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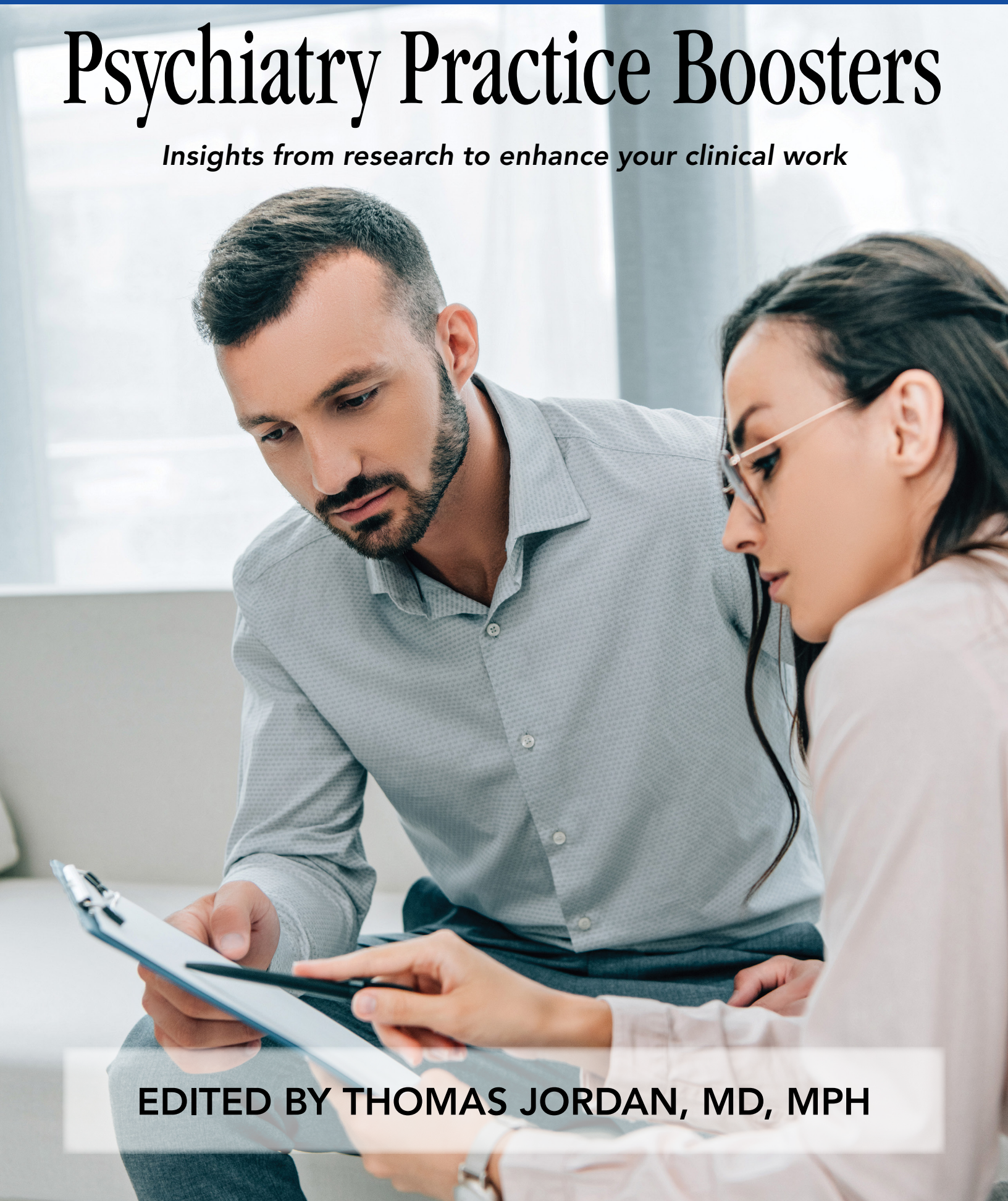
Psychiatry Practice Boosters

Insights from research to enhance your clinical work



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Carlat Psychiatry

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Acknowledgments

This second edition of *Psychiatry Practice Boosters* continues in the tradition of the first by adapting the research updates published in the Carlat family of newsletters (*The Carlat Psychiatry Report, The Carlat Child Psychiatry Report,* and *The Carlat Addiction Treatment Report*) over the past two years. We have expanded our cadre of research update authors with many new names and voices to distill for you the latest in psychiatric publications. Many thanks to the authors of the original research updates: Ricardo Arechiga, PharmD, Ariana Ayon Verduzco, PharmD, Rehan Aziz, MD, Jean Baker, MS, RD, Daniel Carlat, MD, Candace Good, MD, Bret A. Moore, Psy.D, ABPP, Taylor W. Noriega, PharmD, Kirsten Pickard, BA, Colleen Ryan, MD, Adam Strassberg, MD, and Shirley Y. Tsai, PharmD. Special thanks to the editors reviewing the manuscript: Daniel Carlat, MD, Talia Puzantian, PharmD, BCPP, and Janice Jutras.

Introduction

If you are like most practicing psychiatrists, you might tend to develop a fairly standardized approach to treating patients. Over the years, it can become easy for your knowledge to stagnate. Especially for those working independently or in a small practice, it can be difficult to keep up with changing standards of care and new data. Yet, staying up to date with current literature is critical to providing good care. To help you keep track of recently published papers and avoid feeling overwhelmed, we've chosen the journal articles that are most impactful for clinical practice. In addition, we translate the statistical language into something easier to understand, allowing you to evaluate what change (if any) you should make to your clinical practice.

The articles appearing in this second edition of *Psychiatry Practice Boosters* are gleaned from the past two years of research updates. Some of them are newer studies that build upon those of the first edition, like the congenital risk of malformations with antipsychotic medications or the cardiovascular effects of higher doses of citalopram. Most are completely new topics for this edition, including ketamine for depression, effects of adolescent vaping, and strategies for managing opioid addiction.

HOW TO READ THESE UPDATES

We start by telling you where you can find the original study, and then we tell you what kind of study design it is. (See the introductory section on research design so that you'll actually understand the jargon.) The first paragraph of each update provides some context about the disorder or treatment being studied, and that's followed by a paragraph or two on the methodology of the study. We devote a paragraph to the results, followed by "The Carlat Take," which is our evaluation of the study's strengths or weaknesses—basically, this indicates whether we believe what the researchers have to say. Finally, we wrap up with "Practice Implications," a couple of lines telling you what, if anything, we think you should do differently in your practice as a result of the study findings.

Whether you should change your practice based on a single study is a matter of judgment, and you're welcome to disagree with our suggestions. Generally, if a clinical trial is very large and shows a marked advantage of a new treatment over placebo (or another treatment), there won't be a lot of debate—the treatment should find its way into your toolbox. But usually it's not so clear-cut. If a study is small, we only err on the side of recommending a new treatment if the intervention (usually a medication) doesn't have a lot of bad side effects, and/or if there aren't many good treatments for the condition targeted. In some cases, if the study is too small or its results are somehow problematic, we may take a wait-and-see approach.

A Quick Primer on Study Design and Statistics

Research articles are, by definition, chock-full of jargon describing research design and statistics. For those of you who need a quick refresher on this specialized vocabulary, here's a review of some of the most important topics.

HOW TO READ A RESEARCH ARTICLE

As you read a research article, you'll want to structure the information so that you can accurately absorb its essence as quickly as possible. Here's one approach you might find helpful. (This section was adapted from the article "How to Read a Journal Article," by Dr. Jeffrey Barkin, originally published in *TCPR*, Feb 2007.)

1. Who funded the study?

If a study is funded by a drug manufacturer, it is more likely to report results favorable to the sponsor's drug than studies funded by other sources (Lundh A et al, *Cochrane Database Syst Rev* 2012;12:MR000033). The reasons for this are not necessarily nefarious. Industry-funded studies are often very well-designed, with large numbers of subjects and gold-standard research methods. Companies may obtain so many positive results because they are picky about which drugs they will study. Often they will start with very small feasibility studies before deciding that a particular compound is worth the financial outlay for a large randomized trial. On the other hand, company-paid scientists sometimes engage in research trickery, such as setting up a control group for failure by providing a too-low dose of a comparison drug, or changing their statistical analysis after the fact to make their drug look better. While industry-funded studies can be well-designed and valuable, you will need to give the conclusions more scrutiny than those funded by more objective sources, such as NIMH or private foundations. Not that NIMH researchers are completely free of bias—you need to scrutinize their research too!

2. Are the patients being studied similar to the patients you treat?

Most randomized, placebo-controlled trials have such strict inclusion criteria that their results may not necessarily apply to the patients in your office. For example, antidepressant trials often exclude patients with symptoms that are too mild or too severe, or patients with comorbid substance use, bipolar disorder, psychosis, or suicidality. One study concluded that patients who make it into research trials represent only about 20% of the patients that real clinicians actually treat (Zimmerman M et al, *Am J Psychiatry* 2005;162(7):1370–1372).

3. What type of study design is it?

There's a hierarchy of medical evidence, from strongest to weakest. In the next section, I'll explain the different types of studies in more detail. But as an overview, the best evidence comes from **double-blind,**

randomized controlled clinical trials. If such a trial includes a placebo group, it's even better. In **open randomized trials**, patients are randomized to treatments, but there is no attempt at blinding. Both the researchers and the patients are aware of the treatments, creating more opportunities for bias. Next on our list are **observational studies**, in which patients are not randomized to different groups, but rather are observed. There are many types of observational studies, and the terminology can get confusing. A **cohort study** is a way of doing a controlled trial without having to assign subjects to groups. Here, two cohorts, or groups, are identified, one which received the treatment of interest and one which did not. Sometimes a cohort study is **prospective**, and sometimes it is **retrospective**. In a prospective cohort study, the two groups are observed prospectively (forward in time), studying the outcome under analysis for each group. A typical example of a prospective cohort study is a study of antidepressant use in pregnancy. Because of concerns of possible risks to the fetus if exposed to antidepressants, pregnant women are not randomly assigned to drug vs placebo. Instead, researchers identify women who happen to have been prescribed antidepressants and compare them with a group who have not. Since the women were not randomized to the two groups, they may differ from one another in important ways. For example, women who opted to receive antidepressants may have been more depressed than the other group. If the study finds that infants exposed to antidepressants have more neonatal problems, it would therefore not be clear if the problems were caused by the medications or by the depression itself. A **case series** is simply a description of a group of patients with a particular illness who have received a particular treatment. This is often retrospective, meaning that the author reviews old charts to extract information on a series of similar patients. Like open-label studies, these reports are suggestive but not definitive.

4. What are the identified primary and secondary outcomes of the study?

Studies are typically designed to assess one or two primary outcomes, such as percent change in the Hamilton depression scale, rate of remission, or time to treatment discontinuation. These outcomes are generally chosen because they are the most clinically relevant measures. If the primary outcomes do not reveal a difference between two groups, the authors will move on to a number of less relevant secondary outcome measures. There's nothing wrong with reporting secondary outcome measures—up to a point. Reporting too many extra outcomes can devolve into a statistical "fishing expedition," wherein a statistically significant difference is likely to eventually appear by chance alone. For this reason, savvy readers will focus on the results of predefined primary outcomes.

5. How did the study deal with patients who dropped out?

Many research patients drop out for various reasons, such as adverse events or clinical worsening, and there are different ways to account for these. The most conservative is called LOCF, or last observation carried forward. Here, each subject's last score is included, regardless of when the subject dropped out. As you can imagine, if a medication causes many early dropouts, the LOCF method will tend to drag the final average depression score down, making the medication appear relatively less effective. This is precisely the kind of information we need to know as clinicians, because the ideal medication should be both efficacious and well-tolerated. By contrast, the weaker method of reporting results is called OC, or observed cases. Here, only the subjects who stayed in the study until the very end are counted, ignoring

all dropouts. Somewhere between LOCF and OC is a complex statistical technique called MMRM, or mixed model repeated measures. Here, patients who dropped out are compared with similar patients who completed the study, and their scores are statistically extrapolated based on these comparisons.

6. Are the results both statistically and clinically significant?

Studies that enroll very large numbers of subjects may report advantages of a medication that are statistically significant but of only marginal clinical significance. For example, the rates of nausea for one antidepressant may be 50% but "only" 45% for the competitor, a result reported as "statistically significant" but of dubious clinical significance. These days, most studies will report effect sizes in addition to statistical significance. Effect sizes give you a better sense of the clinical significance of a new treatment. We get into more detail on these issues later in this section.

THE RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY: A DEEP DIVE

To begin with, let's decipher every researcher's favorite phrase: "A randomized, placebo-controlled, double-blind trial." This is sometimes abbreviated to "randomized controlled trial," or "RCT." The RCT is the gold standard of research studies, and many of our research updates summarize studies designed this way, so it's important that you understand exactly what the term means.

"Randomized"

If you want to fairly test whether one medication works better than placebo, or better than another medication, the patients chosen for the different study arms should be as equivalent as possible. Obviously, if the patients in the treatment group are much less depressed than those in the placebo group, a finding in favor of the antidepressant means very little. The easiest way of balancing the two arms of a study is to randomly assign patients to one group or the other, usually by using a computer equivalent of drawing straws. In most papers, the authors will create a table comparing the baseline characteristics of the active group vs the placebo group, just to prove that their random assignment worked well—or to show that it didn't work so well after all.

"Placebo-controlled"

As clinicians, we see patients improving on medications all the time, but we are savvy enough to realize that many non-medication factors may be at play: positive expectation, changes in the patient's life, sessions with an outside therapist, the desire of patients to please you by saying they've improved even if they haven't, etc. All of these nonspecific or "placebo" factors come into play in research as well. A placebo control group allows us to measure the degree of nonspecific improvement vs medication improvement.

Uncontrolled studies and some open-label studies have neither a placebo control nor an active drug control. Generally, uncontrolled studies yield response rates that are much higher than those in controlled studies. Why is this so? After all, the presence or absence of a control group shouldn't affect

the response rate of a completely separate group of patients who are given active treatment, should it? Oh, but it does, and the reason is that studies which include placebo groups are almost always (this is a teaser for the next paragraph) double-blinded.

"Double-blind"

The purpose of a placebo group is to see how well patients do when they believe they are getting a particular treatment, but are actually getting a sugar pill or some other nonspecific remedy. If they knew they were swallowing a placebo, they might very well still improve—from a sugar high, the passage of time, or other factors. But then a big part of the cure—the effects of the patients' faith in the prescription—would not be measured. So patients have to be fooled, and this is done by "blinding," a brutal term referring to the benign art of disguising the placebo pill as the active medication.

But keeping patients blind to the treatment is only one part of the story. The "double" in double-blind refers to the researcher, too, being in the dark about which treatment patients are receiving. If a researcher knows that a particular patient is taking active medication, this knowledge may bias the evaluation of the patient's degree of improvement. Thus, double-blinding seeks to improve studies in two ways: first, by making the placebo group a more effective measure of nonspecific effects; and second, by reducing potential research bias.

You'll often hear studies referred to as "closed-label"—this is equivalent to double-blinding, in that the "label" identifying the pill is "closed" to patients and researchers. On the other hand, the "open-label" study is one in which patients know exactly what they're getting and researchers know exactly what they're dishing out. We've just said that this is not a great way of designing a clinical trial, so why are so many open-label studies published? Because they're much easier and cheaper to conduct, basically. Nor are they devoid of value: Often an initial uncontrolled, open-label study identifies a drug as having promise for a given diagnosis, leading to a larger controlled study later on.

What about single-blind studies? Usually these are studies that compare two active drugs for a condition without including a placebo group. The patients know what they are taking. The doctor knows what the patients are getting. The only one who is blind is the rater, who is the one assessing the degree of clinical improvement using structured rating scales. As you can surmise, such a design leaves plenty of room for placebo confounding of results, especially when the investigator is being funded by a company that makes one of the drugs in question.

Non-pharmacologic trials. The randomized clinical trial model most often involves a pharmacologic intervention where blinding and placebo control groups are relatively easy to set up. But what about non-pharmacologic clinical trials, such as studies on mindfulness therapy or internet-based CBT? In these cases, using a classic placebo control group is not an option. The control group can instead be set up with a different psychotherapy intervention, placement on a waitlist, or even a pharmacologic intervention that's already shown efficacy in the disorder being studied. Standardization of treatment intervention is very important, and the study will often mention the training of treatment providers or the use of manual-based therapies. Double-blinding the study is also a problem, as it's often impossible to blind the treatment provider or the patient receiving the therapy intervention, but single-blinding of the researcher administering the rating scales is standard practice.

STATISTICAL SIGNIFICANCE: WHAT DOES IT MEAN?

You won't get very far into any journal before you start reading about statistical significance and its close sibling, 95% confidence intervals. But what do these terms mean, and how do they help us draw conclusions about studies?

Let's say you are going old-school and doing a study comparing Prozac with placebo. Yes, it's been done before, but you want to make sure. Your primary outcome measure is the response rate, as measured by the trusty Hamilton depression scale. You find that 60 of 100 people on Prozac responded vs only 40 of 100 people on placebo. 60% is better than 40%, so you've once again proven that Prozac is an effective antidepressant, right? Not necessarily. It's possible that Prozac and placebo are equally effective, but that by pure chance 6 out of 10 people assigned to Prozac got better. An analogy is coin flipping. If you flipped a coin 10 times and got heads 6 times, would you automatically conclude that the coin is rigged—ie, that it is more effective at producing heads than tails? Probably not, because you'd expect that out of 10 coin tosses you might get more heads than tails or vice versa. But what if you tossed the coin 100 times? If you got 60 heads and 40 tails, you'd start to get suspicious that the coin is weighted toward heads. It's pretty unlikely that you'd get 60 heads by chance alone. Not impossible, mind you, but pretty unlikely.

Similarly, it's pretty unlikely, though not impossible, that you got a 60% response rate on Prozac by chance alone. The question that statistical significance aims to answer is, "Exactly how unlikely is it that this result is due to chance alone?" Let's say you do all your statistics and find that the difference between Prozac and placebo is statistically significant ($p = 0.03$). In this sentence, the "p" is for probability, meaning the probability that this difference occurred by chance alone (making it not a "real" finding) is 3 out of 100, or 0.03, or only 3%. The standard cutoff point for statistical significance is $p = 0.05$, or a 5% probability that the results occurred by chance, so you can feel confident calling your results significant.

