.9% by 6 months, and 46.3% by 12 months. This same study also supported the efficacy of maintenance treatment to prevent a relapse. For patients receiving maintenance treatment, the responder rate was 35.8% higher at 3 months and 58.7% higher at 6 months.

TMS is also used to treat depressive relapses in patients who responded to TMS during an previous episode. Over 80% of these patients respond to a second course of TMS (Janicak PG et al, *Brain Stimul* 2010;3(4):187–199). The treatment duration for the relapse is typically shorter than for the index episode.

Costs and side effects

TMS is generally safe, with a rare risk of seizures (1 in 30,000 sessions). The most common side effects are headache (20%) and scalp discomfort (20%), but time and money can be a hindrance. A full course of treatment runs 5 days a week, 20–40 minutes a day, for 6 weeks. The out-of-pocket cost for a 6-week course varies from $1,200 (for a typical $40 copay) to $8,000–10,000 (for in-network patients who have a deductible). Most insurers cover TMS, including some Medicare and Medicaid plans.

The ideal patient

The ideal candidate for TMS is a patient with depression who hasn't responded to

Continued on page 3

FDA Approvals for TMS

Year	Indication	Device
2008	Depressive episode unresponsive to a single medication trial	Neurostar (Neuronetics)
2013	Treatment-resistant depression (episode unresponsive to 2 medication trials)	Deep TMS (Brainsway)
2013	Pain associated with migraine headaches	Cerena TMS (eNeura Therapeutics)
2018	OCD with concurrent medication	Deep TMS (Brainsway)
2018	Express TMS	MagVita (MagVenture)
2020	Nicotine cessation	Deep TMS (Brainsway)
Pending	Bipolar depression (trials in progress)	Neurostar (Neuronetics)

TMS Treatment for Depression: An Update

Continued from page 2

1 or 2 antidepressant trials. Age doesn't seem to influence response, and there is a growing database in children and adolescents. There are no known risks in women who are pregnant or breastfeeding.

Early studies suggest that TMS treats bipolar depression without precipitating mania, and the Neurostar device was recently granted "breakthrough status" to pursue an indication in bipolar disorder. That status will allow the company to speed through the approval process with smaller studies.

TMS also works for patients with comorbid disorders, including agoraphobia, autism spectrum disorder, GAD, OCD, panic disorder, PTSD, and social anxiety disorder. In eight studies, those disorders improved when TMS was used to treat comorbid depression.

Which TMS protocol is best?

The first TMS device was FDA approved based on 4–6 weeks of treatment for 5 days a week, and this pattern of treatment remains the norm. Studies have evaluated several factors: number of treatments per day, frequency, length of treatment, intensity, pulse patterns, different areas of the frontal cortex, unilateral vs bilateral applications, types of patients appropriate for treatment, maintenance schedules for responders, and MRI-guided localization or other navigational methods versus approximation. But no variation in the treatment method has so far proved significantly more effective than any other.

TMS can be used as monotherapy, but is more effective when used as an add-on to an antidepressant medication. The benefits of TMS build up as the treatment is continued over time, but it's unclear if there is any benefit beyond 6 weeks. Treatment is typically continued beyond 6 weeks if the patient has not remitted but is continuing to show improvement.

Typical Insurance Reimbursement to Providers for TMS

CPT Code	Description	Reimbursement Range
90867	Mapping of rTMS at first session	$290–475
90868	rTMS treatment at subsequent sessions	$270–350
	6 weeks of daily treatments ➡	$8,120–10,625

Which TMS device is best?

There are two types of TMS machines in clinical use: the figure-8 coil and the H-coil. The figure-8 coil is the more affordable because it's off-patent ($50–$120K), while the patented H-coil is $220K. Most machines have additional maintenance costs, and we've compared the various leasing and pricing strategies offered by their manufacturers in an online supplement (see this table at www.thecarlatreport.com/TMS).

