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Chris Aiken, MD
Editor-in-Chief

Volume 19, Issue 2
February 2021
www.thecarlatreport.com

IN THIS ISSUE

Focus of the Month:
Stopping Psych Meds Part 1

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

1. Identify the advantages and disadvantages of buspirone.
2. Evaluate the role of stimulants in the context of ADHD and creative thinking.
3. Describe best practices for tapering off of antipsychotics.
4. Summarize some of the current research findings on psychiatric treatment.

Buspirone: Still Effective After All These Years?

Eugene Rubin, MD. Psychiatrist in private practice, Bingham Farms, MI.

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

Highlights From This Issue

The controversial theory of dopamine supersensitivity suggests that antipsychotic withdrawal can worsen dyskinesias and prolactinemia, and even cause a rebound psychosis.

Stimulants may dampen creative thinking, but the effect varies by patient.

Buspirone is only approved for generalized anxiety disorder, but we review its off-label potential in depression, aggression, alcohol use disorders, premenstrual dysphoric disorder, and tardive dyskinesia.

When buspirone was released in 1986, it was advertised as providing "a different kind of calm." Unfortunately, physicians and their patients weren't ready to accept the kind of calm that required several weeks to take effect, when punchier, quicker benzos were the standard route to tranquility. Although buspirone is FDA approved for generalized anxiety disorder (GAD), some question whether it treats anxiety at all. In this article, we will look at how buspirone works and what it can and can't do for our patients.

How buspirone works

Buspirone, an azapirone, is in a class of its own. It was a failed antipsychotic before it was shown to be effective for GAD. Its primary mechanism of action is $5HT_{1A}$ partial agonism, which is a

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Q&A With the Expert

How to Come Off a Psych Med Part 1: Antipsychotics
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: There are a lot of books on deprescribing from the antipsychiatry movement, but your book seems to take a different approach.

Dr. Gupta: The biggest difference is that the authors of this book all acknowledge that there is a place for psychotropic medications. They can be extremely beneficial for the patient in the right situation. My concern is with continuing prescriptions without periodic reevaluation for their need.

TCPR: So we need to think about a stopping point as well as a starting point?

Dr. Gupta: I think so. And we need to be talking about stopping or discontinuation at the time of prescribing. In my practice, I talk about the difficulties of discontinuing SSRIs when I start them because it's important to factor that into the decision to actually start an SSRI.

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component of the mechanism in the antidepressant vilazodone and a few antipsychotics (aripiprazole, brexpiprazole, cariprazine, clozapine, and quetiapine). Buspirone's other mechanisms, which include mild D_2 antagonism and noradrenergic effects, are less understood.

What it can and can't do

Buspirone clearly works in GAD, but does it work as well as other treatments? In a meta-analysis of studies in patients with GAD, its effect size was smaller (0.17) than that of other GAD meds, such as SSRIs (0.36) and benzodiazepines (0.38) (Hidalgo RB et al, *J Psychopharmacol* 2007;21(8):864–872). On the other hand, buspirone has held up well in head-to-head comparisons with multiple benzodiazepines, and patients do just as well when switched from benzodiazepines to buspirone (Delle Chiaie R et al, *J Clin Psychopharmacol* 1995;15(1):12–19). Its other advantages include lack of dependence, tolerance, withdrawal, and abuse potential. It does not impair cognition or increase the risk of falls.

Buspirone is popular as an augmentation strategy in major depression, although the evidence for its role there is tenuous. It ranked below lithium, the atypical antipsychotics, and thyroid augmentation in a meta-analysis, and bupropion outperformed it in the augmentation phase of the STAR*D trial. To its favor, buspirone did work better in severe depression in a large randomized augmentation trial, and it may be worth trying when tolerability is the priority (Zhou X et al, *J Clin Psychiatry* 2015;76(4):e487–e498; Appelberg BG et al, *J Clin Psychiatry* 2001;62(6):448–452). Buspirone may also relieve two common side effects of SSRIs: sexual dysfunction and bruxism (Garrett AR and Hawley JS, *Neurol Clin Pract* 2018;8(2):135–141).