You will often see studies in which results are reported like this: "The difference between Drug A and Drug B showed a trend toward statistical significance ($p = 0.06$)." This means that the results didn't quite meet the crucial 0.05 threshold, but they came close. Why is 5% the magic number? As befits an arbitrary number, its choice was also somewhat arbitrary. In 1926, R. A. Fisher, one of the fathers of modern statistics, wrote an article in which he argued that it was "convenient" to choose this cutoff point, for a variety of reasons related to standard deviations and the like (for more information, see Dallal GE, *The Little Handbook of Statistical Practice* at http://www.jerrydallal.com/LHSP/LHSP.HTM). This number has stood the test of time throughout all the scientific disciplines. Why? Because it has some intuitive appeal.

Look at it this way: Before we accept a finding as scientific fact, we want to be pretty certain that it didn't occur through some coincidence of random factors. But how certain is "pretty certain?" Would 80% certainty ($p = 0.2$) be enough for you? Probably not. Most doctors would not feel comfortable basing important treatment decisions on only an 80% certainty that a treatment is effective. Much better would be 99% certainty ($p = 0.01$), but if that were the required threshold, very few treatments would be shown as significantly better than placebo, and hence we would have very little to offer our patients.

It just so happens that 95% certainty has felt right to scientists through the last 50 years or so. Of course it's arbitrary, but if we don't agree on some threshold, we open ourselves up to researchers creating their own threshold values depending on how strongly they want to push acceptance of their data (and some still do this anyway). Because the scientific community has settled upon p = 0.05, the term "statistical significance" has a certain, well, significance!

That being said, you, as a reader and clinician, have every right to look at a study reporting p = 0.06 and say to yourself, "There's only a 6/100 chance that this was a coincidental finding. It may not meet the 0.05 threshold, but, at least in this clinical situation, that's good enough for me, so I think I'll try this treatment."

WHAT'S AN EFFECT SIZE?

Knowing that the apparent advantage of Prozac over placebo in these patients is statistically significant is all well and good. But how do we get a handle on measuring how strong this advantage is? This is where effect size comes into play. The effect size is the size of a statistically significant difference. To calculate it, you divide the difference between the two treatment groups' outcome measures by the standard deviation. (Sorry, I'm not going to define standard deviation, since understanding this is not crucial for a basic comprehension of effect size.)

If the effect size is 0, this implies that the mean score for the treatment group was the same as the comparison group, ie, no effect at all. And just as obviously, the higher the effect size, the stronger the effect of treatment. Here are the standard benchmarks: effect sizes of 0 to 0.3 represent little to no effect, 0.3 to 0.6 a small effect, 0.6 to 0.8 a moderate effect, and 0.8 or greater a strong effect.

Here's an example of an effect size calculation. If the reduction in Hamilton depression score was 7.6 in the Prozac group and 4.4 in the placebo group, and the standard deviation was reported to be 3.9, the calculation for effect size would be: (7.6 – 4.4) / 3.9 = 0.82, which is a strong effect size in favor of Prozac.

BIBLIOGRAPHY

I've found two books to be extremely helpful in explaining research design. If you want to deepen your understanding of the topics I've touched on above, I suggest you read these.

Gehlbach SH. *Interpreting the Medical Literature.* 5th ed. New York, NY: McGraw-Hill Education / Medical; 2006.

Ghaemi SN. *A Clinician's Guide to Statistics and Epidemiology in Mental Health.* New York, NY: Cambridge University Press; 2009.

MOOD DISORDERS

Does Vagus Nerve Stimulation Work for Treatment-Resistant Depression?

REVIEW OF: Aaronson ST, Sears P, Ruvuna F, et al. A 5-year observational study of patients with treatment-resistant depression treated with vagus nerve stimulation or treatment as usual: comparison of response, remission, and suicidality. *Am J Psychiatry*. 2017;174(7):640–648. doi:10.1176/appi.ajp.2017.16010034.

STUDY TYPE: Prospective cohort study

Treatment-resistant depression (TRD) is typically defined as a major depression that fails to remit after at least 2 trials of 2 different classes of antidepressants. Other than electroconvulsive therapy (ECT), there remain few evidence-based biological treatment options for TRD.

In 2005, the FDA approved vagus nerve stimulation (VNS), where a small stimulator device is surgically implanted in the chest, with 3 small electrodes wrapped around the vagus nerve. The device was originally approved for use with treatment-refractory epilepsy, although the approval was very controversial due to the poor quality of the data. As a condition of approval, the FDA required post-marketing surveillance, and so the Treatment-Resistant Depression Registry was established.

The authors of this 5-year longitudinal observational study, conducted at 61 separate U.S. sites, used the registry to follow the clinical course and outcome of 2 large groups of patients diagnosed with TRD. One group received adjunctive VNS, and the other group received treatment as usual (TAU).

The patients could select their treatment—VNS or TAU—and 795 patients were included (494 patients in the VNS arm and 301 in the TAU arm). All patients had previously failed 4 or more treatments, with an average of 8.2 failed treatments. Response was defined as a decrease of ≥ 50% in baseline Montgomery-Åsberg Depression Rating Scale (MADRS) score, and remission was based on a MADRS score ≤ 9.

RESULTS

The adjunctive VNS group had better clinical outcomes than the TAU group, including a significantly higher 5-year cumulative response rate (67.6% compared to 40.9%, $p < 0.001$), and a significantly higher remission rate (43.3% compared to 25.7%, $p < 0.001$).

THE CARLAT TAKE

This study suggests that VNS is effective for TRD, but this treatment does not work quickly. Differences did not emerge until 6–9 months after treatment. Further, the study design had many limitations. Patients were not randomly assigned to treatment groups, there was no sham "placebo" comparison, and neither patients nor researchers were blinded to treatment. In addition, the study was funded by Cyberonics, the manufacturer of the device. While commercial

funding does not necessarily imply that a study's results are invalid, it does behoove us to give the results extra scrutiny.

PRACTICE IMPLICATIONS

VNS is a complicated surgical procedure requiring a large investment in both time and money. Whether the potential benefits are worth the costs must be weighed individually for each patient. This study does suggest, however, that VNS is a potentially useful treatment for a small group of patients with treatment-refractory depression.

Switching Antidepressants May Be No Better Than Staying the Course

REVIEW OF: Bschor T, Kern H, Henssler J, Baethge C. Switching the antidepressant after nonresponse in adults with major depression: a systematic literature search and meta-analysis. *J Clin Psychiatry*. 2018;79(1):16r10749. doi:10.4088/JCP.16r10749.

STUDY TYPE: Meta-analysis of randomized, active-controlled trials

Clinical trials have shown that the response rate of major depression to a course of antidepressants is 50%–70%. After a non-response, what should we do? Increase the dose? Switch to another medication? Augment with a different one? Unfortunately, we have remarkably little to guide us in the way of empirical studies. The largest "real-world" study of antidepressants, the oft-cited STAR*D trial, enrolled plenty of patients and compared various strategies (Rush AJ et al, *Am J Psychiatry* 2006;163(11):1905–1917). Unfortunately, that study was limited because there was no placebo group, and patients were not fully randomized to group assignments.

The authors of this meta-analysis sought evidence to answer a specific question: Is it better to stay the course with the original antidepressant, or is it better to switch? They searched the literature for studies that enrolled patients with major depressive disorder who did not respond to at least a 2-week trial of an antidepressant. These patients were then randomly assigned to either a continuation of the same medication or a switch to a different one. They found 8 relevant studies, and a combined 783 patients were randomized to continuation arms while 844 were assigned to switching arms. Some of the studies blinded participants to their treatment, but others did not; the follow-up lasted from 4 to 12 weeks, depending on the study.

The studies spanned a long time period, with the oldest published in 2001 and the most recent in 2014. Medications compared included the following (listed in order of continuation medication, switched-to medication): fluoxetine, mianserin; nortriptyline, fluoxetine; venlafaxine, fluoxetine; escitalopram, duloxetine (2 studies); various SSRIs, duloxetine; various SSRIs, mirtazapine; desipramine or citalopram, desipramine or citalopram.

RESULTS

There were no statistically significant differences between patients who continued vs those who switched medications. This was true both for the primary outcome of change in depression scale score and for the secondary outcomes of response rate and remission rate.

THE CARLAT TAKE

This is the largest and best study yet looking at whether it's better to switch antidepressants or stay the course, and the implication is that there is no advantage to switching. The studies

included a variety of switch strategies, from within-class changes to switching to an antidepressant with a different mechanism of action.

PRACTICE IMPLICATIONS

When patients do not respond to an antidepressant, you may be tempted to switch to another one and then rotate through your list of favorites. But given the surprising finding that switching antidepressants incurs no discernible benefit, you may want to instead consider augmentation strategies or a psychotherapy referral.

Statins and SSRIs Together Lead to Better Outcomes in Depression

REVIEW OF: Köhler O, Gasse C, Petersen L, et al. The effect of concomitant treatment with SSRIs and statins: a population-based study. *Am J Psychiatry*. 2016;173(8):807–815. doi:10.1176/appi.ajp.2016.15040463.

STUDY TYPE: Retrospective cohort study

Is depression a disorder of inflammation? This intriguing hypothesis has been floating around in the literature over the past few years. Thus far, the findings are suggestive but not definitive. For instance, one marker of inflammation, C-reactive protein, was found to be higher in people with psychological distress and depression (Wium-Andersen MK et al, *JAMA Psychiatry* 2013;70(2):176–184). In addition, small clinical trials have shown that adding anti-inflammatory medications (such as celecoxib and the statin lovastatin) to antidepressants is more effective than adding placebo. But we need more data before we start routinely prescribing these meds to our depressed patients.

While statins are used primarily to lower cholesterol, they also have direct anti-inflammatory effects. In order to explore whether statins might augment the effects of SSRIs, researchers from Denmark mined data from the Danish National Prescription Registry, a national database that collects information on all prescription medications picked up at pharmacies across the country. Between 1997 and 2012, a total of 872,216 patients started SSRIs, of whom 113,108 (13%) also took a statin drug at the same time. The two groups were compared on the following outcomes: rate of psychiatric hospital contacts (any reason), psychiatric hospital contacts related to depression, suicidality, and overall mortality.

RESULTS

Compared to SSRIs alone, those in the combined SSRI and statin group were 36% less likely to present to a psychiatric hospital specifically for depression. They were also 25% less likely to show up at a psychiatric hospital for any reason. Statin users had no increased risk of suicidality, an important finding given that earlier data suggested a connection between lowered cholesterol and suicide risk.

THE CARLAT TAKE

This is a strong study because it analyzed data from literally all people in Denmark who had been on an SSRI over a 15-year period. Therefore, we can be certain that any findings from this sample are generalizable to the Danish population as a whole. However, since it is an observational study, it's not clear that statin use actually caused less depression; there may be other factors responsible. For example, patients who received statins may have made healthy lifestyle changes to combat high cholesterol, such as exercising more. We know that exercise is good for mood, so this could be one confounding factor among others. The authors statistically controlled for many confounders, but they did not control for diet or exercise.

PRACTICE IMPLICATIONS

The study is intriguing, but it's probably too soon to start augmenting SSRIs with statins as a treatment for depression. We need more clinical trial data. On the other hand, you might want to share the results of this study with your patients who are considering going on statins for hyperlipidemia but are ambivalent. These data are a check mark in the positive column.

A Cautionary Consensus on the Use of Ketamine for Depression

REVIEW OF: **Sanacora G, Frye MA, McDonald W, et al. A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry*. 2017;74(4):399–405. doi:10.1001/jamapsychiatry.2017.0080.**

STUDY TYPE: **Systematic review of double-blind, randomized, placebo-controlled trials**

Ketamine has become increasingly popular as an off-label medication for rapid treatment of refractory depression. Recently, the American Psychiatric Association convened a task force to review the data and come up with some recommendations. The task force reviewed 7 double-blind, randomized, placebo-controlled trials involving a total of 147 depressed patients.

In terms of patient selection, there are no clearly defined parameters regarding which patients are most appropriate for ketamine. The most evidence is in patients with depressive episodes without psychotic features, and the dose most often shown to be effective is 0.5 mg/kg given intravenously (IV) over 40 minutes. For perspective, the anesthesia dose ranges from 1 to 4.5 mg/kg IV. Anecdotally, the authors note that many ketamine clinics administer doses 2 to 3 times a week for 2 to 3 weeks and then taper, depending on patient response. One study showed that doses given 3 times weekly were not more effective than doses given twice weekly. Common side effects after infusion include confusion, blurred vision, and poor coordination. Because approximately 30% of patients in 3 clinical trials experienced a spike in blood pressure over 180/100 mmHg and heart rates over 110 beats per minute, it's recommended to do basic monitoring (electrocardiogram, blood pressure, O_2 saturation). Patients at a higher risk of complications (those with cardiovascular disease, those on other depressants, and elderly patients) should be treated at a facility equipped to manage cardiorespiratory events.

Some are reporting the use of lower or higher doses of ketamine, intranasal administration instead of IV, or take-home ketamine, but the authors could not find enough evidence in the literature to endorse these practices. For example, the authors describe trials using lower doses (0.1–0.4 mg/kg IV) or intranasal ketamine (50 mg/ml nasal spray), both of which seemed to show less robust efficacy.

Another unknown is how long to use ketamine. Response may be fast, but the studies reviewed by these experts showed relapse rates up to nearly 90% just 4 weeks following the ketamine treatment. We have no long-term safety data either, and the authors share concerns about some of the known risks, such as cognitive impairment or abuse.

THE CARLAT TAKE

Overall, the consensus statement makes one thing clear: We need more data. Though the rapid response is promising, the effects may be transient, and maintenance infusions may be required for some patients, similar to electroconvulsive therapy.

PRACTICE IMPLICATIONS

Consider using ketamine in severe, refractory, or suicidal depression without psychotic features, at a dose of 0.5 mg/kg IV over 40 minutes. Schedule infusions twice a week for up to 4 weeks, while monitoring for relapses of depression. Ketamine may be particularly useful in patients who are not good candidates for electroconvulsive therapy.

Celecoxib as Adjunctive Treatment in Acute Mania

REVIEW OF: Mousavi SY, Khezri R, Karkhaneh-Yousefi MA, et al. A randomized, double-blind placebo-controlled trial on effectiveness and safety of celecoxib adjunctive therapy in adolescents with acute bipolar mania. *J Child Adolesc Psychopharmacol*. 2017;27(6):494–500. doi:10.1089/cap.2016.0207.

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

Emotional stress can trigger an inflammatory cascade response and increase blood levels of proinflammatory cytokines—including IL-1, IL-6, and tumor necrosis factor (TNF-α). These same inflammatory markers intensify in acute episodes of depression and mania. So, would blocking the inflammatory cascade aid in treating acute episodes of mood disorders?

Celecoxib works by selective inhibition of cyclooxygenase-2 and reducing prostaglandin synthesis. The authors of this research previously demonstrated positive benefit during trials of celecoxib as an adjunctive treatment in adults with acute bipolar mania, obsessive compulsive disorder, and depression. This study explores the safety and efficacy of celecoxib in treating acute mania in adolescents.

This study was an 8-week, randomized, double-blind, placebo-controlled, parallel-group clinical trial conducted at an inpatient psychiatric hospital with 40 adolescents (ages 12–17). The subjects met criteria for a moderate to severe episode of bipolar mania without psychosis. In the treatment protocol, all adolescents received treatment with lithium (target blood level of 0.8–1.1) and risperidone (1 mg per day, then increasing to 3 mg per day). The treatment group also received celecoxib (100 mg twice daily), while the control group received a placebo over an 8-week period. Treatment started in the hospital setting, then continued in an outpatient clinic when the patients were ready for discharge.

RESULTS

The primary outcome was change in the Young Mania Rating Scale (YMRS), measured at baseline and at weeks 2, 4, and 8. At week 8, there was a significant difference in the change in YMRS scores between the celecoxib and control groups ($p = 0.04$). A secondary outcome measured was the Clinical Global Impressions—Improvement (CGI-I) scale: There was a trend in favor of the celecoxib group that did not reach significance ($p = 0.09$). For the safety analysis, the most common adverse events reported were increased appetite and dry mouth, but there were no significant differences between the groups in any of the reported adverse events. Cardiovascular health was also monitored by physical exam and electrocardiogram, and no patient experienced a cardiovascular event during the study.

THE CARLAT TAKE

Reducing the inflammatory cascade as part of the treatment for mood disorders is garnering more traction in the mental health community. This study is another mark in the positive

column, particularly for celecoxib. Other anti-inflammatory medications are also being looked at, including the statins and N-acetylcysteine.

PRACTICE IMPLICATIONS

While the idea of reducing inflammation as part of the treatment regimen for a manic episode shows promise, more research is necessary before recommending use of celecoxib. The data show that celecoxib may be helpful in the acute treatment of a mood episode, but how long should treatment last? Should we follow blood levels of inflammatory markers to guide treatment? What are the risks of longer-term treatment? More studies are needed to answer these questions.

Lithium Favored in Treatment Effectiveness Study of Bipolar Disorder

REVIEW OF: Lähteenvuo M, Tanskanen A, Taipale H, et al. Real-world effectiveness of pharmacologic treatments for the prevention of rehospitalization in a Finnish nationwide cohort of patients with bipolar disorder. *JAMA Psychiatry*. 2018;75(4):347–355. doi:10.1001/jamapsychiatry.2017.4711.

STUDY TYPE: Retrospective cohort study

A new study from Finland shows that lithium may be more effective than other treatments in reducing the risk of psychiatric rehospitalization in patients with bipolar disorder. Using a nationwide Finnish database, the authors examined the risk of rehospitalization for 18,000 patients with bipolar disorder—including psychiatric, cardiovascular, and all-cause hospitalization—from January 1, 1987 to December 31, 2012, then determined the risk of a rehospitalization based on the patients' use of various medications.

RESULTS

Over the study period, 9,721 of the patients (54%) suffered at least 1 psychiatric rehospitalization. Patients on lithium had the lowest risk for all-cause rehospitalization (hazard ratio [HR] 0.71 [95% CI, 0.66–0.76]) and a robust effect for psychiatric rehospitalization (HR 0.67 [95% CI, 0.60–0.73]).