The H-coil is also called "deep TMS" because it penetrates a bit deeper into the brain (6 cm vs 5 cm). However, this theoretical advantage did not translate to a meaningful difference in the only head-to-head trial comparing the devices (see *TCPR*, Jan 2020). The figure-8 coil requires longer sessions than the H-coil (40 minutes vs 20 minutes). A faster protocol, dubbed "Express TMS," was recently released for a MagVenture device. It uses "theta-burst stimulation" and only takes 3 minutes. Express TMS seems just as effective as the other devices, but comes at a cost of greater scalp discomfort.

TCPR VERDICT: TMS is better tolerated but less effective than ECT. It works in depression, whether treatment-resistant, unipolar, or bipolar, and has a growing list of other psychiatric indications.

Expert Interview

Continued from page 1

then raises the risk of relapse 11-fold (Baldessarini RJ et al, *J Clin Psychopharmacol* 2015;35(1):75–76). But that's about relapse, which is going back into the current episode, not recurrence, which means that a new episode has come on. We know a lot less about whether antidepressants prevent recurrences of future episodes.

TCPR: What do we know?

Dr. Gupta: Rif El-Mallakh looked at this in 2012 and found only 18 randomized, blinded trials comparing antidepressants with placebo over the long term (≥ 1.5 years). On the one hand, nearly all the trials found that continued antidepressant use prevented depressive symptoms. On the other hand, their prophylactic benefits were limited to the first 6 months, suggesting that they kept people out of the original episode but didn't necessarily prevent future episodes (El-Mallakh RS and Briscoe B, *CNS Drugs* 2012;26(2):97–109).

TCPR: When would you consider coming off an antidepressant?

Dr. Gupta: If someone has recovered from a first episode of mild to moderate depression for 6–9 months, I'd consider coming off the antidepressant.

TCPR: What would steer you away from discontinuation?

Dr. Gupta: If the episode was severe, I'd be more hesitant to taper off the antidepressant. There's also some evidence that patients with multiple past episodes are at greater risk for relapse after discontinuation. The recommendation for indefinite continuation of antidepressants in patients who have had more than 3 episodes of depression is based on this finding. However, the syndrome of antidepressant withdrawal was not taken into consideration in these discontinuation studies. Antidepressant withdrawal can encompass emotional lability, insomnia, anxiety, and a host of other symptoms that could easily be mistaken for a recurrence of depression (Récalt AM and Cohen D, *Psychother Psychosom* 2019;88(2):105–113). Another consideration is how clear the patient's response to the antidepressant was. Patients who have a true treatment response are more likely to relapse if the antidepressant is withdrawn (Berwian IM et al, *Psychol Med* 2017;47(3):426–437).

TCPR: What about antipsychotics in psychotic depression?

Continued on page 4

Expert Interview

Continued from page 3

Dr. Gupta: You could consider tapering off the antipsychotic after the psychotic features have subsided completely, but there is a risk of relapse if you taper the antipsychotic. In one study of psychotic depression, relapses were 2–3 times greater in those who were randomized to taper off olanzapine while staying on the antidepressant. On the other hand, the ones who came off olanzapine had better metabolic profiles and fewer falls (Flint AJ et al, *JAMA* 2019;322(7):622–631).

TCPR: How do you taper an SSRI or SNRI?

Dr. Gupta: I would suggest the hyperbolic taper that Horowitz and Taylor developed last year (see *TCPR,* Jun/Jul 2019). It's an exponential taper that goes faster at first and then slows down toward the end, much like we use for benzodiazepines. A rough way to estimate it is to drop the dose first by 50%, then wait about 3 months and reevaluate; then lower by 50% of what is left over, wait and evaluate again; then by 50% of the remaining, etc, until they are successfully off. Generally I wait 3 months between each step, but I may go faster or slower depending on how the patient responds to the first reduction. A successful taper could take several years. The theory behind all this is that the binding at the serotonin receptor falls off exponentially (or "hyperbolically") as the dose is lowered (Horowitz MA and Taylor D, *Lancet Psychiatry* 2019;6(6):538–546). To taper like this, you usually can't depend on the tablet sizes that are on the market and may need to get creative with liquid forms or compounding pharmacies. Some patients create microdoses of antidepressants or benzos on their own with compounding solutions like Ora-Plus. (*Editor's note: While professional compounding is preferred, we've printed directions for Ora-Plus in the table below so you can guide patients if they go that route.*)