Buspirone does not treat depression on its own, but an intriguing pilot study suggests it may work as an antidepressant when combined with melatonin. The trial was inspired by animal research, where low-dose buspirone had neuroprotective effects when combined with melatonin, but not on its own. In the multicenter placebo-controlled trial of 132 patients with acute major depression that followed, buspirone 15 mg + melatonin sustained-release 3 mg qhs, but not buspirone alone, improved depression and cognition with a moderate effect size (0.43) (Fava M et al, *J Psychiatr Res* 2012;46(12):1553–1563).

Buspirone may relieve physical and psychological symptoms of premenstrual dysphoric disorder, according to small controlled trials that either dosed it continuously or in the 2 weeks before menses (10–30 mg/day) (Nazari H et al, *Arch Gynecol Obstet* 2013;287(3):469–472). It may also have anti-aggressive effects in various populations, including dementia, traumatic brain injury (TBI), mental retardation, and children with ADHD or oppositional defiant disorder (Cantillon M et al, *Am J Geriatr Psychiatry* 1996; 4(3):263–267). Jonathan Silver, MD, editor of the APA textbook on TBI, uses buspirone first-line for irritability and aggression in TBI at doses up to 30 mg bid (See *TCPR,* Aug 2020).

Buspirone failed as an antipsychotic, but the doses used in those studies (up to 1,200 mg/day) confirmed its safety, and open-label studies suggest high doses (up to 180 mg/day) improve tardive dyskinesia (Moss LE et al, *J Clin Psychopharmacol* 1993;13(3):204–209). Buspirone has been extensively tested in alcoholism, where the best that can be said is that it helped subjects' anxiety but not their addiction. Studies in cocaine and nicotine dependence were also negative. Buspirone does not work in social anxiety or panic disorder, and studies in OCD are inconclusive.

When and how to use it

Buspirone is a good choice when tolerability is needed, whether for GAD or antidepressant augmentation. More challenging is starting buspirone in patients with a history of benzodiazepine use. There the dosage needs to be primed with psychoeducation, emphasizing its lack of tolerance, withdrawal, and cognitive side effects. Help the patient understand that while they may be giving up the rewarding effect, the antianxiety effects of buspirone will be comparable to benzos in the long term.

I usually start with 5–7.5 mg bid and raise to 15 mg bid over a week. From there, I'll let it rest 2–4 weeks to determine its efficacy and raise as needed. Buspirone is licensed up to a max of 60 mg/day, and some authors go up to 90 mg/day for anxiety. With its 3-hour half-life, tid dosing is usually recommended, but one study found equal benefit with bid dosing—much more feasible for many patients (Sramek JJ et al, *Depression and Anxiety* 1999;9(3):131–134).

Buspirone is a substrate of CYP3A4, so you will want to use higher doses in patients on inducers such as carbamazepine and lower doses in patients on inhibitors such as fluvoxamine, nefazodone, or grapefruit juice. Taking it with food can increase its absorption up to 2-fold and reduce nausea. Other side effects to watch

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Buspirone: Still Effective After All These Years?

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for are headache and dizziness. In bipolar disorder, buspirone can rarely induce mania.

TCPR VERDICT: When patients need a tolerable medication for GAD that lacks sexual side effects and has no potential for tolerance or abuse, buspirone is first-line. For antidepressant augmentation, buspirone is not clearly effective, but it can be used when tolerability is the main concern.

To learn more, listen to our 2/22/21 podcast, "Does Buspirone + Melatonin = An Antidepressant?" Search for "Carlat" on your podcast store.

Buspirone at a Glance	
FDA Indications	Generalized anxiety disorder (GAD)
Advantages	Generally well tolerated, non-controlled substance
Disadvantages	Slower onset of effect as compared to benzodiazepines, less useful than SSRIs in GAD patients with comorbid depression
Dosage	Start at 5–7.5 mg bid, raise to 15 mg/day over a week; if no response after 4 weeks, titrate to 60–90 mg/day (divided bid or tid); see text for use in tardive dyskinesia or with melatonin in depression
Interactions	Substrate of CYP3A4: adjust dose accordingly in the presence of inducers (carbamazepine) and inhibitors (fluvoxamine, nefazodone, ketoconazole, ritonavir, grapefruit juice)
Other Uses	Augmentation in major depression; bruxism or sexual side effects on serotonergic antidepressants; agitation in neurologic disorders; possibly effective in PMDD and tardive dyskinesia
Side Effects	Dizziness, nervousness, nausea, headache, jitteriness

Expert Interview

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TCPR: How do you discuss deprescribing with patients?