In addition to the findings on lithium, researchers also revealed the following about other psychotropic treatments:

- Long-acting injectable formulations of antipsychotic medications were more effective than their oral antipsychotic counterparts at reducing the risk of psychiatric rehospitalization (HR 0.70 [95% CI, 0.55–0.90]).
- Quetiapine fumarate, the most frequently used antipsychotic treatment in the population, was only modestly effective at reducing the risk of psychiatric rehospitalization (HR 0.92 [95% CI, 0.85–0.98]).
- Benzodiazepines were linked to an increased risk for both psychiatric and all-cause rehospitalization (HR 1.19 [95% CI, 1.12–1.26]).

THE CARLAT TAKE

Although most of our treatment guidelines are based on randomized controlled trials, observational studies have many important findings to contribute to evidence-based medicine, and they are an alternative means to gauge effectiveness of various treatments.

PRACTICE IMPLICATIONS

The study findings correlate well with our clinical and anecdotal experience. Lithium is highly effective for bipolar disorder and should be a first-line treatment; it is also particularly effective for maintenance therapy. Long-acting antipsychotics may be more effective than their corresponding oral agents in preventing rehospitalizations, and we should consider their use whenever feasible. Long-term benzodiazepine use remains risky and problematic.

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ADHD

Neurofeedback and Adult ADHD

REVIEW OF: Schönenberg M, Wiedemann E, Schneidt A, et al. Neurofeedback, sham neurofeedback, and cognitive-behavioural group therapy in adults with attention-deficit hyperactivity disorder: a triple-blind, randomised, controlled trial. *Lancet Psychiatry*. 2017;4(9):673–684. doi:10.1016/S2215-0366(17)30291-2.

STUDY TYPE: Randomized, triple-blind, sham-controlled trial

With neurofeedback, patients are hooked up to an electroencephalogram (EEG) and shown images through various forms of media. The idea is that the EEG can detect brain waves that are associated with improvement in various symptoms, and then the patient can be taught to produce "healthier" brain waves. Some studies have shown that neurofeedback improves ADHD in children and adolescents. However, the results are controversial, and neurofeedback in general needs further research to prove its efficacy.

This investigation tested neurofeedback treatment in adults. The triple-blinded, randomized controlled study was conducted at Germany's University of Tübingen. Eligible participants met the DSM-IV TR criteria for ADHD, were ages 18–60, and had no or stable use of medication.

Overall, 118 people were randomly assigned to neurofeedback (38), sham neurofeedback (39), or meta-cognitive group therapy (41). In the neurofeedback group, participants received 30 treatments, while the sham group underwent 15 sham sessions followed by 15 treatment sessions. In the therapy arm, patients attended 12 weekly group therapy sessions. The primary outcome was scores on the Conners' Adult ADHD Rating Scale (CAARS), assessed before treatment, at mid-treatment (8 weeks), after treatment (16 weeks), and 6 months later.

RESULTS

Significant improvement on the CAARS from pre-treatment to the 6-month follow-up was observed for all treatment groups. For the neurofeedback group, scores dropped from 135 to 104. For sham neurofeedback, they decreased from 132 to 94. For meta-cognitive group therapy, they fell from 138 to 104. However, there were no significant differences in the drop in CAARS scores between the neurofeedback group and the sham treatment ($p = 0.168$), nor between the neurofeedback group and meta-cognitive therapy ($p = 0.639$). Clinical improvements in the neurofeedback group were unrelated to EEG brain activity changes. No serious adverse events resulted from any treatment.

THE CARLAT TAKE

These findings suggest EEG neurofeedback is not superior to a sham condition or group psychotherapy in adults with ADHD. Data supporting ADHD EEG neurofeedback remain sparse, but we're interested to see if further research proves it to be an option for adults who do not respond to medications, who have significant side effects, or who object to using medication.

PRACTICE IMPLICATIONS

Neurofeedback is expensive and time-consuming, and at this point there remains little evidence to support recommending neurofeedback for the treatment of ADHD in adults. There are simply more efficient therapies available, such as the meta-cognitive group therapy used in this study, that are at least equally as effective.

Defining a Role for Nutrition in Managing Children With ADHD

REVIEW OF: Lange KW, Hauser J, Lange KM, et al. The role of nutritional supplements in the treatment of ADHD: what the evidence says. *Curr Psychiatry Rep*. 2017;19:8. doi:10.1007/s11920-017-0762-1.

STUDY TYPE: Systematic review

Parents of kids with ADHD often ask about the role of diet and nutrition in their child's symptoms, and research has uncovered some interesting possibilities. For example, there is some evidence that concentrations of long-chain polyunsaturated fatty acids (LC-PUFAs, which includes omega-3 fatty acids) may be lower in people with ADHD. Since these PUFAs can potentially affect cognitive functions via effects on the composition of neural membranes, supplementation in those with low levels might help. Zinc, iron, and magnesium are also essential to normal brain function, so it's possible that supplemental doses of these nutrients can help alleviate symptoms and perhaps allow for reductions in medication dosages. A recent review attempted to shed some light on these questions.

A group of researchers from Germany and Japan reviewed the literature on the use of nutritional supplements for ADHD, focusing on studies published from January 2014 to April 2016. They highlighted several intriguing results, especially relating to omega-3 and omega-6 fatty acids.

RESULTS

For instance, a 16-week, randomized, double-blind, placebo-controlled trial of children with ADHD (n = 95) who received omega-3 fatty acid supplements found improved memory function but no change in behavior. A similar trial of boys ages 12–16 (n = 79) with and without ADHD found that omega-3 supplementation was associated with parent-rated improvements in attention in both groups. A meta-analysis of 10 trials (n = 699) demonstrated a significant treatment effect of omega-3 supplements, albeit modest when compared with standard pharmacotherapy. Another meta-analysis of 13 trials (n = 1,011) found some improvement with combined omega-3 and omega-6 supplementation, but no benefit with either one alone.

Less promising findings come from studies of supplemental use of zinc, iron, and magnesium. Several trials demonstrated a modest effect when zinc or magnesium was added to stimulant therapy, but the slim findings so far have not outweighed the potential for toxicity with extended use of mineral supplements in children, according to the authors.

THE CARLAT TAKE

While the authors do not specify doses used, this review adds marginal weight to the argument that supplementation with LC-PUFAs, chiefly omega-3 fatty acids, may play a role in

helping to manage symptoms in children with ADHD. Mineral supplements appear to be helpful only if there is a deficiency of that specific mineral.

PRACTICE IMPLICATIONS

For children with ADHD who are not adequately managed on standard therapy or who could potentially benefit from alternate therapy, you might consider a trial of omega-3 fatty acid supplements. To be extra thorough, check mineral levels and supplement only enough to bring levels into the normal range. However, the optimal dose of any of these supplements hasn't been fully vetted, and other more recent systematic reviews have found no benefit from either omega-3 or omega-6 fatty acids (Kemper AR et al. *Attention Deficit Hyperactivity Disorder: Diagnosis and Treatment in Children and Adolescents*. Comparative Effectiveness Review No. 203. AHRQ Publication No. 18-EHC005-EF. Rockville, MD: Agency for Healthcare Research and Quality; January 2018). So, don't expect miracles.

Can a 10-Minute Intervention Improve Sleep in Children With ADHD?

REVIEW OF: Peppers KH, Eisbach S, Atkins S, Poole JM, Derouin A. An intervention to promote sleep and reduce ADHD symptoms. *J Pediatr Health Care*. 2016;30(6):e43–e48. doi:10.1016/j.pedhc.2016.07.008.

STUDY TYPE: Open-label, non-controlled trial

We know that kids with ADHD often have sleep issues, and that the stimulants we use to treat them can cause insomnia. What would happen if we focused our treatment on the insomnia portion of ADHD? Presumably kids would sleep better, but would their ADHD symptoms also improve?

The authors of this new study based this pilot project on an earlier randomized controlled trial of a sleep intervention with 244 Australian children (Hiscock H et al, *BMJ* 2015;350:h68. doi:10.1136/bmj.h68). In that study, children with ADHD were randomly assigned to either a brief intervention to improve sleep or a control condition. Those in the intervention group were seen twice by a clinician, who evaluated the sleep problem and provided tips on sleep hygiene. Clinicians recommended a regular bedtime routine, avoidance of caffeine after 3:00 p.m., and no screen media in the bedroom. Children in the intervention group showed significant improvements in ADHD symptoms and sleep quality.

The goal of the current 20-week project was to see whether a similar intervention delivered by video and not requiring highly trained clinicians would also be successful. Twenty-three children, between 5 and 11 years of age, with both ADHD and sleep problems as assessed by the Children's Sleep Habits Questionnaire (CSHQ), were enrolled in an open, non-controlled trial. In this intervention, children and parents watched a single 6-minute video, which described good sleep hygiene practices like those in the Hiscock intervention described above. After the video, the provider gave the parents a written sleep hygiene plan. Six weeks after the intervention, the children were assessed again.

RESULTS

After 6 weeks, the children showed significant improvement in both ADHD and sleep symptoms. Improvement on the Parent Visual Analogue Scale was significant on questions 1–9 dealing with inattention ($p < 0.001$) and questions 10–18 dealing with hyperactivity ($p < 0.004$). The scores on the CSHQ showed significant improvement from baseline to the 6-week re-assessment ($p < 0.001$).

THE CARLAT TAKE

This study implies that a very brief and easy-to-administer sleep intervention may lead to improvement in both ADHD and insomnia symptoms in children. The study was limited by the lack of a control group, so it's possible that these improvements were the result of placebo factors having little to do with the intervention. In addition, there was no teacher rating of ADHD symptoms, decreasing our confidence that the improvement in those symptoms was

robust enough to be apparent in school as well as at home. The original study by Hiscock et al from 2015 is more compelling: There were a larger number of participants, and it was a randomized controlled trial.

PRACTICE IMPLICATIONS

When you evaluate patients for ADHD, make sure to ask diligently about sleep issues, and take some extra time to talk about sleep hygiene. Always have a sleep hygiene handout at the ready for parents to take home. This may pay dividends for improving sleep and ADHD symptoms.

Meds for ADHD Not Working? Add CBT

REVIEW OF: **Sprich SE, Safren SA, Finkelstein D, Remmert JE, Hammerness P. A randomized controlled trial of cognitive behavioral therapy for ADHD in medication-treated adolescents. *J Child Psychol Psychiatry*. 2016;57(11):1218–1226. doi:10.1111/jcpp.12549. Epub 2016 Mar 17.**

STUDY TYPE: **Randomized, single-blind, controlled trial**

Medication is an effective and necessary treatment for many adolescents struggling with ADHD. Unfortunately, even when patients and parents report significant relief from meds, symptoms persist, which can lead to ongoing problems at school, at home, and with peers. That's why psychosocial interventions are an important part of any treatment plan for adolescents with ADHD. Given the need for effective non-medication treatments, researchers looked at a modified form of cognitive behavioral therapy (CBT) specifically for adolescents with ADHD who were stable and doing well on meds but still had troubling symptoms.

A group of 46 adolescents ages 14–18 with ADHD who had responded only partially to medication were randomly assigned to either medication plus CBT (24 subjects) or to a therapy waitlist with medication treatment alone (22 subjects). CBT consisted of 12 weekly sessions that taught skills related to self-regulation, procrastination, negative thinking, and relapse prevention. It took, on average, 17 weeks for participants to complete the sessions. The patients who were assigned to medication alone were allowed to cross over to the CBT arm of the study after 4 months; 15 of them did so. All patients were assessed blindly at baseline, 4 months, and 8 months on 3 outcomes: parent and child ratings of symptom severity (ADHD Current Symptom Scale) and overall distress (Clinical Global Impressions Scale).

RESULTS

At the end of the 4-month treatment, CBT clearly added value. Compared to the waitlist group, average scores on parent, adolescent, and distress ratings dropped by 10.93 ($p < 0.0001$), 5.24 ($p < 0.0001$), and 1.17 ($p < 0.0001$) points, respectively. Researchers also used a 30% reduction on the ADHD rating scale to identify "treatment responders." They found that, per the parents' view, 50% of adolescents improved, and per the adolescents' view, 58% improved.

THE CARLAT TAKE

Adolescents already on ADHD medications, and not fully responding, can likely do even better with CBT. Even though no teacher evaluations were done, both child- and parent-reported symptoms improved greatly.

PRACTICE IMPLICATIONS

Consider a referral for a short course of ADHD-specific CBT for those patients with persistent symptoms on optimal medication management. However, as in all treatments, adherence is key—this study protocol offered late-afternoon and evening appointments and was liberal in rescheduling appointments that were missed or canceled.

Is Modafinil an Effective Alternative for the Treatment of ADHD?

REVIEW OF: Wang SM, Han C, Lee SJ, et al. Modafinil for the treatment of attention-deficit/hyperactivity disorder: a meta-analysis. *J Psychiatr Res*. 2017;84:292–300. doi:10.1016/j.jpsychires.2016.09.034.

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

Modafinil (Provigil) is FDA-approved for narcolepsy, obstructive sleep apnea, and shift work sleep disorder, but not for ADHD. Given that it has some of the same stimulating properties of psychostimulants, it should theoretically be effective. Wang and colleagues performed a meta-analysis of five randomized, double-blind, placebo-controlled trials (RCTs) testing modafinil for the treatment of ADHD in children and adolescents.

RESULTS

Of the 927 participants in these studies, 640 were randomly assigned to modafinil (doses ranged from 170–425 mg/day), and 287 were assigned to placebo. All five RCTs were short-term studies (all < 9 weeks). Patients on modafinil showed more improvement on ADHD scores than patients on placebo, with a standard mean difference vs placebo of -0.77 (95% CI, -1.11 to -0.44) and -0.71 (95% CI, -0.96 to -0.47) for the ADHD-RS-IV home and school versions, respectively. Modafinil patients experienced significantly more insomnia and decreased appetite than the placebo group. Four cases of serious adverse events (Stevens-Johnson syndrome, duodenitis, and 2 cases of dehydration) were reported in the modafinil group.

THE CARLAT TAKE

This meta-analysis was well-done and included high-quality RCTs, though the individual studies were each relatively small. The statistical measure here, the standard mean difference, is also known as the effect size. An effect size of -0.77 or -0.71 is moderate to large. For perspective, in previous meta-analyses, effect sizes for stimulants have been in the 0.6–0.8 range.

PRACTICE IMPLICATIONS

Modafinil appears to work about as well as stimulants for children and adolescents with ADHD. It is a good off-label option for kids who don't respond to or don't tolerate stimulants. Just be aware that there is a small (likely very small) risk of Stevens-Johnson syndrome.

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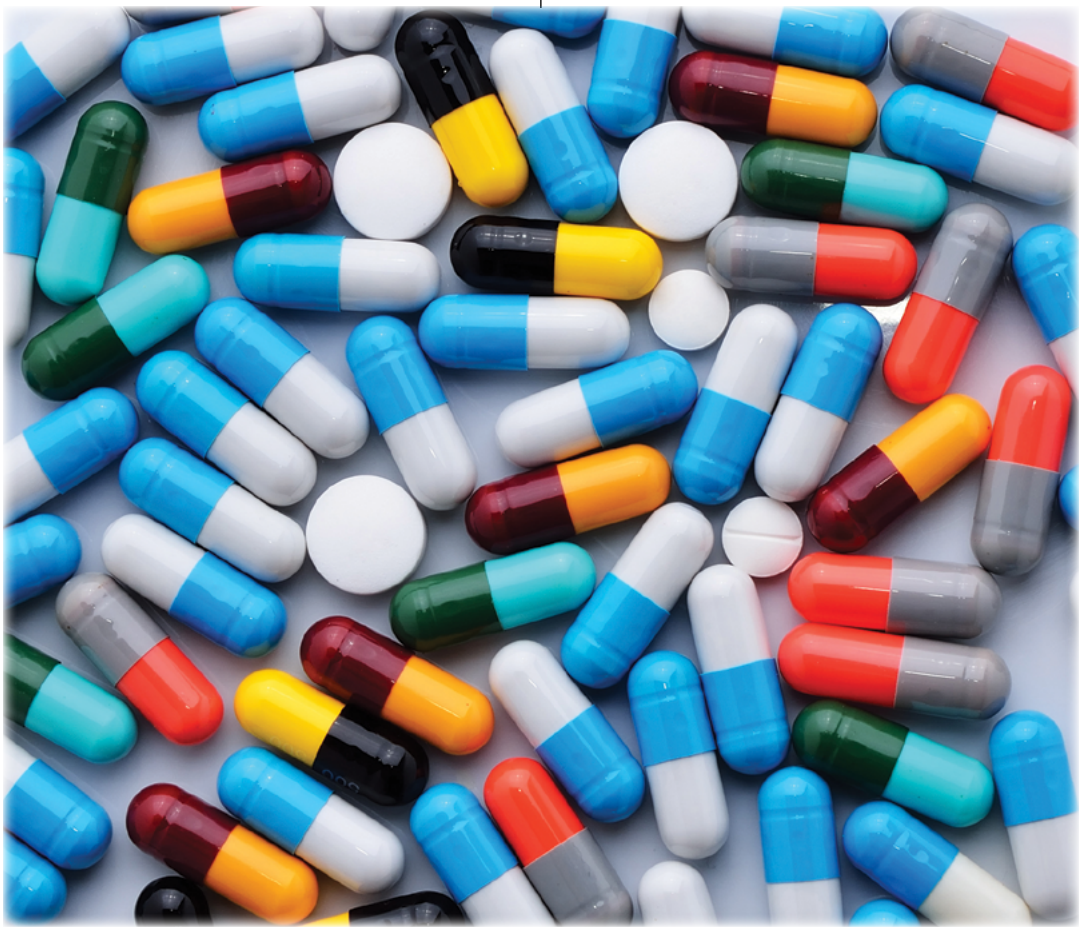
MEDICATION SIDE EFFECTS



High-Dose Citalopram and Escitalopram: Undeserved Bad Rap?

REVIEW OF: **Ray WA, Chung CP, Murray KT, Hall K, Stein CM. High-dose citalopram and escitalopram and the risk of out-of-hospital death. *J Clin Psychiatry*. 2017;78(2):190–195. doi:10.4088/JCP.15m10324.**

STUDY TYPE: **Retrospective cohort study**

SSRIs are considered the first-line treatment for depression; however, our confidence in their safety took a hit when the FDA issued a warning in 2011 about doses of citalopram above 40 mg causing QTc prolongation. The FDA originally said that high-dose citalopram was "contraindicated," but in 2012 softened its language to "not recommended." However, even this gentler warning remains controversial, and the study examined here attempts to further pinpoint whether QTc prolongation is any more likely with high-dose citalopram than with other SSRIs.