> **"We actually have data that coming off lithium too fast can lead to rebound episodes, particularly if it was tapered off over less than a month. I would probably taper it off over 3–6 months."**
>
> Swapnil Gupta, MD

How to Compound With Ora-Plus
1. Check with the pharmacist to make sure the medication can be crushed. For more information, see: www.ismp.org/recommendations/do-not-crush
2. Crush tablets with a mortar and pestle to a fine powder. For capsules, spill the contents out and smooth out to a fine powder with the mortar and pestle.
3. Add a small amount of Ora-Plus and grind to a thick, smooth paste with the mortar and pestle.
4. Calculate how much solution you'll need to create the desired dose, then use 10% less to adjust for any losses in the process. Example: To create 0.1 mg/day of alprazolam, start with 1 mg tablets, then add 10% less than 150 mL (= 135 mL) Ora-Plus to the paste. The solution is then 1 mg/150 mL, or 0.1 mg/15 mL. This can be taken as 1 tablespoon a day (= 15 mL).
5. To create a flavored syrup, dilute the Ora-Plus with Ora-Sweet before the final mix.
6. Refrigerate the solution in a tight, light-resistant amber bottle and label with the medication, dose, and date. It should keep for 30–60 days in the fridge.
Ora-Plus is available from www.perrigorx.com or www.amazon.com.

TCPR: Lithium is one where a slow taper is usually recommended. How slow would you go?

Dr. Gupta: I would probably taper it off over 3–6 months. With lithium we actually have the data that coming off too fast can lead to rebound episodes, particularly if it was tapered off over less than a month. For the anticonvulsants, there isn't much data.

TCPR: Are there times when you think it's appropriate to keep a person on a benzo long term?

Dr. Gupta: That's a hard question in some ways, and it's an easy question in some ways. I think that there are no situations where I would keep people on a high dose of a benzo for a long time, but if I'm able to drop the dose down to 0.25–0.5 mg/day of clonazepam and can't get down to zero, I'd be comfortable leaving them on that dose for a long time. About 10%–15% of patients have protracted withdrawal symptoms after stopping a benzo that can last from months to years. Sometimes it's just not worth the suffering that complete discontinuation would cause.

TCPR: How would you handle this case: A patient presents for their first visit with a history of depression but no clear history of ADHD or panic disorder. They are taking an antidepressant, but they've also been on Adderall 80 mg/day and clonazepam 3 mg/day for a decade.

Dr. Gupta: First I would find out how they got on this combination of medications and whether it's helping them. I would spend one or two sessions trying to understand what they think about these drugs and what they feel about them because there are a lot of powerful feelings attached to the medications that we prescribe. Once I have a good idea of what's going on for the patient, then I might say, "Well, look, these two medications have opposite effects. One enhances cognitive functioning and can increase energy and worsen sleep (Adderall). The other is a sedative that dulls cognition (clonazepam). I'm concerned that one drug is treating the effects of the other, which may be why you are on high doses of both. What do you think?" And over five or six sessions, hopefully, we'll be able to reach some sort of consensus.

TCPR: And if the patient says, "No way, I'm not going to stop them"?

Dr. Gupta: I would probably drop the conversation for a few weeks and then bring it up again: "You know, as a responsible physician, I cannot continue to prescribe two drugs with significant abuse potential to you without adjusting the dose, and the Adderall 80 mg is pretty high." Establishment of that trust is important, and we must clearly

Continued on page 6

A Closer Look at Alpha-2 Agonists for ADHD

C. Jason Mallo, DO. Attending Psychiatrist, Maine Medical Center, Portland, Maine.

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

The alpha-2 agonists guanfacine ER (Intuniv) and clonidine ER (Kapvay) were approved for ADHD in 2010–2011, but three things have held back their use:

1. They are less effective than stimulants (effect size of 0.5 vs. 0.8)
2. They are only approved in children and adolescents
3. Cost

Recently, the ER versions went generic and the first major trial in adult ADHD came out, so we decided it was time to take a closer look at these novel medications.