Dr. Gupta: Often I'll start by writing down their entire medication list on a whiteboard and say, "With 5 different medications on board, I don't know what's happening with the neurochemicals in your brain. My recommendation is that we taper off drug X for this reason. What do you think?" Then the patient may suggest something else, and we often talk about it for months before we decide on something. It's a collaborative decision. Even if they don't want to come off anything, just bringing up the idea that we are open to doing that fosters transparency from both sides. Very often it happens that I tell my patients, "You know, let's try cutting this blue pill by 0.25 mg." And then the patient reveals, "Oh, the blue one? I haven't taken that for 6 months."

TCPR: Patients can get worse for all kinds of reasons during a taper. There's withdrawal, relapse, stress, and the "nocebo" effect where they worsen because of a psychological attachment to the medication. How do you minimize those risks?

Dr. Gupta: The key factors are good preparation, close monitoring, communication, and flexibility. For example, if we are planning on tapering an SSRI, I tell patients, "When we reduce the medication, you are not going to feel good at least for the first 2 or 3 weeks. You might get anxious; you might get weepy. You might have these odd sensations in your hands and feet." I make sure they all know how to reach me after hours. I also include their significant other so they don't get scared by the patient's emotional upheavals. We often discuss it for months before we actually start the taper. You have to be flexible because it's a different journey with every patient. Recently with sertraline, a patient developed brain zaps when we got down to 25 mg/day, so we went back up to 100 mg and are tapering it even slower.

TCPR: You said you talk about it for months in advance. What do you talk about?

Dr. Gupta: Sometimes I use a decision-making grid to show the risks and benefits for each med. It's a 4x4 box, and in the boxes are the 1) benefits of staying on, 2) benefits of coming off, 3) risks of staying on, and 4) risks of coming off. I'll fill in the boxes with patients' input and ask them to take it home and think about it. That way I'm not just telling them what to do and they are a part of the decision-making process.

TCPR: What are some areas where you think psychiatrists tend to keep patients on meds too long?

Dr. Gupta: Let's start with the "low-hanging fruit"—for instance, an anticholinergic like benztropine (Cogentin) to control extrapyramidal symptoms on antipsychotics. Those could usually be discontinued or lowered after 6 to 8 months. Although they may not cause serious side effects in the average healthy person, they do have small side effects that can add up and reduce quality of life, like dry mouth. That worsens oral health, causes bad breath, and makes people have to carry a water bottle around all the time. Others that may be easy and worthwhile to deprescribe are the antihistamines like hydroxyzine (Vistaril) for sleep or anxiety, and trazodone for sleep. After that is antipsychotic polypharmacy. We don't have evidence that multiple antipsychotics improve outcomes in schizophrenia, but they do increase the side effect burden. Aripiprazole (Abilify) and clozapine are possible exceptions. Combinations with clozapine reduce hospitalization rates, and aripiprazole antipsychotic combinations reduce metabolic side effects and hyperprolactinemia (Gallego JA et al, *Expert Opin Drug Saf* 2012;11(4):527–542).

TCPR: What are some other examples of excessive polypharmacy in schizophrenia?

Dr. Gupta: Another area is divalproex added to antipsychotics. It's often added for aggression in schizophrenia on inpatient units. In the short term, those benefits are contestable, but there's usually no need to continue it long term.

TCPR: Should antipsychotics be continued long term in psychotic disorders?

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Expert Interview

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Dr. Gupta: Not always. If someone had a single episode of a brief reactive psychosis that lasted less than a month, you could consider tapering the antipsychotic. There is really no one-size-fits-all. It's not a good idea to say that any person with psychosis needs to take antipsychotics forever. A reasonable approach is to lower the dose as much as possible. There are risks with long-term antipsychotics, and we want to minimize them.