The authors reviewed the records of Tennessee Medicaid enrollees who had prescriptions for high doses of SSRIs between 1998 and 2011. "High doses" were defined as > 40 mg of citalopram, paroxetine, or fluoxetine; > 20 mg of escitalopram; or > 150 mg of sertraline. The study endpoint was sudden unexpected deaths, which included sudden cardiac deaths, other cardiovascular deaths, and unintentional medication overdose deaths in non-hospitalized patients. The authors believed that these deaths were more likely to be related to cardiac arrhythmias.

RESULTS

There were 54,220 persons with 557,519 prescriptions meeting criteria for high-dose SSRIs. There were 245 deaths during the study period, including 145 sudden unexpected deaths and 100 other deaths. In comparing deaths among patients taking the different SSRIs, the authors adjusted for various comorbidities, such as other risk factors for heart disease. The adjusted risk of sudden unexpected death was not significantly higher in citalopram-treated patients than in patients treated with any other SSRI. Here are the numbers for the hazard ratios for citalopram vs each of the SSRIs examined: citalopram vs escitalopram, 0.84 (95% CI, 0.40–1.75); citalopram vs fluoxetine, 1.24 (95% CI, 0.75–2.05); citalopram vs paroxetine, 0.75 (95% CI, 0.45–1.24); citalopram vs sertraline, 1.53 (95% CI, 0.91–2.55). Because all of these confidence interval ranges cross 1.00, the risk is considered nonsignificant.

When the authors zeroed in on the subset of patients who had particularly high cardiac risk factors, they still found no significant difference among the medications in the risk of sudden unexpected death.

THE CARLAT TAKE

This was a retrospective chart review, and it's hard to ascertain causes of death with certainty. However, the study size was quite large, meaning that it is likely to be generalizable to the larger patient population. There is still concern about QTc prolongation with citalopram, but

at least in this study, the risk of sudden unexpected death was not significantly different with high-dose citalopram than with high-dose escitalopram, fluoxetine, paroxetine, or sertraline users. This finding is aligned with another recent study showing that when VA patients were taken off of citalopram after the FDA warning, they were at higher risk for depression and not at lower risk of arrhythmias (Rector TS et al, *Am J Psychiatry* 2016;173(9):896–902).

PRACTICE IMPLICATIONS

Research continues to chip away at the FDA warning on citalopram. While it's prudent to be aware that there is some concern about citalopram, don't hesitate to prescribe it in high doses when you and your patient think the benefits outweigh the questionable risks.

Which Are the Most Dangerous Antidepressants?

REVIEW OF: Nelson JC, Spyker DA. Morbidity and mortality associated with medications used in the treatment of depression: an analysis of cases reported to U.S. poison control centers, 2000–2014. *Am J Psychiatry*. 2017;174(5):438–450. doi:10.1176/appi.ajp.2016.16050523.

STUDY TYPE: Retrospective cohort study

We often prescribe antidepressants to patients who are suicidal, and unfortunately, some people use these very medications to try to kill themselves. It's been known for some time that tricyclic antidepressants are among the most toxic in overdose, so we embraced the SSRIs and later medications in part because they are considered to be safer. But how safe are they? A new study attempts to answer that question.

Researchers identified all 48 FDA-approved medications likely to be prescribed for depression, and then searched for these drugs in the National Poison Data System, which lists all reports of poisoning in the U.S. There were more than 950,000 poisoning reports involving these medicines from 2000 through 2014.

The hazard level of the drugs was measured in two ways: a morbidity index, which described the proportion of exposures that led to an injury serious enough to require hospitalization (like an ICU admission for cardiac monitoring after a tricyclic ingestion); and a mortality index, which is the proportion of exposures that led to death. The people involved in these events had a mean age of 35.8 years, and 62.8% were female.

RESULTS

This study reports a cornucopia of interesting results, and there's no way to cover them all in this synopsis. Here are some of the highlights that we found especially clinically relevant.

1. The two most dangerous drugs of all 48 studied were the tricyclic amitriptyline (morbidity index of 345/1,000 and mortality index of 3.8/1,000) and lithium (325/1,000 and 1.3/1,000).
2. Not surprisingly, tricyclics and MAOIs as classes had the highest morbidity and mortality rates.
3. Clomipramine was the safest of all tricyclics and had overdose indexes similar to drugs like citalopram and mirtazapine.
4. The "second generation" antidepressants were generally much safer than tricyclics and MAOIs (these included SSRIs, SNRIs, and others such as bupropion and mirtazapine). Within this group of safer drugs, here were some outliers:
   - Bupropion and venlafaxine were ranked #1 and #2 respectively in highest mortality rates among the second-generation antidepressants; bupropion had the highest morbidity rate.

- Among the SSRIs, citalopram was the most dangerous, and in one comparison, it was 4 times more likely to be fatal than sertraline and escitalopram.

5. Among atypical antipsychotics, olanzapine and quetiapine had the highest morbidity rates, with respiratory depression being a particularly common problem with these agents.

THE CARLAT TAKE

Before making wholesale changes in your prescribing habits, you should step back and realize how uncommon these bad events actually are. For example, bupropion, the "most lethal" of the second-generation antidepressants, led to 47 deaths out of over 62,000 overdoses over 15 years. The chance that one of your patients will OD on bupropion is already very scant, and then, among those rare overdose victims, less than 1 person out of 1,000 will die.

PRACTICE IMPLICATIONS

Nonetheless, there are a lot of thought-provoking data points in this paper that might affect our practices. If you're deciding between amitriptyline and duloxetine for fibromyalgia, go with the much safer duloxetine. Bupropion and venlafaxine are the most likely to be hazardous among the newer antidepressants—which is unfortunate, since bupropion is on the list of first-line antidepressants for many clinicians. Citalopram really is more dangerous than its racemic cousin escitalopram, meaning that the FDA warning about citalopram dosing is sounding more reasonable than before.

The bottom line is that you should add these data to the many other factors you consider in deciding which antidepressant to prescribe. And don't forget the basics, such as limiting refills to a weekly supply in patients at high risk of overdosing.

SSRIs and Bipolar Switching

REVIEW OF: Altshuler LL, Sugar CA, McElroy SL, et al. Switch rates during acute treatment for bipolar II depression with lithium, sertraline, or the two combined: a randomized double-blind comparison. *Am J Psychiatry*. 2017;174(3):266–276. doi:10.1176/appi.ajp.2016.15040558.

STUDY TYPE: Randomized, double-blind, active-controlled trial

Do antidepressants cause bipolar II patients to switch from depression to hypomania? It's a controversial question, and you'll find academic psychiatrists who will argue passionately that antidepressants are either safe or dangerous in these patients. The latest study appears to endorse the "safe" camp.

In this multisite clinical trial, researchers conducted a 16-week study of 142 outpatients with bipolar II disorder. All were between 18 and 65 (mean age late 30s), and all met DSM-IV criteria for bipolar II disorder, major depressive episode. They were randomized to receive sertraline (n = 45; minimum target dose 100 mg/day), lithium (n = 49; minimum target dose 900 mg/day), or combination treatment with both (n = 48). The primary outcome was rate of switching to a hypomanic or manic episode, and secondary outcomes were treatment response, dropout rates, and side effects.

RESULTS

After 16 weeks, the switch rate (hypomania only) was 17.9% overall (19.4% lithium, 19.9% sertraline, and 13.4% combination treatment). There were no statistically significant differences in switch rate among the treatment arms, although patients with a history of drug use (stimulants in particular) had a higher risk of switching. Most of the switches occurred in the first 5 weeks of treatment. The overall treatment response was 62.7%, also with no differences found between treatments. While rates of side effects did not differ, the dropout rate was higher in the lithium/sertraline arm (70.8%) than the monotherapy arms (55.1% for lithium, 42.2% for sertraline).

THE CARLAT TAKE

This is the largest randomized, double-blind trial comparing switch rates in bipolar II patients taking lithium, sertraline, or their combination. The findings suggest that in bipolar II disorder, monotherapy with an SSRI is as effective and as safe as combination therapy with lithium.

PRACTICE IMPLICATIONS

This is another data point endorsing the efficacy and safety of SSRI monotherapy in patients with bipolar II disorder. While it is the largest study to date, it is still relatively small, with only about 50 patients in each treatment arm. Some other studies have reported conflicting findings. Regardless of your medication decisions, watch particularly closely for a switch during the first 5 weeks of treatment.

Does Methylphenidate Use in Children and Young Adults Increase Risk of Suicide?

REVIEW OF: Man KKC, Coghill D, Chan EW, et al. Association of risk of suicide attempts with methylphenidate treatment. *JAMA Psychiatry*. 2017;74(10):1048–1055. doi:10.1001/jamapsychiatry.2017.2183.

STUDY TYPE: Retrospective case series

Some studies have indicated that patients with ADHD may be at an increased risk of suicide. While these studies have shown associations between methylphenidate use and suicide, it is not clear whether the stimulant actually causes suicidality or whether patients taking stimulants are suicidal for other reasons. This study sought to directly investigate a causal association.

This retrospective population-based case series study used data from a comprehensive patient reporting system in Hong Kong. In total, 25,629 patients ages 6–25 who had taken methylphenidate between January 2001 and December 2015 were identified. Of these patients, 154 of them had attempted suicide during the 15-year study period. In order to try to determine if methylphenidate was actually causing the suicidality, researchers zeroed in on the suicide attempt rate during 3 periods, or "risk windows," as they were called: the pre-exposure period (90 days), the first 90 days of methylphenidate use, and any subsequent methylphenidate use.

RESULTS

Here's what the researchers found after their analysis. The chances of a suicide attempt were highest during the 90 days before the methylphenidate prescription (6.5-fold higher than baseline), and the risk dropped a little bit during the first 90 days of methylphenidate use down to a 4-fold risk. There was essentially no elevated suicide attempt risk observed with subsequent long-term methylphenidate use.

THE CARLAT TAKE

The authors conclude that the "most parsimonious interpretation of this pattern" is that methylphenidate use does not in itself increase the risk of suicide. Instead, the decision to start methylphenidate is preceded by a period of increased suicidal ideation, which gradually drops once the methylphenidate is started.

PRACTICE IMPLICATIONS

When patients are considering starting a stimulant, they are going through difficult times, and it's not surprising that the risk of a suicide attempt is high. We should feel comfortable medicating such patients with stimulants to treat their ADHD symptoms without the fear that the medication itself might aggravate suicidality. Indeed, another more recent population-based study has already replicated similar results (Huang KL et al, *Br J Psychiatry* 2018;212(4):234–238).

Youth, Antidepressant Medications, and Type 2 Diabetes

REVIEW OF: Burcu M, Zito JM, Safer DJ, et al. Association of antidepressant medications with incident type 2 diabetes among Medicaid-insured youths. *JAMA Pediatr.* 2017;171(12):1200–1207. doi:10.1001/jamapediatrics.2017.2896.

STUDY TYPE: Retrospective cohort study

Over the last decade, several published studies have reported an increased risk of type 2 diabetes associated with antidepressant use in adults. But does the same hold true for children and adolescents? This paper is the first population-based study to examine the risk of onset of type 2 diabetes with the use of antidepressants in younger patients.

Medicaid administrative claims data from California, Florida, Illinois, and New Jersey were analyzed in a cohort of 119,608 youths, ages 5–20, who initiated treatment with antidepressants from 2005 through 2009. Regression models were used to analyze the risk of onset of type 2 diabetes relative to antidepressant use, duration, and dosing.

RESULTS

Current use of antidepressants was associated with a 1.92 adjusted relative risk for type 2 diabetes (95% CI, 1.43–2.57). Current users of SSRIs or SNRIs had a 1.88 adjusted relative risk (95% CI 1.34–2.64), and current users of tricyclics had a 2.15 adjusted relative risk (95% CI 1.06–4.36). There were no elevated risks in current users of antidepressants other than SSRIs, SNRIs, or TCAs.

For SSRIs or SNRIs, the risk of onset of type 2 diabetes increased with longer durations of exposure and with larger cumulative dosing. Compared to risk for their use for the first 90 days, there was a relative risk of 1.68 (CI 0.83–3.40) for 91–150 days of use, 2.56 (CI 1.29–5.08) for 151–210 days of use, and 2.66 (CI 1.45–4.88) for > 210 days of use.

Compared to risk after a cumulative antidepressant dose of 1 mg–1,500 mg of fluoxetine hydrochloride equivalents, there was a relative risk of 1.22 (CI 0.59–2.52) for 1,501 mg–3,000 mg of dose equivalents, 2.17 (1.07–4.40) for 3,001 mg–4,500 mg of dose equivalents, and 2.44 (1.35–4.43) for > 4,500 mg of dose equivalents.

THE CARLAT TAKE

The study suggests that long-term antidepressant use, particularly with SSRIs or SNRIs, is associated with increased risk of onset of type 2 diabetes mellitus in children and adolescents. This increased risk is particularly prominent with long-term use and higher daily doses. But the study is observational and must be interpreted with caution. Causality cannot be inferred; however, there is a correlation.

PRACTICE IMPLICATIONS

Metabolic complications may not only appear for antipsychotic use, but for antidepressant use as well. Type 2 diabetes mellitus represents a rare but serious adverse outcome to discuss with patients and families, and we should vigilantly monitor for it.

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ANTIPSYCHOTICS

Antipsychotic Use During First Trimester Not Associated With Congenital Malformations

REVIEW OF: Huybrechts KF, Hernández-Díaz S, Patorno E, et al. Antipsychotic use in pregnancy and the risk for congenital malformations. *JAMA Psychiatry*. 2016;73(9):938–946. doi:10.1001/jamapsychiatry.2016.1520.

STUDY TYPE: Retrospective cohort study

The use of antipsychotics during pregnancy has doubled over the past decade, and there have been ongoing concerns about the risk of congenital malformations. In the first edition of *Psychiatry Practice Boosters,* we reviewed a pregnancy registry study showing no significant association between atypical antipsychotic use and major malformation (Cohen L et al, *JAMA Psychiatry* 2016;173(3):263–270). Another study was published reinforcing those results by looking at a larger population.

Using national Medicaid data, researchers identified pregnant women who filled at least one antipsychotic prescription during their first trimester, the most critical time for fetal development. Out of over 1.3 million women between 12 and 55 years of age, 9,258 (0.69%) filled an atypical antipsychotic (eg, olanzapine) and 733 (0.05%) filled a typical antipsychotic (eg, haloperidol). The study outcomes were straightforward: risk of overall congenital and cardiac malformations identified within 90 days after delivery.

RESULTS

Prior to adjusting for potential study confounders (eg, psychiatric and physical comorbidities), the risk of congenital malformations was higher in women treated with atypicals (44.5 per 1,000 births) and typicals (38.2 per 1,000 live births) compared to those not treated (32.7 per 1,000 live births). However, the women prescribed antipsychotics were older, had higher rates of psychiatric and medical comorbidities, and took more psychiatric and teratogenic medications. Once the researchers controlled for these factors, there were no significant differences between the groups in the rates of overall congenital or cardiac malformations.

One outlier, however, was risperidone. Risperidone had a 26% increased risk for causing both overall or cardiac malformations than no antipsychotic, but this increased risk was only statistically significant for overall malformations, not cardiac malformations.

THE CARLAT TAKE

A major strength of the article is the sample size, which is about 17 times the size of any previous study on the topic. It's not clear what to make of the finding that risperidone may be the only teratogenic antipsychotic. More data should help clarify this issue.

PRACTICE IMPLICATIONS

Explain to patients that the baseline rate of malformations in all women (even those who are not taking any medication) is around 2%–4%, and that large studies have shown that antipsychotics are unlikely to increase the risk. For the time being, risperidone should be at the bottom of your list if an antipsychotic must be prescribed during pregnancy. This caution is reinforced by a more recent review of atypical antipsychotics in pregnancy; this review again found an increased risk of congenital malformations for those women taking risperidone or paliperidone that was not found with other atypical antipsychotics (Damkier P et al, *CNS Drugs* 2018;32(4):351–366).

Metformin Use in Autistic Children Taking Atypical Antipsychotics

REVIEW OF: Anagnostou E, Aman MG, Handen BL, et al. Metformin for treatment of overweight induced by atypical antipsychotic medication in young people with autism spectrum disorder: a randomized clinical trial. *JAMA Psychiatry*. 2016;73(9):928–937. doi:10.1001/jamapsychiatry.2016.1232.

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

Atypical antipsychotics are commonly used to reduce irritability and agitation in children with autism spectrum disorder (ASD). Although effective, these medications lead to weight gain and other metabolic problems. Strategies like tailored diet plans and exercise can help, but they are often not enough. If not interrupted early, for many, continued weight gain will lead to diabetes, hypertension, and heart disease later in life.

A promising approach for managing antipsychotic-associated weight gain is metformin. Through its ability to suppress glucose production in the liver, metformin stabilizes blood sugar levels, reduces hunger, and promotes fat loss. Previous studies with adults reveal that metformin can indeed stop or reverse weight gain associated with the use of atypical antipsychotics. Similar data exist for children as well, but we know little with respect to those with ASD.

To explore this issue, researchers randomized 61 children with ASD between the ages of 6 and 17 to receive metformin (n = 29) or placebo (n = 32). Nearly all were on either risperidone (60%) or aripiprazole (38%). The children were tracked for 16 weeks for changes in body mass index (BMI) and adverse events. For kids between 6 and 9, metformin and placebo were initially titrated to a maximum of 500 mg twice daily (1,000 mg/day average); older children received up to 850 mg twice daily (1,587 mg/day average).

RESULTS

Metformin beat placebo, but not dramatically so. Patients on placebo had no weight loss over the 16-week trial, whereas those on metformin had an average decrease in BMI of 5%. Three of the 28 kids on metformin (11% of the sample) achieved an 8%–9% BMI reduction, but 4 children on metformin dropped out due to increased agitation, and 1 dropped out because of sedation. Gastrointestinal (GI) distress was also noted in 25% of those on metformin, vs less than 7% on placebo.

THE CARLAT TAKE

These results are consistent with previous research on metformin and weight gain. It's certainly useful to have additional data for our youngest patients with ASD. However, this is a small study, making it difficult to generalize. GI discomfort is a known side effect of metformin and is often cited as a reason for early discontinuation. It's important to remember that children with

ASD have a difficult time reporting physical discomfort: Some may have suffered through 16 weeks of GI distress with no one the wiser.