A little history

The alpha-2 agonists were developed in the 1960s for hypertension but fell out of favor as newer blood pressure medications came on the market. Their use in psychiatry took off in the 1980s after they were found to improve executive functioning in primates. Guanfacine and clonidine were tested back then in small studies of ADHD, tic disorders, anxiety, insomnia, agitation, and withdrawal from opioids, alcohol, and nicotine. The development of ER guanfacine and clonidine revitalized interest in larger studies, and these led to their FDA approval for pediatric ADHD in 2009–2010.

How they work

Stimulants increase norepinephrine activity, but alpha-2 agonists inhibit norepinephrine release, so how can they treat ADHD? The answer lies in their downstream effects. Alpha-2 agonists strengthen norepinephrine signals in the prefrontal cortex that are critical in mediating attention and behavior. Other mechanisms are likely involved; for instance, their effects on the locus coeruleus may attenuate inattention, hyperactivity, and impulsivity.

Use in ADHD

Guanfacine and clonidine have never been compared head-to-head, but judging by their individual trials, they appear to be equally effective for ADHD. Both are approved as monotherapy and as adjunctive to stimulants. Unlike stimulants, their effects build gradually over 2–5 weeks. When used adjunctively, the added benefit they bring to stimulants is small, but there is some evidence that the two classes of medications are better tolerated when taken together. Stimulants are less likely to cause hypertension, anxiety, and insomnia when taken with an alpha-agonist, and the alpha-agonists are less sedating when paired with a stimulant. In one study, 59% of patients reported sedation, somnolence, or fatigue with guanfacine monotherapy, but the rate was 11% when taken with a stimulant (Sallee FR et al, *J Child Adolesc Psychopharmacol* 2009;19(3):215–226).

We only know of one well-designed study of alpha-2 agonists in adult ADHD, and that involved guanfacine (see *TCPR*, October 2020). In this 12-week randomized controlled trial, guanfacine ER outperformed placebo ($p = 0.0005$; effect size 0.5). There were some limitations: The study was funded by big pharma, and 20% of participants in the guanfacine group discontinued treatment due to side effects (Iwanami A et al, *J Clin Psychiatry* 2020;81(3):19m12979).

Side effects and alternative uses

A major difference between guanfacine and clonidine is that guanfacine is less sedating, while clonidine has more research in psychiatric disorders that may be comorbid with ADHD. Those include PTSD-related nightmares, irritability in autism, bipolar mania, and self-cutting in borderline personality disorder (where clonidine worked better than placebo when taken PRN for urges to self-cut). Both alpha-agonists are helpful in nicotine cessation, alcohol withdrawal, and opioid use disorders, where they alleviate opioid withdrawal symptoms and prevent relapse. While the trials behind these various off-label uses are small, they are relevant because many of these disorders can worsen on stimulants, including bipolar disorder, borderline personality disorder, sleep, addictions, and tics (Canadian Agency for Drugs and Technologies in Health, 2018 Feb 21; www.tinyurl.com/5heorgde).

Overall, the alpha-agonists are not very well tolerated, with dropout rates that are higher than average for psychiatry. Dry mouth, constipation, fatigue, sedation, hypotension, bradycardia, and QTc prolongation are all impediments. On the other hand, alpha-agonists can relieve physical symptoms like tics, sweating on SSRIs, salivation on clozapine, perimenopausal hot flashes, and restless legs syndrome. Side effects are particularly common during initiation and titration, are dose related, and may lessen with time. Check HR and BP at initiation and dose increases. If daytime side effects are a problem, you can transition your patient to an evening dose. On the other hand, daytime dosing may be useful when targeting anxiety or agitation. Sudden discontinuation can cause rebound hypertension, particularly with clonidine (Hirota T et al, *J Am Acad Child Adolesc Psychiatry* 2014;53(2):153–173).