TCPR: Is it just physical side effects you're concerned with, or are there mental side effects as well?

Dr. Gupta: There can be cognitive side effects. It varies by patient, but on average antipsychotics reduce processing speed, particularly at high doses. On the other hand, verbal and working memory tend to improve on antipsychotics. But they can also impair functioning without affecting cognition, such as by constricting affect and motivation (Ballesteros A et al, *Psychol Med* 2018;48(13):2247–2256; Clissold M and Crowe SF, *J Clin Exp Neuropsychol* 2019;41(1):26–42).

TCPR: What's the evidence for that?

Dr. Gupta: The main study that raised this issue was a randomized controlled trial of 128 patients with first-episode psychosis. After recovery, half were randomized to continue their antipsychotic dose, and for the other half the dose was either lowered or discontinued. They were followed for 7 years, and at the end of the study the ones who had their dose reduced or discontinued had much better functioning but were no worse in terms of psychotic relapse. The study is by no means definitive, and it's difficult to interpret because some of the patients in the "lower or discontinue" group went on and off the medication (Wunderink L et al, *JAMA Psychiatry* 2013;70(9):913–920). On balance, I think for most patients with schizophrenia their functioning is better on the antipsychotic than off, but there is a subset to be concerned about.

> **"If someone had a single episode of a brief reactive psychosis that lasted less than a month, you could consider tapering the antipsychotic. There is really no one-size-fits-all. It's not a good idea to say that any person with psychosis needs to take antipsychotics forever. A reasonable approach is to lower the dose as much as possible."**
>
> Swapnil Gupta, MD

TCPR: When you do decide to taper an antipsychotic in schizophrenia, how slow do you go?

Dr. Gupta: That varies a lot. 12 to 18 months is ideal, and anything less than 3 months is too fast. I recommend lowering the dose by 50%, then by 50% of the remaining dose, and then by 50% of that dose until they are off (the timing of these dose reductions needs to be personalized for each patient). You have to watch more closely at the lower end of the taper; that's when symptoms might break through. I might go slower if the patient started on a high dose or has risk factors for relapse like a history of recurrent or severe episodes. I also consider how the patient feels about the taper when planning it. Then there are practical concerns, like how often can I check on them? Are there family that can help? If they are on two antipsychotics, I might taper off faster than if they are on just one.

TCPR: There's a theory that chronic antipsychotic use can sensitize the dopamine receptors, and that this can lead to a withdrawal psychosis when antipsychotics are tapered, even in patients who were taking them for mood disorders and had no prior history of psychosis.

Dr. Gupta: Yes, this is a controversial theory called dopamine supersensitivity. It was proposed in the 1970s by Guy Chouinard in Toronto. Their idea was that the D_2 receptors upregulate in response to chronic D_2 blockade from an antipsychotic. When the hypersensitive D_2 receptors become activated by dopamine as the antipsychotic is stopped, it causes a rebound psychosis. The theory has also been used to explain why adverse effects like tardive dyskinesia and prolactinemia can worsen during antipsychotic withdrawal (Servonnet A and Samaha AN, *Neuropharmacology* 2020;163:107630; Chouinard G et al, *Psychother Psychosom* 2017;86(4):189–219).

TCPR: Is there any evidence to support this?

Dr. Gupta: Yes. There are neuroimaging studies of the D_2 receptor that support it. The evidence I find most compelling are case reports of D_2-blocking medications like metoclopramide that were prescribed in mentally healthy people for nausea, and then psychotic symptoms develop when metoclopramide is abruptly discontinued (Lu ML et al, *Ann Pharmacother* 2002;36(9):1387–1390). It is so embedded in our clinical culture that if someone discontinues their antipsychotic and develops psychotic symptoms again, we instantly interpret it as a relapse. And we don't really think about the fact that this might be a rebound psychosis. Most likely it is somewhere in between: Someone has a predisposition for becoming psychotic, and the abrupt dopamine excess that is created by the abrupt discontinuation of D_2 blockade ends up causing the psychotic episode.