PRACTICE IMPLICATIONS

Metformin may be a reasonable choice for reducing weight gain in your patients with ASD who need to be on an atypical antipsychotic, but any weight loss is likely to be rather small. The authors have since published a 16-week open-label extension of this trial, in which the weight loss of those taking metformin was continued with no change, and those who switched from placebo achieved the same small, but statistically significant, weight loss as reported here (Handen BL et al, *J Am Acad Child Adolesc Psychiatry* 2017;56(10):849–856.e6). If you are unsure whether metformin is appropriate for your patient, consult with an endocrinologist.

Aripiprazole Augmentation May Improve Remission Rates in Major Depression

REVIEW OF: Mohamed S, Johnson GR, Chen P, et al. Effect of antidepressant switching vs augmentation on remission among patients with major depressive disorder unresponsive to antidepressant treatment: the VAST-D randomized clinical trial. *JAMA*. 2017;318(2):132–145. doi:10.1001/jama.2017.8036.

STUDY TYPE: Randomized, single-blind, controlled trial

It seems like an endless debate: When a patient does not respond to the first trial of an antidepressant, what should we do? Switch to something else? Augment with another agent? If the latter, how often should that augmenting agent be an atypical antipsychotic? The VA Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) trial was conducted to answer some of these questions. Specifically, the study compared the effectiveness and adverse effects of switching to bupropion SR, augmenting with bupropion SR, or augmenting with aripiprazole.

In this randomized controlled trial, 1,522 patients with non-psychotic major depressive disorder (MDD) who had failed at least one adequate 6-week course of an SSRI, an SNRI, or mirtazapine were recruited from the Veterans Administration (VA). Most of the patients were male (85%) and white (69%), and had an average age of 54.4. Patients were randomly assigned to one of three groups: switching to bupropion SR (most common dose 200 mg twice daily, n = 511), augmenting with bupropion SR (most common dose also 200 mg twice daily, n = 506), or augmenting with aripiprazole (most common dose 10 mg daily, n = 505).

RESULTS

After 12 weeks of treatment, remission and response rates were: switch-bupropion: remission 22.3%, response 62.4%; augment-bupropion: remission 26.9%, response 65.6%; augment-aripiprazole: remission 28.9%, response 74.3%. Augmenting with aripiprazole yielded statistically superior remission rates than switching to bupropion ($p = 0.02$) and superior response rates than either of the bupropion arms. Somnolence, akathisia, and weight gain occurred more frequently in the aripiprazole group. Most dramatically, in a subset of patients who continued the trial for 36 weeks, 25% of the aripiprazole group gained at least 7% of body weight as opposed to only 5% of both bupropion groups.

THE CARLAT TAKE

Aripiprazole augmentation was the most effective strategy for patients who had not responded to a single antidepressant trial, beating both switching to and augmenting with bupropion. But the price of this higher response rate is a cluster of side effects, including weight gain, akathisia, and somnolence.

PRACTICE IMPLICATIONS

This large and well-designed study should encourage us to consider aripiprazole augmentation as a solid second-step strategy in depression treatment. However, these results may not generalize to non-VA populations, such as women of any age and younger men.

Cannabis and Psychosis: The Debate Continues

REVIEW OF: Schoeler T, Petros N, Di Forti M, et al. Effects of continuation, frequency, and type of cannabis use on relapse in the first 2 years after onset of psychosis: an observational study. *Lancet Psychiatry*. 2016;3(10):947–953. doi:10.1016/S2215-0366(16)30188-2.

Schoeler T, Petros N, Di Forti M, et al. Association between continued cannabis use and risk of relapse in first-episode psychosis: a quasi-experimental investigation within an observational study. *JAMA Psychiatry*. 2016;73(11):1173–1179. doi:10.1001/jamapsychiatry.2016.2427.

STUDY TYPE: Prospective cohort studies

Cannabis users seem to be at higher than normal risk to develop psychotic symptoms, but so far researchers haven't solved the chicken-and-egg problem. An association between cannabis use and psychosis might reflect a causal relationship—ie, perhaps smoking too much pot causes people to become psychotic. On the other hand, it's possible that people who are already psychotic gravitate toward smoking pot, in which case cannabis per se is not such a danger.

These articles further investigate the association with cannabis use and increased relapse rates and length of hospitalization in patients with psychosis. This study attempts to further sort out the association-vs-causation issue. It's unusual for a study to be reported in two journals almost simultaneously, but that's what occurred in this case.

The two articles are from the experiment described here: Patients experiencing first-episode psychosis (FEP) were recruited consecutively from local community early-intervention programs for psychosis and from psychiatric inpatient units in South London between 2002 and 2013. 256 subjects completed the study. They were assessed when first hospitalized by face-to-face or telephone interview, and again 2 years later. The Cannabis Experiences Questionnaire was used to assess marijuana use in the 2 years after hospitalization. Subjects were divided into former users, never users, intermittent users, continuous users of low-potency hash-like cannabis, continuous low-frequency users of "skunk" (high-potency) cannabis, and continuous high-frequency users of skunk cannabis.

RESULTS

In the *Lancet* article, researchers measured the relapse rates of these patients, then did statistical analyses to figure out whether degree of use was correlated with relapse. The definition of relapse was rehospitalization for psychosis. In fact, more cannabis use did predict higher relapse rates. Specifically, relapse rates were 24% for former users, 30% for never users, 40% for intermittent users, 44% for continuous users of hash-like cannabis, 54% for low-frequency users of skunk cannabis, and 58% for high-frequency users of skunk cannabis. The statistical analysis showed that subjects who did not use cannabis after

FEP had the best outcome. The high-frequency skunk cannabis users had more relapses, shorter time to relapse, longer hospitalizations, and a need for more intensive community services.

The *JAMA Psychiatry* article reported some of the same findings but added interesting information that touches on the causality issue. These researchers found that for any given patient, there was an increased risk of relapse to psychosis during periods of cannabis use as opposed to periods of nonuse, and that the risk of relapse increased as frequency of cannabis use increased.

THE CARLAT TAKE

The *Lancet* article focuses on both usage pattern and potency, comparing different user groups based on how often they used marijuana and how potent a formulation they consumed. The *JAMA Psychiatry* article focuses on the risk of psychotic relapse in individual subjects during periods of marijuana use vs nonuse. A significant limitation in both articles is the use of self-report or chart review to assess cannabis use. Another is that the authors did not consider length of untreated psychosis prior to hospitalization, nor did they have access to doses of antipsychotic medication used to treat the subjects. Additionally, although the number of completers in each article (256 in the *Lancet* article and 220 in the *JAMA Psychiatry* article) is respectable, the numbers in each group were relatively small after division into several groups.

Despite these limitations, there is important information here for patients and clinicians. It's encouraging that former cannabis users had a lower risk of relapse when they did not use after FEP than those who continued their use. The study results also suggest that the association between cannabis and psychosis involves more than simply self-medicating psychotic symptoms. In this study, the authors found that relapse risk changed within subjects based on changes in their individual patterns of use. That weakens the argument that people who are more susceptible to psychosis are also more likely to use cannabis.

PRACTICE IMPLICATIONS

These studies reinforce our efforts to discourage cannabis use in patients at risk for psychosis. Patients who have had a psychotic episode should be counseled to discontinue cannabis use. For patients who are reluctant to stop altogether, it may be helpful if they decrease their frequency of use or switch to a less potent strain, as both frequency of use and potency seem to play a role in psychosis risk.

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CHILD AND ADOLESCENT PSYCHIATRY

Is Minocycline Effective When Added to Risperidone for Autism Spectrum Disorder?

REVIEW OF: Ghaleiha A, Alikhani R, Kazemi MR, et al. Minocycline as adjunctive treatment to risperidone in children with autistic disorder: a randomized, double-blind placebo-controlled trial. *J Child Adolesc Psychopharmacol.* 2016;26(9):784–791.

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

The only medication treatments approved for autism spectrum disorder (ASD) are the antipsychotics risperidone and aripiprazole, which are indicated specifically to manage irritability associated with ASD. There's been some interest in minocycline, which is a second-generation tetracycline antibiotic, for various psychiatric disorders, including depression, schizophrenia, and Parkinson's disease. Why would an antibiotic be helpful in psychiatry? Minocycline crosses the blood-brain barrier and may have neuroprotective effects. A recent study tested whether minocycline might be useful as an adjunct to risperidone for ASD.

Ghaleiha and colleagues conducted a 10-week, randomized, double-blind, placebo-controlled trial with 46 children with ASD, ages 4–12. Participants were randomly assigned to receive either risperidone plus minocycline 50 mg twice a day, or risperidone plus placebo. Risperidone was titrated up to 1 mg or 2 mg a day based on body weight.

RESULTS

Each child was evaluated at baseline, week 5, and week 10. Based on the Aberrant Behavior Checklist scale, patients assigned to minocycline plus risperidone showed significantly more improvement on measures of irritability ($p = 0.003$) and hyperactivity/noncompliance ($p = 0.002$). There were no differences between the groups in the other measures of ASD, such as lethargy/social withdrawal, stereotypic behavior, inappropriate speech, and side effect profiles. The minocycline group showed at least partial response (> 25% irritability reduction) or complete response (> 50% irritability reduction) in 91.3% of children as opposed to placebo's 65.5% at the end of the study. No serious side effects were reported, and frequency of side effects were comparable between the groups.

THE CARLAT TAKE

Adding minocycline 50 mg twice a day to risperidone may help with symptoms of irritability and hyperactivity. And though not tested in this trial, adding the antibiotic might theoretically allow us to use a lower dose of risperidone, leading to potentially fewer side effects.

PRACTICE IMPLICATIONS

The study was small and needs replication, but given the good tolerability of minocycline, this is an augmentation strategy you might want to try for some of your kids with irritability and ASD. However, we still don't know how long treatment should last beyond the 10-week period studied in this trial.

Efficacy and Safety of SSRIs and SNRIs for Child and Adolescent Psychiatric Disorders

REVIEW OF: Locher C, Koechlin H, Zion SR, et al. Efficacy and safety of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and placebo for common psychiatric disorders among children and adolescents: a systematic review and meta-analysis. *JAMA Psychiatry*. 2017;74(10):1011–1020. doi:10.1001/jamapsychiatry.2017.2432.

STUDY TYPE: Systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials

Since the 2004 FDA black-box warning on all antidepressants for pediatric use, controversy continues over the use of SSRIs and SNRIs in children and adolescents. Both classes of medication are still commonly used for pediatric depressive disorders, anxiety disorders, and obsessive-compulsive disorder. A recently published systematic review and meta-analysis takes another look at the evidence base for these medications.

The authors reviewed 36 randomized, double-blind, placebo-controlled trials with 6,778 participants (48.6%/51.4% boys/girls, average age ~13 years). Each study compared an SSRI or an SNRI vs placebo for children or adolescents with a diagnosis of depressive disorder (17 studies), anxiety disorder (10 studies), OCD (8 studies), or PTSD (1 study). Effect sizes were calculated as standardized mean differences, and risk ratios for adverse events were also addressed. A rule of thumb for interpreting effect sizes is that ≥ 0.8 is considered a large effect, 0.5 a medium effect, and ≤ 0.2 a small effect.

RESULTS

The authors found medium to small effect sizes for the disorders examined: 0.56 for anxiety disorders, 0.39 for obsessive-compulsive disorders, and 0.20 for depressive disorders. (The single study for PTSD showed no statistical effect size.) For all disorders grouped together, the SSRIs and SNRIs were more beneficial than placebo by only a small to medium effect size of 0.32. However, compared with participants receiving placebo, patients receiving an antidepressant reported a statistically significant increase in adverse effects, including headache, nausea, and suicidal thoughts and behaviors, although the clinical significance of these differences is less clear.

THE CARLAT TAKE

These results are not particularly surprising. Clinicians have long noticed that serotonergic agents work better for anxiety disorders in kids than they do for depression—in line with the higher effect sizes reported for anxiety disorders (a fairly impressive 0.56) in this study. Especially given the elevated risk for serious side effects, the small effect size of 0.20 for depression is disquieting.

PRACTICE IMPLICATIONS

This is yet another reminder that we should think carefully before using SSRIs and SNRIs for depression in children. Always have a good referral network for child/adolescent therapists well-versed in the treatment of depression.

Guanfacine XR Improves ADHD Symptoms in Autism

REVIEW OF: Scahill L, McCracken JT, King BH, et al. Extended-release guanfacine for hyperactivity in children with autism spectrum disorder. *Am J Psychiatry*. 2015;172(12):1197–1206. doi:10.1176/appi.ajp.2015.15010055.

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

Children with autism spectrum disorder (ASD) often have symptoms of ADHD. While it's not always easy to distinguish them from the core features of autism, symptoms such as impulsivity, hyperactivity, and distractibility do occur, and we often use medications to target them. Stimulants are fairly effective but tend to cause more side effects in autistic ADHD kids than in children with pure ADHD. Atomoxetine was only equivocally effective in one trial, and the immediate release (IR) version of guanfacine was tested in a small open-label trial, resulting in improvement in about half the subjects.

Recognizing the need for more data, researchers conducted the first ever randomized, placebo-controlled trial of guanfacine in ASD/ADHD, in this case using the extended release (ER) version. Children between the ages of 5 and 14 with a diagnosis of ASD with accompanying impulsivity, hyperactivity, and distractibility were randomly assigned to either ER guanfacine (n = 30) or placebo (n = 32). During this 8-week trial, ER guanfacine was started at 1 mg once a day for all children. Depending on the child's weight and response, a maximum of 4 mg daily could be prescribed. The primary outcome measure was change from baseline on the parent version of the Aberrant Behavior Checklist (ABC) hyperactivity subscale, which was assessed at weeks 4, 6, and 8. The Clinical Global Impressions—Improvement (CGI-I) scale was also used.

RESULTS

ER guanfacine was effective. At the end of 8 weeks, the medication group showed a 44% reduction in scores on the ABC hyperactivity subscale compared to 13% for the placebo group ($p < 0.0001$). For the ER guanfacine group, half were rated "much improved" or "very much improved" on the CGI-I, whereas fewer than 10% of the placebo group were so rated ($p = 0.0001$). Significant improvements were seen in both hyperactivity and inattention vs placebo. The most frequently prescribed dose in both groups was 3 mg.

Overall, ER guanfacine was well-tolerated. The most common complaints were drowsiness, fatigue, and loss of appetite. Drops in blood pressure and heart rate from baseline were seen in the guanfacine group. Blood pressure normalized by the end of 8 weeks, but heart rate did not, remaining about 10 points below baseline. This effect was not considered clinically significant.

THE CARLAT TAKE

This was a small study of short duration, but the results were promising. It's great to have alternative medications for ADHD symptoms when stimulants are not tolerated or are ineffective. Recently updated consensus guidelines list methylphenidate, atomoxetine, and guanfacine as

preferred agents for the hyperactivity symptoms of ASD (Howes OD et al, *J Psychopharmacol* 2018;32(1):3–29).

PRACTICE IMPLICATIONS

When using ER guanfacine, start with 1 mg in the morning and titrate up slowly as needed. Dose it in the evening if the child becomes drowsy. By the way, ER guanfacine is now available as a cheap generic, so don't feel guilty prescribing it. On the other hand, the ER version's duration of action is only marginally longer than the IR version (about 24 hours vs about 17 hours), so you don't gain much by choosing it.

Negative Efficacy of Desvenlafaxine and Fluoxetine for Children and Adolescents With Major Depressive Disorder

REVIEW OF: **Weihs KL, Murphy W, Abbas R, et al. Desvenlafaxine versus placebo in a fluoxetine-referenced study of children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol.* 2018;28(1):36–46. doi:10.1089/cap.2017.0100.**

STUDY TYPE: **Randomized, double-blind, placebo-controlled trial**

The debate about whether antidepressants work in children has been with us since the tricyclic era. A recent study evaluated the short-term efficacy and safety of a newer agent, desvenlafaxine (Pristiq).

This multi-center, randomized, double-blind, placebo-controlled study included 339 children and adolescents ages 7–17 who met DSM-IV-TR criteria for major depressive disorder (MDD). A fluoxetine 20 mg/day group was included as a reference for assay sensitivity, but not as a comparison to the study drug. Enrolled patients had a Children's Depression Rating Scale—Revised (CDRS-R) total score > 40 at baseline. Patients were excluded from the study if they had psychotic features, if they had a personal or family history of bipolar disorder or suicide, or if they were felt to be at significant risk of suicide.

Patients were randomly assigned (1:1:1) to placebo, desvenlafaxine, or fluoxetine. Desvenlafaxine dose was chosen by body weight: 20 to < 35 kg: 25 mg/day; 35 to < 70 kg: 35 mg/day; and ≥ 70 kg: 50 mg/day. The patients were assessed weekly for the first month and again at weeks 6 and 8.

RESULTS

The primary endpoint, change in the CDRS-R score from baseline to week 8, did not differ statistically from placebo (-23.1) for either desvenlafaxine (-22.6) or fluoxetine (-24.8). Adverse events attributed to medications were present in all study groups (desvenlafaxine, 28.7%; fluoxetine, 32.1%; and placebo, 34.8%). The most common treatment-emergent adverse events were headache, upper abdominal pain, and nausea. There were no deaths in the study, but 5 patients receiving either desvenlafaxine or fluoxetine experienced serious adverse events—suicidal ideation, a suicide attempt, disinhibition, and postpartum hemorrhage.

THE CARLAT TAKE

High placebo response rates in the pediatric population make it difficult to demonstrate the benefit of even established treatments such as fluoxetine, and clinicians should closely monitor for suicidal thoughts during initial stages of treatment with SSRIs and SNRIs. New-onset suicidal ideation was reported for 8, 10, and 7 patients in the desvenlafaxine, fluoxetine, and placebo groups, respectively; suicidal behavior was reported for 1 fluoxetine-treated patient, who reported suicidal ideation at baseline.

PRACTICE IMPLICATIONS

It's important to note that this publication of a negative study, where neither desvenlafaxine nor fluoxetine were efficacious for treating MDD in children and adolescents, was conducted with financial and medical writing support from Pfizer Inc. At the same time as this article was released, another negative study of depression in children was published on desvenlafaxine by the same journal (Atkinson S et al, *J Child Adolesc Psychopharmacol* 2018;28(1):55–65). When medication is indicated, we generally advise to stick with the agents that have the most positive evidence. Up to now, that's been fluoxetine; however, the possibility of negative study suppression makes it difficult to know with certainty whether it is in fact more effective than alternatives.