Formulations and pharmacokinetics

Both the IR and ER forms of guanfacine and clonidine are effective for ADHD. The ER versions are a good place to start, as they are the only ones FDA approved for ADHD, and they are more affordable now that their patents have expired. Clonidine ER and IR are usually dosed twice a day, as the ER and IR forms have a 12-hour half-life. If sedation is a problem, try dosing most or all of it at night. There is also a generic, weekly, transdermal clonidine patch that reduces the rate of sedation and dry mouth and was successfully used in psychiatric trials, including for ADHD.

Guanfacine IR and ER have a longer half-life of 16–18 hours and can be dosed once a day. Notably, both alpha-agonists have shorter half-lives in children. Guanfacine is more likely to become the victim of drug interactions (CYP3A4 inhibitors like fluvoxamine and nefazodone can raise it, while inducers like carbamazepine can lower it).

When converting patients between IR and ER forms, it is important to know that only 60%–75% of the ER form gets

Continued on page 6

Expert Interview

Continued from page 4

convey that we are not just being withholding. You don't want countertransference to influence prescribing or deprescribing, such as withholding a drug because you don't like a patient. The patient needs to be assured that you have their best interest at heart.

TCPR: OK, so let's say the patient is convinced. How would you taper them?

Dr. Gupta: First we'd decide together on which drug to taper first. Unless there's a serious medical issue at stake, I'd be flexible on where we start. Let's say we start with the clonazepam 3 mg/day. I would prescribe 2.5 mg/day and give them 5 separate 0.5 mg tablets and say, "Hold on to them. If the taper feels like it's intolerable, take one. You may not need to, but you've got 5 per month to use as needed because I don't want you to suffer." That way they have some control in the taper. It also helps them gain perspective on their anxiety. Since they only have a limited amount, they have to ask themselves, "Is it really so bad that I need to take this?" Anything that helps patients see the big picture is good for anxiety, because anxiety narrows perspective.

TCPR: How long does it take to taper a benzo?

Dr. Gupta: It can vary from a few weeks to a few years. At the slow end, I may lower the dose by as little as 5%–10% a month. It all depends on the patient. Things that point to the need for a longer taper are long-term use, high doses, and pre-existing anxiety disorders. (*Editor's note: See "Tips for Benzodiazepine Tapers" table on this page.*)

TCPR: What makes stimulant withdrawal difficult?

Dr. Gupta: As with other medications, it's usually the end of the taper, when you're down to the smallest dose and trying to stop it, that becomes difficult. Outside of that, stimulant withdrawal is not a big problem. Sometimes patients have insomnia, fatigue, and slowing for the first 2 or 3 days, but that gradually goes away. You may also see depression, irritability, agitation, high appetite, vivid dreams, and aches and pains. It can take a long time, though. A successful taper off Adderall 60–80 mg/day usually takes me 2–3 years if you count all the sessions where we discuss the issue but don't lower the dose.

TCPR: Do you ever use antidotes for withdrawal, like gabapentin for benzos or modafinil for stimulants?

Dr. Gupta: Generally no. It's getting out of one hole and digging another one, especially with gabapentin. During benzo withdrawal, some doctors use trazodone or melatonin for sleep, or hydroxyzine or propranolol PRN for anxiety. Many antidotes have been tested for benzodiazepine withdrawal, but none have worked. However, one study noted some benefit from a specialized form of CBT that employs a lot of relaxation skills (deep breathing, progressive muscle relaxation) and cognitive work on decatastrophizing—similar to what is used in CBT for panic disorder (Otto MW et al, *Am J Psychiatry* 1993;150(10):1485–1490; the treatment manual is *Stopping Anxiety Medication* by Otto & Pollack).