TCPR: Do these withdrawal psychoses have a different quality than regular psychoses?

Dr. Gupta: In the descriptions, the withdrawal psychosis is usually much worse than any previous episodes the patient has had.

TCPR: Is it fair to say, then, that in your view schizophrenia represents a group of varied patients, and we need to individualize the treatment approach more?

Dr. Gupta: Yes. I think schizophrenia is a group of disorders; it's not one unitary disorder. We really need to factor in substance use, stress, and trauma. Nearly 90% of patients with chronic psychotic disorders do have a history of trauma, and we don't know how that influences the phenomenology and psychopathology of these disorders. It's possible that what we are calling schizophrenia is neurobiologically not a schizophrenia, so these people may not need antipsychotics for life while others with classical schizophrenia do.

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

To learn more, listen to our 2/8/21 podcast, "How to Stop a Psych Med: An Interview With Swapnil Gupta." Search for "Carlat" on your podcast store.

Stimulants and Creativity

Sean Ransom, PhD. Assistant Clinical Professor, Department of Psychiatry at the LSU Health Sciences Center - New Orleans, and Clinical Director, Cognitive Behavioral Therapy Center of New Orleans.

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

Your patient is a 25-year-old music teacher with ADHD. Though her organizational skills have improved with methylphenidate, she complains that it impairs her performance as a jazz musician: "I feel self-conscious, like a robot."

Popular lore holds that creative people have ADHD traits and that ADHD bestows advantages in creative thinking. Stock characters like the distracted artist or the absent-minded professor promote this generalization, but what does the research show? In this article, I'll look at the relationship between ADHD and creativity and whether stimulants help or harm creative thinking.

There are many ways to measure creativity, but the two that come up most often are divergent and convergent thinking. Divergent thinking asks the respondent to create a variety of novel responses from a single prompt (eg, "Name all the possible uses of a newspaper"). This type of creativity is what's most at play in jazz improvisation. Convergent thinking asks the respondent to come up with a single correct answer from a set of apparently unrelated stems (eg, "What is found in droves at the Sturgis Motorcycle Rally, at University of Arkansas sporting events, and at the world's largest pork processing plant in Tar Heel, North Carolina?" See answer at end of article.*)

The research on creativity and stimulants is scant. Fewer than a half-dozen studies have examined psychostimulants' effect on creativity, and added together, these studies provide data from fewer than 250 participants total. Early studies from the 1990s did not find any consistent effects on creativity when stimulants were used in ADHD, but two recent randomized controlled trials (total n = 67) did find a decrease in divergent creative thinking—the type that's needed for jazz improvisation—when children with ADHD were treated with stimulants (Hernandez GGC and Selva JPS, *Psicothema* 2016;28(1):20–25; Ten W et al, *Psychiatry Res* 2020;284:112680).

What about when stimulants are given to healthy adults without ADHD? A handful of studies have looked at creative measures here with mixed results. One result that was replicated suggests that stimulants have different effects on creative and non-creative people. The researchers gave Adderall (10–20 mg) to healthy subjects with high or low creative traits and measured their convergent creative thinking before and after. The non-creative people saw a small gain in their creative abilities after taking Adderall, while the high creatives had a modest decrease (Ilieva I et al, *Neuropharmacology* 2013;64:496–505).

Researchers have also considered modafinil (Provigil), a wakefulness-promoting agent with benefits in ADHD. Modafinil has dopaminergic effects, and dopamine is thought to be a key neurotransmitter in the performance of creative tasks (Beversdorf DQ, *Curr Opin Behav Sci* 2019;27:55–63). Modafinil improves memory, executive functioning, and subjective task enjoyment in adults without ADHD, but it does not improve creative thinking and may even worsen it. In a study of 64 adults, modafinil broadly reduced divergent creative thinking (Mohamed AD, *J Creat Behav* 2016;50(4):252–267).

While this body of research is far from definitive, we can at least conclude that stimulants are not likely to improve creativity, and there's a small signal that they may sometimes impede it in creative people.

Are people with ADHD more creative?