Can Guanfacine XR Be Used to Treat Anxiety in Kids?

REVIEW OF: Strawn JR, Compton SN, Robertson B, Albano AM, Hamdani M, Rynn MA. Extended release guanfacine in pediatric anxiety disorders: a pilot, randomized, placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2017;27(1):29–37. doi:10.1089/cap.2016.0132.

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

We use guanfacine XR (GXR), an alpha-adrenergic agonist, for various psychiatric issues in children, though its only FDA indication in psychiatry is for ADHD. Surprisingly, no studies have been conducted on the efficacy and safety of GXR for pediatric anxiety disorders—until now.

Researchers recruited 83 patients ages 6–17 years from 32 clinical sites in the U.S. The average age of participants was 12 years (SD = 3.38), and they were mostly white (81.9%) and female (57.8%) with a normal body mass index (63.9%). Participants all met DSM-IV-TR criteria for generalized anxiety disorder, separation anxiety disorder, or social anxiety disorder. Patients were randomly assigned (3:1) to GXR or placebo, and treatment continued for 12 weeks, which included 6 weeks of dosage titration followed by 6 weeks of maintenance treatment. Participants received 1 mg–6 mg of GXR daily, with a maximum dose of 0.12 mg/kg/day. The mean dose was 2.7 mg/day.

The primary objective of this study was to assess the safety and tolerability of GXR, as measured by vital signs, ECGs, and side effects. Secondarily, the researchers assessed efficacy by administering standard symptom rating scales to patients.

RESULTS

GXR was as safe as placebo, with no clinically significant differences in vital sign parameters and no reported suicidal behaviors. Patients on GXR had slightly more side effects than those on placebo, and the most frequent were headache (35.5%), somnolence (27.4%), and fatigue (21.0%).

In terms of efficacy, patients taking GXR improved a bit more on various measures than those on placebo, though no statistical tests were done. Efficacy was only an exploratory outcome in this feasibility study as it was not powered for statistical comparisons.

THE CARLAT TAKE

This small phase-two study found GXR to be safe and well-tolerated but not clearly beneficial with respect to anxiety. There was no worsening of anxiety symptoms, which may happen with stimulant medications. We'll be on the lookout for the efficacy studies when they are published at a later date.

PRACTICE IMPLICATIONS

If your patient's anxiety does not budge in response to an antidepressant, trying GXR is reasonable. It is safe, pretty tolerable, and may be effective—though we won't know for sure about its efficacy until we see larger studies confirming the efficacy signals present in this one.

Can Atomoxetine Improve Reading Skills in Children With Dyslexia?

REVIEW OF: Shaywitz S, Shaywitz B, Wietecha L, et al. Effect of atomoxetine treatment on reading and phonological skills in children with dyslexia or attention-deficit/hyperactivity disorder and comorbid dyslexia in a randomized, placebo-controlled trial. *J Child Adolesc Psychopharmacol.* 2017;27(1):19–28. doi:10.1089/cap.2015.0189.

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

Dyslexia, a learning disability characterized by difficulty in reading skills, is highly prevalent, with rates between 5% and 17%. Treatments are largely non-medical interventions but have limited success. Research suggests a critical role for attentional mechanisms in the development of dyslexia. Previous small studies have shown stimulants as well as atomoxetine (Strattera) may improve reading in patients who have comorbid attention deficit hyperactivity disorder and dyslexia (ADHD+D). This new study is a larger, placebo-controlled trial to evaluate atomoxetine's efficacy in patients with ADHD+D as well as those with dyslexia or ADHD only.

The researchers randomized 209 children and adolescents, ages 10–16 years, into a placebo group (n = 89) and a treatment group (n = 120). The placebo group consisted of dyslexia-only (n = 29) and ADHD+D patients (n = 60), while the treatment arm consisted of dyslexia-only (n = 29), ADHD+D (n = 64), and ADHD-only (n = 27) patients. The patients were treated with either atomoxetine (starting at 0.5 mg/kg daily for 3 days, then 1.0–1.4 mg/kg per day) or placebo.

RESULTS

Reading abilities were measured with a variety of standardized tests after 16 weeks. Both ADHD+D and dyslexia-only patients receiving atomoxetine showed statistically significant improvement in phonologic processing (sounding out words), basic reading skills, and reading vocabulary compared to those receiving placebo ($p < 0.02$). Effect sizes were moderate to high (ranging from 0.5 to 0.73), and literacy improvement in comorbid patients was not correlated with improvements in ADHD symptoms. More adverse events occurred in the atomoxetine group than the placebo group, most commonly nausea, fatigue, upper abdominal pain, decreased appetite, somnolence, and aggression.

THE CARLAT TAKE

While the study shows promising results, it's not clear whether the improvement seen is clinically significant, whether it would be seen in a range of kids with varying levels of dyslexia, or whether it would be sustained over time. Nonetheless, atomoxetine is a well-tolerated medication and is one of the few agents shown to be helpful for dyslexia. Readers should know that the study was funded by Eli Lilly, the manufacturer of atomoxetine, although there were no obvious signs of bias in research design or analysis.

PRACTICE IMPLICATIONS

While not indicated for dyslexia, you can feel comfortable telling parents of children with dyslexia that they may see some improvement in reading skills when treated with atomoxetine. Be sure to also educate parents on the most common side effects of the medication.

SUBSTANCE USE

N-acetylcysteine Shows Promise in Treatment of Co-Occurring PTSD and SUD

REVIEW OF: Back SE, McCauley JL, Korte KJ, et al. A double-blind, randomized, controlled pilot trial of N-acetylcysteine in veterans with posttraumatic stress disorder and substance use disorders. *J Clin Psychiatry*. 2016;77(11):e1439–e1446. doi:10.4088/JCP.15m10239.

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

Post-traumatic stress disorder (PTSD) is the most common psychiatric disorder in veterans who seek treatment at the Veterans Administration (VA), and substance use disorder (SUD) is a common comorbid condition. While SSRIs can be effective for PTSD symptoms, they don't treat SUD well.

N-acetylcysteine (NAC) is an antioxidant approved for the treatment of acetaminophen overdose and pulmonary disease, and it has been used in psychiatry for patients with trichotillomania and gambling, among other conditions. Neurochemically, NAC normalizes synaptic glutamate transmission, and hypothetically such transmission is disordered in both PTSD and SUD. Therefore, researchers decided to try the medication in a group of veterans with PTSD and SUD.

Thirty-five veterans ages 18–65 from the Ralph H. Johnson VA Medical Center were enrolled; they all met DSM-IV criteria for SUD and PTSD. 81.5% met criteria for alcohol use disorder and 77.8% met criteria for another SUD. After at least 1 week of sobriety, they were randomly assigned to double-blind treatment with either NAC or placebo. The active treatment group received 2,400 mg of NAC daily for 8 weeks. Both groups attended a cognitive behavioral therapy–based outpatient program that met 5 days per week during the study. All patients were assessed with standard research scales for PTSD symptoms, such as the Clinician-Administered PTSD Scale (CAPS) and the PTSD Checklist Military (PCL-M); they were also assessed for depression and substance craving. The study was funded by several government agencies, including the Department of Veterans Affairs and the National Institute for Drug Addiction.

RESULTS

Over the course of 8 weeks, patients in the NAC group (n = 13 after dropouts) improved significantly on all measures ($p < 0.05$), whereas those assigned to placebo (n = 14) improved on only 1 measure: the CAPS re-experiencing subscale. By week 8, the NAC group had reductions of 46% in the CAPS and 32% on the PCL-M, while the placebo group had reductions of 25% and 3% respectively. There was an 81% reduction in craving in the NAC group compared to 32% in the placebo group. Substance use at week 8 was low in both groups with no significant differences. Adverse effects were mild, with the most common being dry mouth and heartburn. Only one serious adverse event, a syncopal episode, was thought to be possibly related to the study medication.

THE CARLAT TAKE

The pilot study has some limitations: The sample size was small, and it lacked any measure of whether quality of life was improved by symptom reduction. Nonetheless, the symptom improvements for both PTSD and substance craving in the NAC group were impressive.

PRACTICE IMPLICATIONS

NAC is yet another anti-inflammatory treatment that has been shown to be helpful in the management of psychiatric illness. Given the lack of effective treatments for co-occurring PTSD and SUD, it's reasonable to try NAC titrated to 2,400 mg/day for such patients. The side effects are minimal, and the improvements in symptoms may be significant.

Do Prizes for Abstinence Increase Sobriety in People With Serious Mental Illness?

REVIEW OF: McDonell MG, Leickly E, McPherson S, et al. A randomized controlled trial of ethyl glucuronide-based contingency management for outpatients with co-occurring alcohol use disorders and serious mental illness. *Am J Psychiatry*. 2017;174(4):370–377. doi:10.1176/appi.ajp.2016.16050627.

STUDY TYPE: Randomized, open-label, active-controlled trial

Although studies have demonstrated the effectiveness of contingency management (CM) for illicit drug use, there's less evidence for treatment of alcoholism—in part because a standard breathalyzer has a short detection window of 12 hours, meaning patients must only abstain from drinking since the previous night to pass the test.

Over the past few years, however, a more effective alcohol biomarker has been introduced. Ethyl glucuronide (EtG) is an alcohol metabolite that is present in the urine for at least 5 days after a patient's last drink. It can therefore verify longer-term abstinence.

Researchers in Seattle recruited 79 patients who had both alcohol use disorder and serious mental illness such as schizophrenia, bipolar disorder, and recurrent depression. Roughly two-thirds were men, half were white, and the average age was in the mid-40s. All were in outpatient substance use disorder (SUD) treatment. Before being randomly grouped, participants had to complete a 4-week induction period designed to identify those who were most likely to stay in the actual 12-week study. Those who showed up during the induction phase were randomly assigned to a CM group (n = 40) or a non-contingent reinforcement (control) group (n = 39). Participants in both groups provided urine samples 3 times a week.

After the induction phase, participants in the CM group who submitted 3 consecutive urine samples negative for EtG earned "prize draws" from a container of tokens. Half of the tokens simply said "good job," while the other half could be turned in for prizes ranging in value from $1 to $80. Participants also received $10 gift cards for attending SUD groups each week. Those in the control group received prize draws for each urine sample submitted, no matter what the result. Control participants also received gift cards regardless of whether they attended groups.

RESULTS

The CM group had a significantly longer period of EtG-negative urine samples (mean of 8.56) than the control group (mean 4.11). This translated to 1.5 weeks of additional continuous abstinence. Moreover, the CM group had significantly fewer drinking days and fewer days of drinking to intoxication throughout the study. These differences persisted into a 3-month follow-up period.

THE CARLAT TAKE

This well-designed study supports the effectiveness of CM for patients dually diagnosed with mental illness and alcohol use disorder. Point-of-care EtG costs money but can lead to good benefits in terms of improved sobriety.

PRACTICE IMPLICATIONS

Consider adding CM to your substance use treatment. And these don't necessarily need to be gift cards—think of creative prizes that may be low-cost to the clinic, but high-value to your patient population. There is currently a trial (Oluwoye O et al, *Contemp Clin Trials* 2018;69:92–98) being proposed to look more specifically at what type of CM is most effective for those with alcohol use disorder and serious mental illness. There is an up-front cost to providing the prizes, but the positive reinforcement for good behavior (drug-free urine screens) may be well worth it.

Reports of Gabapentin Misuse and Abuse Appear to Be True

REVIEW OF: **Smith RV, Havens JR, Walsh SL. Gabapentin misuse, abuse and diversion: a systematic review. *Addiction*. 2016;111(7):1160–1174. doi:10.1111/add.13324.**

STUDY TYPE: **Systematic review**

Gabapentin is FDA-approved for seizures and neuropathic pain, but it's commonly used off-label for a variety of psychiatric and physical conditions, including anxiety, insomnia, borderline personality disorder, alcohol use disorders, and multiple pain disorders. Another aspect of gabapentin use that has come to light in recent years is a seemingly pervasive pattern of misuse and abuse. This has perplexed clinicians and researchers alike as gabapentin has long been considered to have no abuse potential. While the DEA has classified pregabalin as a Schedule V substance, gabapentin is only considered a Schedule V drug in some states, including Kentucky, Tennessee, and West Virginia. In order to understand the magnitude of and reasons behind the misuse and abuse of gabapentin, University of Kentucky researchers did a systematic review on the issue.

Multiple databases were mined for peer-reviewed articles on the misuse of gabapentin, which was defined as taking medication without a prescription or at a higher dose than prescribed. The final analysis included 47 case studies and 11 epidemiological reports from around the world. Here's what the researchers found.

RESULTS

Based on a study of 1,500 people in the U.K., it's estimated that gabapentin is abused by a tad over 1% of the general population. Not surprisingly, the groups most at risk of gabapentin misuse are those with a history of alcohol, illicit drug, or opioid abuse or dependence. People mostly misuse the medication in order to get high, self-medicate, and harm themselves. And they aren't using it in isolation. Gabapentin is commonly combined with alcohol, benzodiazepines, and opioids. Regarding the latter, upwards of 22% of opioid abusers in the U.S. and U.K. are believed to also abuse gabapentin. Interestingly, those who misuse gabapentin report subjective sensory and psychological experiences similar to benzodiazepines, opioids, and psychedelics.

The range of doses being abused varies and often falls within the standard therapeutic range of 900–3,600 mg/day. But, when euphoria is the goal of the abuser, gabapentin may be crushed into powder and inhaled. In some cases of misuse, doses of up to 12,000 mg have been seen, but 4,800 mg seems to be the upper limit if the intent is to create a sense of sedation or relaxation. With abrupt discontinuation of doses greater than 3,600 mg/day, some have experienced withdrawal symptoms, including confusion, tremor, agitation, and sweating.

THE CARLAT TAKE

As noted above, gabapentin is typically not used in isolation. Abusers can achieve feelings of euphoria and calmness at much lower doses when gabapentin is combined with other medications like buprenorphine, methadone, baclofen, or quetiapine. The street value of gabapentin also supports the anecdotal reports of its abuse potential, particularly when it comes to recreational use. Several studies from the U.S. and U.K. found that gabapentin was often traded for illicit drugs and commanded up to $7 per pill on the street.

PRACTICE IMPLICATIONS

It appears there is validity to the anecdotal reports we all hear about the misuse and abuse of gabapentin. Therefore, we should prescribe it conservatively, especially to those using benzodiazepines and opioids, individuals battling alcohol and drug addiction, or patients already taking psychiatric medications that can potentiate gabapentin's abusive properties.

Neurostimulation for Opioid Withdrawal Symptoms

REVIEW OF: Miranda A, Taca A. Neuromodulation with percutaneous electrical nerve field stimulation is associated with reduction in signs and symptoms of opioid withdrawal: a multisite, retrospective assessment. *Am J Drug Alcohol Abuse.* 2018;44(1):56–63. doi:10.1080/00952990.2017.1295459.

STUDY TYPE: Retrospective case series

A challenging barrier for patients with opioid use disorders is the discomfort that can occur during the "induction phase" of their treatment, which is the period between discontinuation of opioids and initiation of medication-assisted therapy (MAT). Difficulties with induction arise due to several factors, including fear of withdrawal itself and poorly managed withdrawal symptoms.

In 2017, the FDA cleared a device for the use of electrical stimulation to reduce opioid withdrawal symptoms. The prescription-only product, called NSS-2 BRIDGE®, is attached behind the ear using adhesives and does not require surgery. It generates low-voltage electrical current that stimulates percutaneous nerves around the ear. This results in diminished withdrawal-associated pain and negative emotional states. It is worn continuously for 5 days during the withdrawal period, which covers the full life of the device's battery. BRIDGE® is thought to produce rapid and sustained improvements in withdrawal symptoms, leading to higher MAT transition rates.

The FDA's approval of the device was based on an open-label, uncontrolled, retrospective study in adult patients. Seventy-three medical records were reviewed from outpatient clinics in several Midwestern states. Concerning patient characteristics, the mean length of opioid dependence was 70 months, and most used heroin. Outcomes assessed included withdrawal scores during the induction phase measured by the Clinical Opiate Withdrawal Scale (COWS) and the percentage of patients who transitioned to MAT after 5 days.

RESULTS

Overall, most patients had moderate withdrawal symptoms, and their average initial COWS score was 20.1. But using the device for 20 minutes produced a 63% drop in average COWS scores, to 7.5. Scores then dropped to 3.1 after 60 minutes and 0.6 after 5 days. On the fifth day, 64 of 73 participants (88%) returned to the clinic and successfully transitioned to MAT. No rescue medications were administered, and no adverse events were noted.

THE CARLAT TAKE

Since this article was published, there have been new revelations about the legitimacy of this study. Investigative reporters have looked into the methodology and circumstances surrounding BRIDGE®. While the article claims to be a retrospective study, it is more akin to a clinical

trial, but did not follow the stricter internal review board requirements that are standard for a clinical trial. Only a select group of patient charts were analyzed, and there was no reporting on the full extent of the dropout rate. Furthermore, the researchers did not disclose significant financial interest in the BRIDGE® treatment protocol. The *American Journal of Drug and Alcohol Abuse* published an addendum about this conflict of interest and is even considering retracting the article altogether (Corrigendum, *Am J Drug Alcohol Abuse* 2018;44(4):498).

This pilot study provides us with exciting data but falls short of indicating whether use of this device leads to improved short- and long-term outcomes for patients with opioid use disorders. While it provides an outpatient-based, medication-free method of managing detox symptoms, it is unclear how the device compares to standard detox protocols. Randomized controlled trials are needed to assess whether BRIDGE® is truly an improvement over current standard treatment.

PRACTICE IMPLICATIONS

BRIDGE® may very well be appropriate for cash-pay detox and MAT programs if future data support its use. But it costs approximately $600 and is not covered under insurance plans, limiting its utility in many patient populations. It is for one-time use and requires special training to place. Ultimately, BRIDGE® is an encouraging step in addiction treatment, but may not make a profound impact for the general population.

How Low Can You Go? Ultra-Low Magnitude Reinforcers in a Methadone Clinic

REVIEW OF: Kropp F, Lewis D, Winhusen T. The effectiveness of ultra-low magnitude reinforcers: findings from a "real-world" application of contingency management. *J Subst Abuse Treat*. 2017;72:111–116. doi:10.1016/j.jsat.2016.06.012.