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

Tips for Benzodiazepine Tapers	
Go slow	The entire taper may take a year or more.
Educate	Make it very clear to the patient that they are not going to feel good when you drop the dose.
Be available	Be available by phone and return calls within 24 hours.
Give control	As far as possible, let the patient have some control over what's happening.
Provide a back-up PRN dose	Dispense a few extra tabs (eg, 5) each month that the patient can use as needed for intolerable symptoms.

To learn more, listen to our 3/22/21 podcast, "How to Stop Antidepressants, Benzos, and Stimulants: An Interview With Swapnil Gupta." Search for "Carlat" on your podcast store.

❖ ❖ ❖

A Closer Look at Alpha-2 Agonists for ADHD

Continued from page 5

absorbed. So 3 mg/day of guanfacine IR is comparable to 4 mg/day of guanfacine ER, and 0.3 mg of clonidine IR is comparable to 0.4 mg of clonidine ER. Also, guanfacine's absorption increases with high-fat meals, which could contribute to adverse events. Clonidine's absorption is not affected by food.

TCPR VERDICT: With their modest benefits and not-so-modest side effects, guanfacine and clonidine are not ideal for generalized use in ADHD. They do have a niche in a handful of comorbidities that can worsen with stimulants, including PTSD, bipolar disorder, borderline personality disorder, and addictions.

To learn more, listen to our 10/26/20 podcast, "How to Use Guanfacine and Clonidine." Search for "Carlat" on your podcast store.

Dosing Alpha-2 Agonists for ADHD in Adults	
Guanfacine	Start 1 mg every morning, then increase by 1 mg/day every 1–4 weeks up to 6 mg/day max. If daytime side effects are an issue, divide the dose BID or prescribe at bedtime.
Clonidine	Start 0.1 mg daily, then increase by 0.1 mg/day every 1–4 weeks up to 0.6 mg/day max. Divide the dose BID and, if indicated, prescribe a higher dose in the evening to avoid daytime side effects.
When converting from IR to ER, raise the daily dose by about 30%.	

Research Update IN PSYCHIATRY

ANTIPSYCHOTICS

Antipsychotic Use Associated With Increased Risk of Mortality

REVIEW OF: Gerhard T et al, *PLoS One* 2020;15(9):e0239206

TYPE OF STUDY: Population-based comparator cohort study

We know that atypical antipsychotics increase mortality in elderly patients with dementia—the FDA has long required a black box warning to that effect. But are these medications also dangerous when prescribed to younger people with depression?

To answer this question, researchers analyzed mortality rates of depressed adults (ages 25–64) enrolled in Medicaid between 2001–2010. Patients with major depression (but not other major Axis I disorders) who had failed to respond to > 3 months of antidepressant monotherapy were included. The researchers compared two cohorts: patients who had their antidepressant augmented with an antipsychotic (n = 22,410) vs those who had it augmented with a second antidepressant (n = 17,172). The outcome of interest was all-cause mortality rates over the next year for patients who remained on their medications.

In total, 105 deaths occurred during 7,601 person-years of follow-up in the antipsychotic augmentation cohort (138 per 100,000 person-years) versus 48 deaths during 5,727 person-years of follow-up in the antidepressant augmentation cohort (84 per 100,000 person-years). These numbers translate into an absolute risk of about 0.4% per year with antipsychotic augmentation, and a relative risk of 45% compared to antidepressant augmentation. To contextualize this figure, the relative risk in elderly patients with dementia is just slightly higher (around 54%), and this was concerning enough to the FDA to trigger a black box warning. Among the four antipsychotics with sufficient sample sizes, olanzapine and risperidone were associated with the highest risks of mortality, while quetiapine and aripiprazole the lowest—findings that are consistent with geriatric research.

The main weakness of the study was the lack of randomization, leaving open the possibility that prescribing bias could have contributed to the excess mortality in the antipsychotic augmentation group. For example, clinicians might have chosen atypicals for more severely depressed patients. Working in the opposite direction, however, clinicians might have preferred antidepressant augmentation for patients with medical comorbidities, which would artificially inflate mortality rates in this cohort instead. Furthermore, we should be cautious in generalizing results from Medicaid patients to the overall population.