A small number of studies over the past three decades have compared individuals with and without ADHD on measures of creativity, but the results have been wildly inconsistent. Furthermore, these studies were small and limited by idiosyncratic samples or other methodological problems, so no result seems to stand out as the clear answer—as attested by a 2016 meta-analysis that showed no difference in creativity between ADHD and non-ADHD groups (Park HP et al, *Gift Child Q* 2016;60(2):117–133).

A separate issue is whether creative people have mild ADHD traits that don't meet criteria for the full disorder. It's possible, for example, that highly creative people with ADHD symptoms use their creativity to cleverly compensate for what might otherwise be an impairment. This possibility emerges from a small but fascinating study that compared 89 children who were divided into four groups: a non-creative ADHD group, a creative ADHD group, a creative group without ADHD, and a control group that was neither creative nor diagnosed with ADHD. In the development of their study, however, these researchers discovered that a full 40% of the creative individuals without an ADHD diagnosis actually rated in the clinical range on the parent version of the Conners ADHD scale. These parents did not see their child's symptoms as impairing, and these children's teachers did not report ADHD-related problems at school (Healey D and Rucklidge JJ, *Child Neuropsychol* 2006;12(6):421–438).

What could be said, at best, is that functioning separates the distracted creative from the person with true ADHD. Because ADHD is a disorder of self-regulation, when a creative person has true ADHD, the impairments will show up in their creative output, which is likely to be disorganized, incomplete, and not up to the person's potential. On the other hand, mild distractibility and a more spontaneous decision-making style might allow people to take in a broader swath of information and synthesize it into new ideas. Stimulants would usually not be indicated for these subsyndromal cases that lack impairment, but such people still might show up at your office and nervously admit that their focus improved when they illicitly "tried" their roommate's Adderall.

Getting back to our example patient (the jazz musician with ADHD), we see this problem fairly often when treating ADHD, and the answer is usually to lower the dose of their stimulant. There's a fine line between treating impulsivity vs dampening spontaneity; raising self-awareness vs heightening self-consciousness; and sharpening focus vs promoting hyperfocus. That line is different for

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Research Updates IN PSYCHIATRY

ANTIDEPRESSANTS

Are SSRIs Associated With Increased Rates of Violence?

REVIEW OF: Lagerberg et al, *Eur Neuropsychopharm* 2020;26:1–9

TYPE OF STUDY: Analysis of Swedish national registries

Soon after the introduction of SSRIs in 1988, case reports began to emerge suggesting that they might trigger violence in a small subset of patients. At the time, such reports were mostly dismissed and attributed to the fact that patients receiving antidepressant therapy presented during times of crisis, so correlation was thought to be mistaken for causation. So far, the epidemiological studies have provided conflicting results on this issue.

In this study, researchers utilized various Swedish databases to examine rates of violent acts (such as homicide, robbery, assault, and threats) for individuals aged 15–60 who received SSRI therapy between 2006 and 2013. They specifically focused on the timing of violent acts in relation to SSRI treatment by demarcating 6 phases of treatment: 3 on SSRI therapy (days 0–28, days 29–84, and days > 84) and the same 3 time frames after the SSRI was discontinued. The researchers attempted to control for a variety of confounding variables.

In total, 785,337 individuals were included and followed for an average of 7.3 years. Violent crime convictions occurred in 2.7% (n = 20,821) of the cohort. Overall, SSRI use was associated with a modest increase in violent crime (risk = 1.10, confidence interval 1.06–1.13). Further analyses suggested that most of this increase occurred in the subset of individuals who (1) were under the age of 35, and (2) had a prior history of violence. Benzodiazepines were also associated with an increased risk of violence (risk = 1.32, confidence interval 1.21–1.55) in this analysis, but other psychotropic medications were not.

In examining the 6 phases of treatment, no pattern emerged other than that the risk of violence dissipated about 3 months (84 days) after SSRI discontinuation.