STUDY TYPE: Open-label, non-controlled trial

Contingency management (CM) programs are often effective, but they can be expensive, with typical incentives costing $900–$3,000 for a 12-week program. Expensive CM programs are referred to as "high magnitude." In this new study, researchers tested an "ultra-low magnitude" program (basically, a very cheap program) to see if offering inexpensive reinforcers would be effective for an opioid-abusing clientele.

The staff of a methadone program in the Midwest were trying to improve the abysmal attendance at their optional therapy groups and 12-step groups—only about 6% of patients were showing up. The bare-bones budget allowed no more than $15 per week for incentives, so the team came up with the following system: Any patient who attended group was eligible to enter a raffle drawing for a free methadone dose, which normally required a $15 clinic copay. Attending multiple groups increased patients' odds of winning, and the intervention lasted 12 months total with a 3-month follow-up period.

RESULTS

From 503 to 544 patients participated in the study, depending on the month. A significant boost to overall attendance of groups was recorded at the first month (odds ratio (OR) = 1.48, $p = 0.016$), but this was not sustained throughout the study period. On further analysis, no significant improvement was seen for clinician-led groups in any month. However, the peer-led Methadone Anonymous (MA) groups did see a significant increase in attendance through the full 12 months of the intervention (OR = 3.86, $p < 0.001$) and through the 3-month follow-up period after the intervention was terminated (OR = 4.49, $p < 0.001$).

THE CARLAT TAKE

There were a few research design issues, such as a lack of a control group, that weaken our confidence in the results a bit. The researchers used a pre-post design comparing monthly rates of group attendance to the month immediately before the study period. And there is no proof that the increase in MA attendance led to lower relapse rates or other clinical outcomes. Nonetheless, a very cheap program (it averaged $1 per patient per week) worked surprisingly well for increasing treatment participation, mainly at MA groups.

PRACTICE IMPLICATIONS

CM is effective and need not be costly. Other proven ways to reduce costs of CM include using lottery tickets instead of high-magnitude prizes, because a smaller chance of a bigger prize seems to work just as well as a bigger chance of a smaller prize. This ultra-low magnitude reinforcer study, though, is about as low as you can go with CM cost reduction. It's well worth a try at other treatment programs.

Does Adolescent Vaping Lead to Cigarette Smoking?

REVIEW OF: Goldenson NI, Leventhal AM, Stone MD, McConnell RS, Barrington-Trimis JL. Associations of electronic cigarette nicotine concentration with subsequent cigarette smoking and vaping levels in adolescents. *JAMA Pediatr*. 2017;171(12):1192–1199. doi:10.1001/jamapediatrics.2017.3209.

STUDY TYPE: Prospective cohort study

Considering them less lethal than traditional cigarettes, many adolescents are turning to electronic cigarettes as a "safer" alternative to tobacco products. In 2016, 11% of U.S. 10th graders reported using e-cigarettes for vaping. Adolescents who vape can inhale nicotine concentrations ranging from 0 mg/ml to 25 mg/ml, compared to roughly 10 mg of nicotine in a cigarette. Since nicotine's impact on a developing nervous system is greatest during early adolescence, exposure to high nicotine levels during this period increases the risk of nicotine dependence.

The current study, conducted by researchers at the University of Southern California, looked at vaping habits of 10th graders in Los Angeles to determine if there is an association between baseline nicotine concentrations vaped, and the resulting frequency and intensity of eventual tobacco cigarette smoking at 6 months follow-up. All data were collected using questionnaires. Students who used e-cigarettes in the previous 30 days provided information on the concentration of nicotine vaped, the number of days vaped, the intensity of vaping, the number of days smoking tobacco cigarettes, and the number of tobacco cigarettes smoked. All measurements were collected at baseline and follow-up. Nicotine concentrations were grouped by none (0 mg/ml), low (1–5 mg/ml), medium (6–17 mg/ml), and high (≥ 18 mg/ml).

RESULTS

Overall, 3,252 students completed the initial assessment. The final sample of those who took the second survey included 181 students who vaped, 96 (53%) of whom were boys. At the 6-month follow-up, the 21 adolescents who used high-nicotine e-cigarettes were smoking 7 times as many tobacco cigarettes per day (RR 7.03, CI 6.11–7.95) as those who used non-nicotine e-cigarettes. Adolescents who used medium- or low-nicotine e-cigarettes did not have an increase in daily smoking cigarettes at 6-month follow-up compared to non-nicotine vapers but did have more vaping episodes per day and more puffs per episode.

THE CARLAT TAKE

The results of this study provide evidence that use of e-cigarettes with high nicotine concentrations can lead adolescents to smoke tobacco cigarettes. E-cigarettes are popular among adolescents. However, nicotine remains highly addictive regardless of its formulation. Exposure

to high levels of nicotine concentration during early adolescence increases the risk of addiction and negatively impacts the development of brain circuits controlling attention, complex thinking, and impulsivity.

PRACTICE IMPLICATIONS

This study helps to challenge the perception that vaping nicotine is safe and reinforces that we should continue to advise adolescents to avoid nicotine in any form. In addition, this study shows that the higher nicotine concentration adolescents vape, the more they vape in the future. Vaping is a gateway to cigarette smoking, the deleterious health effects of which are well-established and widespread. A recent *NEJM* perspective article was published alerting physicians of the danger to children in this emerging public health concern (Barrington-Trimis JL and Leventhal AM, *N Engl J Med* 2018;379(12):1099–1102).

Does Moderate Alcohol Use Lead to Cognitive Decline?

REVIEW OF: Topiwala A, Allan CL, Valkanova V, et al. Moderate alcohol consumption as risk factor for adverse brain outcomes and cognitive decline: longitudinal cohort study. *BMJ*. 2017;357:j2353. doi:10.1136/bmj.j2353.

STUDY TYPE: Prospective cohort study

It's well-established that long-term, heavy alcohol use can damage the brain and can cause problems such as Wernicke-Korsakoff syndrome and alcohol-related dementia. But what about the vast majority of our patients, who just drink moderately? A recent study reports an association between light to moderate drinking and hippocampal atrophy.

In the Whitehall II imaging study, 550 civil servants in the U.K. without alcohol use disorder were enrolled. All participants were given the CAGE questionnaire, and to be included, they had to score < 2 (considered not to have an alcohol use disorder). Participants were then followed over 30 years, from 1985 to 2015. Patients were asked to track their weekly consumption and then report on an annual basis through a questionnaire.

Participants' drinking habits were ascertained by asking them to estimate how many drinks they had per week. Based on their answers, they were divided into the following groups: "abstinent" (< 1 unit per week), "light" (1 to < 7 units per week), "moderate" (7 to < 14 units per week for women or 7 to < 21 units per week for men), and "unsafe" (14+ units per week for women or 21+ units per week for men). A standard 6-oz glass of wine would equal 2.4 units of alcohol, and a standard 12-oz beer roughly 2 units. The primary outcomes were the results of cognitive function tests (MoCA and MMSE) and brain imaging results from annual MRI scans administered over the 30 years.

RESULTS

The results of the study showed an association between higher alcohol use and reduced gray matter density, hippocampal atrophy, and reduced white matter microstructural integrity. Even at only moderate alcohol consumption, the risk of hippocampal atrophy was significant (odds ratio 3.4, $p = 0.007$). For the cognitive tests, higher alcohol consumption predicted faster decline of lexical fluency (naming words that begin with the same letter), but no difference in semantic fluency (naming words belonging to the same category) or word recall. Furthermore, there was no difference in the results of the full MoCA or MMSE.

THE CARLAT TAKE

This study shows a correlation between long-term drinking, even light to moderate drinking, and brain abnormalities. The clinical relevance of this, though, is not clear. Drinkers did not do any more poorly than abstainers on 4 out of 5 cognitive tests, so it's possible that the MRI

findings seen do not lead to actual cognitive difficulties. It's also important to point out that the findings were correlations and do not imply causality.

PRACTICE IMPLICATIONS

The results are consistent with the hypothesis that drinking can cause brain changes without clear cognitive consequences. Sharing these findings with patients may be helpful, particularly if they are curious about the topic. But the study does not convincingly argue that everybody should cease drinking alcohol.

Can a One-Week Naltrexone Detox Reduce Outpatient Opioid Relapse Rates?

REVIEW OF: Sullivan M, Bisaga A, Pavlicova M, et al. Long-acting injectable naltrexone induction: a randomized trial of outpatient opioid detoxification with naltrexone versus buprenorphine. *Am J Psychiatry*. 2017;174(5):459–467. doi:10.1176/appi.ajp.2016.16050548.

STUDY TYPE: Randomized, open-label, active-controlled trial

Naltrexone is an opioid blocker that is FDA-approved for the treatment of alcoholism. However, it is also effective off-label for treating opioid use disorder. The medication comes in two forms: an oral pill (brand name ReVia) and an injectable version (XR naltrexone, or Vivitrol). XR naltrexone is composed of 380 mg of naltrexone, given as an intramuscular injection once a month. During that month, patients who try to use opioids will feel little if any high. This works well to prevent relapse if patients keep getting the shot.

However, it is challenging to get patients started on XR naltrexone. If they are actively using, the injection will put them into an immediate and very unpleasant withdrawal. So, a common approach is to first give these patients a tapering dose of buprenorphine for a week, and then to wait a second week to completely wash out any last molecules of opioids in their bloodstream. The problem is that this 2-week delay leads to high rates of attrition and relapse, especially in outpatients. In this study, Sullivan and colleagues compared the standard 2-week delay with a rapid 7-day detox protocol using oral naltrexone as a bridge to injectable naltrexone.

Researchers recruited 150 patients with opioid dependence from an outpatient research clinic, of which 36.7% were primarily prescription opioid users. Participants, who were mostly male (86%), Caucasian (64%), and around 35 years old (SD 11.4), were randomly assigned to either a 1-week naltrexone detox or a 2-week buprenorphine taper/washout. In both arms, participants didn't use for 12–24 hours and arrived at the clinic on day 2 in mild to moderate withdrawal. Both treatment arms received up to 8 mg buprenorphine on the first day to ease withdrawal symptoms. The naltrexone group (n = 98) received scheduled doses of clonidine and clonazepam on days 3–8 and oral naltrexone titrated from 1 mg to 25 mg over days 4–7. On day 8, they received a 380 mg injection of XR naltrexone. The buprenorphine group (n = 52) received a typical 7-day buprenorphine taper followed by a 7-day washout period, during which they were given ancillary comfort medications as needed. On day 15, participants who tolerated a 0.8 mg test dose of oral naltrexone received the XR naltrexone shot.

After getting XR naltrexone, participants in both groups received 4 weeks of outpatient treatment, including weekly medical visits, biweekly therapy, and urine toxicology screens at each visit. In the fifth post-induction week, participants were offered a second dose of XR naltrexone and referrals to continue treatment in community programs as warranted.

RESULTS

Patients randomized to the 1-week detox were more likely to get the injection (56.1% made it) than those in the 2-week detox group (only 32.7% made it). But among those who received XR naltrexone (56), 89.1% of the 1-week group and 82.4% of the 2-week group received a second injection, demonstrating that participants didn't find the rapid detox aversive enough to refuse the second injection. Overall, 50.0% of the full naltrexone group received the second injection compared to 26.9% of the buprenorphine group.

THE CARLAT TAKE

The rapid 1-week naltrexone detox seems to be the better method of getting patients to start the injectable XR naltrexone treatment. Many patients (29%) in the buprenorphine arm relapsed during the 1-week washout period.

PRACTICE IMPLICATIONS

Getting opioid users to stick to treatment is difficult, and the quicker they are linked to effective treatment, the better. If you have opioid-addicted patients who want to try XR naltrexone to prevent relapse, consider this rapid 1-week technique, which allows you to avoid a washout period entirely.

How Effective Is Tramadol for Opioid Withdrawal?

REVIEW OF: Dunn KE, Tompkins DA, Bigelow GE, Strain EC. Efficacy of tramadol extended-release for opioid withdrawal: a randomized clinical trial. *JAMA Psychiatry*. 2017;74(9):885–893. doi:10.1001/jamapsychiatry.2017.1838.

STUDY TYPE: Randomized, double-blind, active-controlled trial

Opioid withdrawal protocols often rely on a buprenorphine taper, but other medications are regularly used either in addition to or in the place of buprenorphine. In particular, tramadol ER, a mild opiate, may be effective and was recently studied at Johns Hopkins University School of Medicine.

A total of 103 participants with opioid dependence were enrolled in this study comparing tramadol ER (n = 36), buprenorphine (n = 31), and clonidine (n = 36) for opioid withdrawal. Overall, 88 of the subjects (85.4%) were male, 43 (41.7%) were white, and average age was 29 years. Past 30-day use of heroin was reported by 96 (93.2%) of the participants vs 49 (47.5%) who reported using prescription opioids in that time period (some used both).

People in the study were randomized to three arms: tapering with tramadol (up to 600 mg/day), clonidine (up to 0.8 mg/day), or buprenorphine (up to 8 mg/day). Following the weeklong taper, all participants were crossed over to placebo for a week, then were given a naloxone challenge to verify successful withdrawal.

The trial used several measures, including the Subjective Opiate Withdrawal Scale (SOWS) completed by participants, the Clinical Opiate Withdrawal Scale (COWS) completed by clinicians, pupil diameter, and concomitant medication use (mostly over-the-counter meds for gastrointestinal symptoms, pain, and sleep).

RESULTS

Researchers found that tramadol ER was significantly more effective than clonidine and comparable to buprenorphine in terms of patient retention and withdrawal symptom suppression during the 7-day detox period. Patients treated with clonidine and tramadol used more concomitant supportive medications during the taper than those on buprenorphine, though the number of medications used was low (average of 0–2 medications) across all three groups.

THE CARLAT TAKE

Based on this study, tramadol seems like an attractive option—you don't need a buprenorphine waiver, and it may be more effective than clonidine. Considering it is an opioid agonist, it's no surprise that tramadol helps alleviate withdrawal symptoms. But the doses of tramadol used were particularly high (usual dose in pain is 50–200 mg/day), whereas the doses of buprenorphine were relatively low (usual dose in detox is 8–16 mg/day).

PRACTICE IMPLICATIONS

If buprenorphine is not an option for your opioid withdrawal protocol, then tramadol could be worth considering. Just be cautious of such high doses of tramadol and drug interactions, especially with serotonergic agents (increased seizure risk).

Guidelines for Switching From Methadone to Buprenorphine

REVIEW OF: Lintzeris N, Monds LA, Rivas C, et al. Transferring patients from methadone to buprenorphine: the feasibility and evaluation of practice guidelines. *J Addict Med.* 2018;12(3):234–240. doi:10.1097/ADM.0000000000000396.

STUDY TYPE: Prospective cohort study

Recent guidelines published by the American Society of Addiction Medicine (ASAM) and nationally in Australia provide support for transferring patients from methadone to buprenorphine-naloxone (BNX). Patients may switch thinking BNX is easier to discontinue or because of methadone side effects. The transition can be complicated by relapses or precipitated withdrawal when starting BNX. To minimize adverse events, the ASAM and Australian guidelines recommend the following (summarized; Kampman K and Jarvis M, *J Addict Med* 2015;9(5):358–367):

1. Consider inpatient treatment for patients with significant medical comorbidities, unstable social conditions, or for those transferring from high methadone doses (> 50 mg/day).
2. Gradually reduce methadone until the patient experiences mild to moderate opioid withdrawal symptoms between doses.
3. Stop methadone and begin monitoring regularly for opioid withdrawal, using measures such as the Clinical Opiate Withdrawal Scale (COWS).
4. Start low-dose BNX at 2 mg, at least 24 hours after the last dose of methadone and after the patient experiences moderate opioid withdrawal (COWS score > 12), monitoring hourly afterwards for precipitated withdrawal.
5. Administer 6 mg after 1 hour; additional doses, 4–8 mg, are symptom-triggered.
6. On successive days: BNX dosage = the previous day's dose plus additional symptom-triggered doses.

Lintzeris and colleagues studied the clinical feasibility of these guidelines. They reviewed medical records of four Australian specialist addiction centers to assess the outcomes of guideline feasibility, transfer practices, and patient responses.

RESULTS

In all, 33 adult participants transferred, 9 from low-dose (LD) methadone (< 30 mg/day), 9 from medium-dose (MD) methadone (30–50 mg/day), and 15 from high-dose (HD) methadone (> 50 mg/day). Most HD transfers occurred in inpatient settings (93%), while most MD/LD transfers occurred in outpatient settings (67%). Inpatient stays were 2.2 days on average. 70% of transfers were consistent with the guidelines. Most patients stabilized their BNX dose by day 3, with 96% using ≥ 12 mg/day.

Overall, 79% (26/33) were still on BNX treatment at day 7 and were considered to have successfully transferred.

Three patients experienced precipitated withdrawal, all in the HD group, and all returning to methadone. Three patients resumed methadone due to anxiety and poor sleep with BNX. One participant relapsed and used heroin for several days before resuming methadone.

THE CARLAT TAKE

Although this was a small sample, the findings are useful. They suggest most patients can successfully transfer from methadone to BNX when using the guidelines. Those transferring from HD methadone require inpatient settings and specialist supervision, while most MD/LD methadone transfers may be suitable for outpatient clinics. It is important to avoid precipitated withdrawal, as that will most likely lead to failed transfer to BNX.

PRACTICE IMPLICATIONS

These guidelines are easy to follow and provide practical advice on how to transition from methadone to BNX. Close monitoring during the initial test doses of BNX is paramount. If followed, precipitated withdrawal is unlikely to happen, and most patients will be able to successfully transition to BNX.

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PSYCHOTHERAPY INTERVENTIONS

Computer Games: Good for Cognitive Disorders?

REVIEW OF: Hill NTM, Mowszowski L, Naismith SL, Chadwick VL, Valenzuela M, Lampit A. Computerized cognitive training in older adults with mild cognitive impairment or dementia: a systematic review and meta-analysis. *Am J Psychiatry*. 2017;174(4):329–340. doi:10.1176/appi.ajp.2016.16030360.

STUDY TYPE: Systematic review and meta-analysis of randomized controlled trials

Can patients train their way to better cognition? We've all seen the ads from companies such as Lumosity implying that fun, computer-based learning games will help your mind work better. Such methods are called computerized cognitive training (CCT), and past systematic reviews have had weaknesses, such as combining CCT with other interventions or including studies that were not randomized controlled trials. These researchers performed a systematic review that was more rigorous.