TCPR'S TAKE

While this is only one study, and the increased mortality risk is small, the results should still give us pause before prescribing atypical antipsychotics in depression. It may be time to recalibrate their risk-benefit ratio.

—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.

CME Post-Test

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

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

This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Learning Objectives (LO) are listed on page 1.

1. According to a 2014 study of depression, which of the following is true about the effectiveness of ECT compared to TMS? (LO #1)
   - [ ] a. ECT had a larger response rate and effect size, but a lower remission rate
   - [ ] b. ECT had a larger effect size, but a response rate equal to that of TMS
   - [ ] c. ECT had a larger effect size, response rate, and remission rate
   - [ ] d. ECT was inferior to TMS on all outcomes

2. Which of the following statements about clonidine vs guanfacine for ADHD is supported by evidence? (LO #2)
   - [ ] a. Guanfacine is more sedating than clonidine
   - [ ] b. Both have shown benefits in nicotine cessation, alcohol withdrawal, and opioid use disorder
   - [ ] c. Guanfacine has more research in bipolar mania and borderline personality disorder
   - [ ] d. While both have shown benefits in nicotine cessation and opioid withdrawal, only clonidine has shown benefits in alcohol withdrawal

3. According to Dr. Gupta, patients with unipolar depression should continue their antidepressant therapy for at least how many months after they've achieved remission? (LO #3)
   - [ ] a. 2 months
   - [ ] b. 9 months
   - [ ] c. 6 months
   - [ ] d. 4 months

4. According to a recent study, what was the absolute risk of all-cause mortality per year for adult patients with depression who had their antidepressant augmented with an antipsychotic? (LO #4)
   - [ ] a. 1.4%
   - [ ] b. 0.8%
   - [ ] c. 0.4%
   - [ ] d. 1.9%

5. For patients with treatment-resistant depression, TMS has an effect size in the medium range, and it's generally less tolerable than ECT. (LO #1)
   - [ ] a. True
   - [ ] b. False

THE CARLAT REPORT
PSYCHIATRY
P.O. Box 626
Newburyport, MA 01950

This Issue:
Stopping Psych Meds Part 2
March 2021

Next Issue:
Metabolism and Mental Health
April 2021

Learn more and search full archives online:
www.thecarlatreport.com

In Brief: Who Needs the Therapeutic Alliance?

Oxytocin levels tend to fluctuate in synchrony when people are in strong, connected relationships, from the mother-child bond to romantic partnerships. A new study extended that to the therapist-patient dyad by comparing the change in oxytocin levels for patient and therapist during each session of psychotherapy for depression. The greater the synchrony in the oxytocin flux, the better the therapy outcomes.

Oxytocin synchrony was lowest when therapists were working with patients who had severe relationship or attachment problems. Earlier studies also found poorer therapy outcomes for these patients, which raises a challenge that I often hear patients express: "How can talking to a therapist help if I'm not good at communication and relationships?"

One answer comes from a large NIMH trial of depression, which found that socially isolated patients did better with an interpersonal than a CBT approach (Sotsky SM et al, *Am J Psychiatry* 1991;148(8):997–1008). Another trial found that the therapeutic alliance did not predict outcomes for adolescents with ADHD when the sessions had a clear agenda and skill-building goals (Boyer B et al, *Behav Ther* 2018;49(5):781–795).

Attachment-oriented approaches can work well for these patients, but the work is more difficult and not well suited for a 12-week course. Patients do better when psychotherapy builds on their strengths, and if attachment is not one of them, a structured approach is a good place to start.

Search "Carlat" in your podcast store for more updates: ***"Duty to Warn" (3/1/21), "What Works Best for Treatment-Resistant Depression?" (3/8/21), "In Memoriam: Hagop Akiskal and the Bipolar Spectrum" (3/15/21), and "Opioids and the Pandemic" (3/29/21).***