TCPR'S TAKE

This study is the most rigorous take yet on the controversial link between SSRIs and violence. However, it still can't confirm causality because it's always possible that SSRI therapy is a proxy for distress, and that patients come off SSRIs when their lives become more stable, causing a false association. Still, paradoxical reactions do occur in psychiatry—benzodiazepines usually calm agitation but can make the occasional patient disinhibited; SSRIs generally lower irritability but may do the opposite if they cause mania or akathisia. Nonetheless, even if the causality implied here is true, it would only represent an increase of roughly 4 violent acts per every 10,000 SSRI trials. While still worthy of pursuit for epidemiological research, such a low risk does not warrant a change in clinical practice.

—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.

To learn more, listen to our 2/15/21 podcast, "Six Depressions That Can Worsen on Antidepressants." Search for "Carlat" on your podcast store.

ANTIPSYCHOTICS

How to Switch Antipsychotics

REVIEW OF: Takeuchi H and Remington G, *J Psychopharmacol* 2020;34(8):914–919

TYPE OF STUDY: Meta-analysis of randomized controlled trials

Antipsychotic switching is a routine part of schizophrenia care, but what's the best way to go from one medication to another? This article compared three strategies: 1) abruptly stopping the old antipsychotic and starting the new one, 2) gradually tapering the old antipsychotic as soon as the new one is added, and 3) performing "wait-and-gradual" discontinuation (ie, waiting more than 1 day after starting the new antipsychotic before tapering off the old one). Earlier meta-analyses found no differences when comparing options 1 vs 2 and 2 vs 3. This new study compared option 1 (abrupt) with option 3 (wait-and-gradual).

The analysis included 6 comparisons of these switch strategies from randomized controlled trials involving 351 patients with chronic schizophrenia. The primary outcomes were dropouts due to all causes, inefficacy, or intolerability. Secondary outcomes included a variety of measures of psychotic symptoms and antipsychotic side effects. Most of the wait-and-gradual studies tapered off the old antipsychotic over 1 week, though one study took 2 weeks to taper and another took 6 weeks. The average follow-up after the switch was 5 to 6 weeks. Sponsorship of the individual studies was not mentioned, but there was no evidence of publication bias. The meta-analysis received no financial sponsorship.

The main finding was that patients were 1.6 times more likely to drop out for any cause (including but not limited to withdrawal of consent and loss to follow-up) with abrupt vs wait-and-gradual discontinuation. For discontinuation due to inefficacy and intolerability, there was a trend favoring the wait-and-gradual method, but it did not reach statistical significance. There were no significant differences in the various measures of side effects and psychotic symptoms between the two strategies. The main weakness of this meta-analysis was the small number of studies included.

TCPR'S TAKE

When switching antipsychotics, first add the new one in, then taper the old one off over at least 1 to 2 weeks.

—Peter Smith, PsyD. Dr. Smith has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

CME Post-Test

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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. Which of the following is true about buspirone vs benzodiazepines for treatment of generalized anxiety disorder (GAD)? (LO #1)
   - [ ] a. Buspirone and benzodiazepines have similar withdrawal periods
   - [ ] b. Buspirone has a slower onset of effect compared to benzodiazepines
   - [ ] c. Buspirone and benzodiazepines have similar abuse potential
   - [ ] d. Buspirone has more side effects compared to benzodiazepines

2. Modafinil improves memory, executive functioning, and subjective task enjoyment in adults without ADHD. According to research, what effect does modafinil have on creative thinking? (LO #2)
   - [ ] a. Improves creative thinking in both the short term and the long term
   - [ ] b. Improves creative thinking in the short term but has no effect in the long term
   - [ ] c. Slightly improves creative thinking in the short term but may worsen it overall
   - [ ] d. Does not improve creative thinking and may worsen it overall

3. In a recent study, what percentage of patients treated with SSRIs were convicted of a violent crime? (LO #4)
   [ ] a. 9.9% [ ] b. 0.6% [ ] c. 5.1% [ ] d. 2.7%

4. According to Dr. Gupta, treating schizophrenia with multiple antipsychotics increases the side effect burden with the possible exceptions of aripiprazole and clozapine. (LO #3)
   [ ] a. True [ ] b. False

5. What is the optimal starting dose for buspirone? (LO #1)
   [ ] a. 2 mg bid [ ] b. 3–5 mg bid [ ] c. 5–7.5 mg bid [ ] d. 8 mg bid

Stimulants and Creativity

Continued from page 5

each patient, and—at least anecdotally—can be fine-tuned by adjusting the dose.

TCPR VERDICT: Pay attention when patients with ADHD report that they feel hyperfocused or less creative on their stimulant. It could be true, and a dose reduction can help patients shift more flexibly from tedious, detail-oriented tasks to those that require more creative flow. In addition, judicious use of immediate-release medications may help creative individuals who could benefit from short-acting stimulants for targeted activities (such as paying bills) but don't need the effect in creative situations. There's no evidence that stimulants improve creative thinking, and they may dampen it in creative people.

*Answer: Hogs

To learn more, listen to our 1/11/21 podcast, "Cognitive Enhancers: The Brain on Chess." Search for "Carlat" on your podcast store.

In Brief: Does Abilify cause more weight gain than Seroquel?

Last October, we published a table on mood stabilizer side effects that raised an understandable alarm among astute readers. The table, which was based on a 2020 meta-analysis, suggested that aripiprazole (Abilify) has a greater chance of causing weight gain than quetiapine (Seroquel). What the table failed to specify was that the figures were based on long-term maintenance studies. In the short-term trials, quetiapine ranked right behind olanzapine for its propensity to increase BMI, while aripiprazole had a non-significant effect.

Mood stabilizers are intended for long-term use, which is why we decided to focus on the long-term data. However, there are far more short-term trials than long-term ones, so we are less confident in these results. In this meta-analysis, the difference between aripiprazole and quetiapine was based on only 3 bipolar maintenance trials (n = 773). Things become more certain when we expand that population to all psychiatric patients, as Maarten Bak and colleagues did in 2014 (Bak M et al, *PLoS One* 2014;9(4):e94112). Pulling together 11 trials that lasted at least 9 months, Bak found similar rates of weight gain for aripiprazole and quetiapine, both in terms of the rate of clinically significant (> 7%) weight gain (1 in 5 for both meds, compared to 1 in 25 for placebo) and the absolute increase in BMI.

Look out for long-term weight gain in your patients. Most of what we know about this side effect comes from short-term trials, and those may not tell the whole story.

To learn about behavioral activation for depression, listen to our 2/1/21 podcast, "The Antidepressant Calendar: How to 'Just Do It.'" Search for "Carlat" on your podcast store.

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

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February 2021

Next Issue:
Stopping Psych Meds Part 2
March 2021

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Anxiety Roundup

CBT for Benzo Withdrawal. Medications have largely proven unsuccessful for benzodiazepine withdrawal, but CBT looked promising in this meta-analysis of three randomized controlled trials. Compared to gradual tapering without CBT, the addition of this psychotherapy allowed an extra 1 in 3 patients to successfully come off their benzodiazepine. A therapist and patient guide to this therapy is available through the Treatments That Work series (*Stopping Anxiety Medication,* 2009) (Takeshima M et al, *Psychiatry Clin Neurosci* 2021 Jan 15).

Silexan Lacks Abuse Potential. In August 2020 we covered Silexan, a proprietary lavender extract, suggesting it had an effect comparable to benzodiazepines but without their addictive potential. Silexan's lack of rewarding qualities was recently confirmed in a randomized controlled trial that allowed 40 recreational users of sedatives to try Silexan (80 and 640 mg), lorazepam (2 and 4 mg), or placebo. Silexan's rewarding and sedative qualities were about equal to placebo and a long way away from lorazepam (Seifritz E et al, *Int J Neuropsychopharmacol* 2020 Dec 10;pyaa064).

Cats Reduce Anxiety in Autism. This small trial randomized 11 children with autism to adopt a cat or continue with treatment as usual. After 18 weeks, cat adoption reduced anxiety, hyperactivity, and externalizing/bullying behaviors, and increased empathy. A practical tip: Cats were screened for calmness and docility with the Feline Temperament Profile (available at www.thecarlatreport.com/feline) (Carlisle GK et al, *J Pediatr Nurs* 2020;58:28–35).