The study authors located 29 studies that met their strict criteria for inclusion in the meta-analysis. All studies had to randomly assign people to both a treatment arm and a control arm, and the CCT interventions had to include at least 4 hours of video games or virtual reality games. In almost all of the trials, the training was given in a group format with supervisors overseeing the process. The studies tested many commercial and nonprofit products, including Lumosity, BrainFitness, CogniPlus, Sociable, and others.

In all, 17 studies enrolled patients with mild cognitive impairment, or MCI (n = 686, CCT: n = 351, mean age = 67–81), while 12 studies enrolled patients with dementia (n = 389, CCT: n = 201, mean age = 66–81). Outcome variables included changes in cognition scores, activities of daily living, and psychosocial functioning. The length of these studies was relatively short, often lasting 1–3 months, with some going a little longer.

RESULTS

CCT bested control groups for patients with MCI on several measures, with an overall moderate effect size on cognition of 0.35 (CI = 0.21–0.50). CCT training led to moderate improvements in most domains, including verbal memory, nonverbal learning, working memory, and attention. Interestingly, there were also improvements in depression and quality-of-life measures. However, CCT-exposed patients did not improve in measures of executive functioning.

CCT was less helpful for patients with dementia. The few significant results hinged on two studies looking at nontraditional, highly stimulating varieties of CCT—virtual reality and Nintendo Wii.

THE CARLAT TAKE

The results appear promising for patients with MCI, and to some degree even for those with dementia. However, the follow-up was short (1–3 months), and it's not yet clear whether such

cognitive gains would be maintained once patients stop the training. In addition, these programs were supervised group programs, whereas most of the heavily advertised commercial products that your patients are likely to choose are home-based and oriented toward individual use.

PRACTICE IMPLICATIONS

Tell your patients with MCI that computerized training programs might be helpful for memory improvement, but that the best evidence is for organized group programs with trained supervisors. They may improve memory and attention in the short term, but no long-term effects are known. Home-based single-player computer games might be helpful, but we need more evidence before giving them a strong endorsement.

Parent-Focused Therapy Outperforms Conjoint Therapy for Anorexia

REVIEW OF: Le Grange D, Hughes EK, Court A, Yeo M, Crosby RD, Sawyer SM. Randomized clinical trial of parent-focused treatment and family-based treatment for adolescent anorexia nervosa. *J Am Acad Child Adolesc Psychiatry*. 2016;55(8):683–692. doi:10.1016/j.jaac.2016.05.007.

STUDY TYPE: Randomized, single-blind, active-controlled trial

Few disorders frustrate clinicians as much as anorexia nervosa (AN). Family-based therapy (FBT) is one of the few effective AN treatments. In FBT, a family therapist works with the entire family to come up with a weight restoration plan for the patient.

FBT works pretty well, with rates of remission in the 40% range at 12 months. But there's room for improvement, and a newer technique has been adapted from FBT. Called parent-focused therapy (PFT), it is essentially FBT but with one crucial difference—the adolescent is not included in the sessions. Instead, the adolescent is separately monitored by a nurse who communicates the patient's weight to the therapist. The theory behind PFT is that the therapist can work more effectively with the parents without the distraction of the patient, who is often resistant to the weight restoration plans being developed.

Various small studies have already been done showing that PFT may work more quickly than FBT. This latest study is the largest one yet. Over the course of 4 years, 107 patients ages 12–18 and diagnosed with AN were randomized to receive FBT or PFT. Both treatments were manualized and included 18 outpatient sessions spanning 6 months. The main outcome of interest was the rate of remission at treatment's end (achieving > 95% of median body mass index). Subjects were assessed at baseline, at end of treatment, and at 6 and 12 months after treatment.

RESULTS

At the end of treatment, the remission rate for the PFT group was 43% compared to 22% for the FBT group, a difference that was highly statistically significant ($p = 0.016$). At the 6-month follow-up, PFT's remission rate was still higher, but it missed statistical significance by a hair (PFT 39% vs FBT 22%; $p = 0.053$). At 12 months, the numbers in favor of PFT were less impressive (PFT 37% vs FBT 29%; $p = 0.444$).

THE CARLAT TAKE

PFT appears to be more effective than FBT in helping anorexic patients regain weight over 6 months, and PFT appeared to be more effective 6 months after treatment, with a p level so close to the 0.05 threshold that many readers will trust the result is "real." At the 12-month follow-up, there was a large cumulative dropout rate of over 40%, limiting what we can conclude about that time point.

PRACTICE IMPLICATIONS

If you have been doing family therapy with your AN patients, you should consider the possibility that seeing the parents alone may be the more effective approach. The authors point out that PFT may lead to greater treatment access, because relatively few therapists have the formal family therapy training required for full FBT. That's likely doubly true for psychiatrists, and many of us feel more comfortable doing therapy with two other people in the room as opposed to an entire family. For either treatment, the results shown in the clinical trials are the outcomes of manualized therapy interventions.

Can Just 11 Minutes of Mindfulness Training Reduce Alcohol Consumption?

REVIEW OF: Kamboj SK, Irez D, Serfaty S, Thomas E, Das RK, Freeman TP. Ultra-brief mindfulness training reduces alcohol consumption in at-risk drinkers: a randomized double-blind active-controlled experiment. *Int J Neuropsychopharmacol.* 2017;20(11):936–947. doi:10.1093/ijnp/pyx064.

STUDY TYPE: Randomized, double-blind, active-controlled trial

Mindfulness is a growing trend in mental health treatment, but it often requires hours of practice to become proficient. What if you could provide your patients with an introductory mindfulness lesson in less than 15 minutes and see meaningful reductions in their risky drinking?

Kamboj and colleagues designed a randomized, double-blind study to examine whether ultra-brief mindfulness training could yield better outcomes than a closely matched active control using relaxation. Participants (n = 68, 50% female) met study criteria for being "hazardous drinkers" by consuming at least 14 or 21 standard units of alcohol per week for women and men, respectively (one 12-oz beer with 5% alcohol = 1.75 units of alcohol).

Following intake, instructions for mindfulness (n = 34) and relaxation (n = 34) were given to participants. Relaxation instructions discussed calming the mind, releasing tension, and gaining control over cravings. Mindfulness instructions focused on being attentive and experiencing cravings as temporary events in the body that could be tolerated without acting on them.

Instructions involved four phases: introduction (30 seconds), explanation of strategy (3 minutes), preliminary experiential practice (4 minutes), and main strategy practice (7 minutes). Participants received practice materials and were instructed to practice their assigned strategy for 15 minutes daily over the following week.

RESULTS

At 1-week follow-up, the mindfulness group showed a significant reduction in alcohol consumed, with a reduction of 9.31 units or 74.5 g of ethanol ($p < 0.001$) compared to a reduction of just 3.00 units or 24.0 g of ethanol for the active control.

THE CARLAT TAKE

This study is very short-term (1 week), and there needs to be longer follow-up to evaluate the sustained effects of this mindfulness training. But even in small doses, teaching patients to use basic mindfulness strategies to tolerate cravings may yield meaningful reductions in alcohol or substance use, at least in the short term. Having an active control group in this study is also important—it shows that the results were not just from the provider taking extra time with the patient, but were more likely to be from the mindfulness technique itself. A recent systematic

review (Sancho M et al, *Front Psychiatry* 2018;9:95) confirms these positive findings for mindfulness techniques in a variety of substance use disorders. But again, no long-term follow-up data were evaluated.

PRACTICE IMPLICATIONS

The great thing about mindfulness is that it can be used by nearly everyone for a variety of mental health problems—depression, anxiety, insomnia, and addiction, to name a few. Like any skill, gaining proficiency will take time, but even beginners can benefit from a quick lesson. It's a good idea to have a few basic mindfulness techniques in your back pocket to practice with patients in your office. It only takes a few minutes and can yield some immediate results.

Grief-Focused Psychotherapy Is More Effective Than Citalopram

REVIEW OF: Shear MK, Reynolds CF III, Simon NM, et al. Optimizing treatment of complicated grief: a randomized clinical trial. *JAMA Psychiatry*. 2016;73(7):685–694. doi:10.1001/jamapsychiatry.2016.0892.

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

Complicated grief (CG) is a relatively common response in those who have suffered the loss of a loved one. In DSM-5, it is listed in the section on conditions for further study, and it is called "persistent complex bereavement disorder." To meet the diagnostic criteria, a patient must have suffered bereavement for at least 6 months and must have had at least 3 of a list of symptoms for 1 month. While there is some overlap with major depression, CG has core symptoms of yearning and sorrow and great difficulty accepting the reality of death. It's one of the more controversial proposed DSM disorders, with critics seeing it as medicalizing a normal human experience. Nonetheless, there has been a lot of research on how to help people with CG, and a specific psychotherapy, called complicated grief treatment (CGT), is clearly effective. But how does therapy compare with a standard antidepressant?

To answer this question, researchers recruited 395 individuals diagnosed with CG; the majority were women, the mean age was 53, and the mean number of years since the loss was 4.7. These patients were randomized to one of four groups: citalopram (n = 101), placebo (n = 99), CGT with citalopram (n = 99), and CGT with placebo (n = 96). The citalopram (CIT) was flexibly dosed with an average of 33.9 mg/day. Spanning 20 weeks, patients were assessed monthly with the Clinical Global Impressions (CGI) scale, which was the primary outcome measure. Secondary measures to assess depression included the self-report version of the Quick Inventory of Depressive Symptomatology (QIDS SR-16) and a modified version of the Columbia-Suicide Severity Rating Scale.

RESULTS

The main outcome measure was the response rate after 20 weeks, defined as "much improved" or "very much improved" on the CGI scale. Patients in the CGT groups did the best, whether the therapy was combined with CIT (83.7% response rate) or with placebo (82.5%). Adding CGT to CIT was more effective than CIT alone (83.7% vs 69.3%, relative risk 1.21, p = 0.05), and CIT alone was numerically superior to placebo, but it didn't quite reach statistical significance (69.3% vs 54.8%, p = 0.11). On the secondary outcome of change in the QIDS SR-16, adding CIT to CGT did outperform CGT alone (p = 0.04).

THE CARLAT TAKE

CGT was clearly more effective for CG than CIT. While CIT alone did not statistically outperform placebo, there is a factor that might have put the medication at a disadvantage. The 2011 FDA warning about high CIT doses causing ECG abnormalities was issued a year into

the study, forcing researchers to decrease the maximum dose allowed from 60 mg to 40 mg. That led to a lower-than-planned CIT average dosing of 33.9 mg, which may have limited its efficacy.

PRACTICE IMPLICATIONS

The loss of a loved one is a life-changing experience that is difficult for anyone. For those who are having prolonged, complicated bereavement, they may need help getting through the grieving process. The bottom line is that while CGT is the treatment of choice for CG, adding an SSRI to this psychotherapy might provide a small efficacy boost for depressive symptoms.

Internet-Delivered CBT for Adolescents With OCD

REVIEW OF: Lenhard F, Andersson E, Mataix-Cols D, et al. Therapist-guided, internet-delivered cognitive-behavioral therapy for adolescents with obsessive-compulsive disorder: a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2017;56(1):10–19.e2. doi:10.1016/j.jaac.2016.09.515.

STUDY TYPE: Randomized, single-blind, controlled trial

The prevalence of obsessive-compulsive disorder (OCD) in childhood and adolescence is 2% (Angst J et al, *EurArch Psychiatry Clin Neurosci* 2004;254(3):156–164). Cognitive behavioral therapy (CBT) is a very effective treatment for pediatric OCD. So why aren't more parents taking advantage of it? It can be costly, and there aren't enough therapists who are well-trained in using CBT for adolescents with OCD. The question is, how can we deliver this proven treatment to the patients who need it? In this study, Lenhard and colleagues attempted to determine whether internet-delivered CBT is effective.

This 12-week study took place in Stockholm, Sweden. In it, 67 patients with OCD between 12 and 17 years of age were randomly assigned to a therapist-guided internet CBT group (ICBT, n = 33) or to a waitlist (n = 34). Participants were recruited through advertising or referral by primary care doctors or mental health specialists. Outcomes were measured at baseline, 12 weeks (the end of treatment), and 3 months post-treatment. The ICBT program, designed by trained CBT therapists for a previous study, consisted of 12 online chapters with text, films, and animations. Some chapters were primarily for the patients, whereas others were designed for parents. Therapists were available to parents via email and phone throughout the study, but there were no face-to-face therapy appointments scheduled.

RESULTS

At the end of treatment, the ICBT group improved significantly more on the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) scores compared with the waitlist group ($p < 0.001$); 9 ICBT subjects responded (≥ 35% reduction in CY-BOCS), and 5 remitted (no longer met diagnostic criteria for OCD for at least 1 week). Interestingly, at the 3-month follow-up, there was even more improvement in the ICBT group, with 10 responders and 8 remitters. By contrast, no one in the waitlist group responded or remitted at any time point.

THE CARLAT TAKE

This was a fairly small study, and it did not include an active control group, but nonetheless the results were impressive. At 3 months post-treatment, 18 of 33 adolescents responded or remitted. The authors point out that the response was not as robust as that seen in studies of adults using ICBT or in studies of face-to-face CBT in pediatric OCD populations. Still, clinicians spent

only about 17 minutes weekly with each participant—far less than in face-to-face CBT—so cost was significantly reduced.

PRACTICE IMPLICATIONS

Internet CBT is not the perfect solution: Patients must have access to the internet and an ICBT program and have a parent who is motivated enough to participate. This is therapist-guided CBT, not just a self-help program. Still, despite its limitations, ICBT may offer a feasible way of getting treatment to individuals who otherwise might suffer the fate of those on the waitlist—that is, no relief.

MOXO-CPT: Short and Sweet, but Is It Useful?

REVIEW OF: Berger I, Slobodin O, Cassuto H. Usefulness and validity of continuous performance tests in the diagnosis of attention-deficit hyperactivity disorder children. *Arch Clin Neuropsychol*. 2017;32(1):81–93. doi:10.1093/arclin/acw101.

STUDY TYPE: Validity study

Diagnosing ADHD continues to be difficult, time-consuming, and expensive. Having an "objective," valid test for ADHD would be of value to clinicians and families alike. Continuous performance tests (CPT) are gaining popularity as a complement to clinical examination, rating scales, and interviews with parents and teachers. Depending on the specific test, the CPT can generate information about impulsivity, focus, distractibility, and sometimes hyperactivity. But do these quick, kid-friendly computer tests actually aid in diagnosis, or are they just another data point without real clinical benefit? Researchers evaluated the ability of the MOXO-CPT (NeuroTech Solutions Ltd), a computer-based test that assesses several variables, including "correct attention," "correct timing," "impulsive commission," and "hyperactive commission," to detect the presence or absence of ADHD.

Researchers recruited 459 drug-naïve children with ADHD from outpatient pediatric clinics at a university hospital neurocognitive center. Children were included if they met DSM-IV-TR criteria for ADHD and if they did not have a comorbid disorder. Controls were normally developing children recruited from regular school classrooms who scored below the cutoff for ADHD or any developmental disorder on all Conners subscales and DSM-IV scales. Altogether, 493 boys and 305 girls ages 7–12 participated. The two groups did not differ in gender distributions.

For all subjects, parents and teachers were asked to fill out the Conners' Rating Scale or ADHD/DSM-IV scales. Participants took the MOXO-CPT, a simple 15-minute computer test in which images appear on screen for 0.5, 1, or 3 seconds, followed by a blank screen for an equal amount of time. Short animated clips (3–15 seconds) with audio and visual features appear randomly and in close proximity to the test images, to simulate the everyday distractions faced by those with ADHD. In this study, participants were instructed to give a timely, accurate response by pressing the space bar once whenever the designated image appeared. Errors were counted and coded to four performance indices: delay (timing), failure to respond (attention), pressing the space bar excessively or pressing other keys (hyperactivity), or response to the wrong image (impulsivity). The sum of the four indices provided a total score. Presumably, children with ADHD who were on medication did not take it when completing the MOXO-CPT, but the authors did not address medication beyond excluding "chronic" use.

RESULTS

Compared to controls, children with ADHD achieved statistically significant lower scores on all four indices, with the total score being the most robust measure. These findings held true when the subjects were stratified by age. Using different post-hoc cutoffs for the MOXO-CPT total scores for each age, the

authors calculated sensitivity ranging from 81% to 91% and specificity ranging from 85% to 89%. The authors concluded that "integration of CPT indices improves the diagnostic capacity of ADHD."

THE CARLAT TAKE

The authors demonstrated that, under the simplest condition (ie, distinguishing children who have only ADHD from those with no developmental issues), the MOXO-CPT performed well. Even so, it still did less well than the gold standard of a clinical diagnosis by a skilled clinician. Moreover, the authors' decision to use only children with ADHD who were not taking medication chronically and who had no common comorbid conditions excluded such a large proportion of the ADHD population that it is impossible to judge how helpful this version of the CPT would be in real-world clinical situations.

PRACTICE IMPLICATIONS

Clinicians who are seeking "hard data" to boost their diagnosis of ADHD may wish to check out this CPT, along with the many others on the market. However, this is clearly not a shortcut that can replace a thorough assessment, especially when other conditions also are present. Always pair the results from such tests with clinical assessment, rating scales, and collateral from caregivers and teachers.

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CME Pre-Test Questions

The learning objectives and pre-test multiple choice questions in this section have been provided solely as a study tool to prepare you for the quizzes associated with this book that award customers eight (8) Category 1 CME Credits™, or 8 ABPN Self-Assessment credits as part of The 2019 Carlat Psychiatry Report Self-Assessment Course. Post-tests can only be submitted online to receive certificate of credit. Faxed/mailed copies cannot be processed.

Visit www.thecarlatreport.com/PracticeBoosters2 to view the answer key to this pre-test, purchase Self-Assessment or CME courses based on this book, or get instructions for how to complete your test and receive credit.

LEARNING OBJECTIVES:

Describe the clinical practice implications of some of the current findings in the literature regarding the following topics:

1. Mood disorders
2. ADHD
3. Medication side effects
4. Antipsychotics
5. Child and adolescent psychiatry
6. Substance use
7. Psychotherapy interventions

MOOD DISORDERS

1. According to data from the Treatment-Resistant Depression Registry, after what time period does vagus nerve stimulation (VNS) show some effectiveness in treatment-resistant depression? (LO #1)
   a. 1 month
   b. 3 months
   c. 6 months
   d. There was no difference in treatment effectiveness

2. In a recent meta-analysis for treatment of major depressive disorder, when a patient was not responding to an antidepressant, it was better to stay with the same antidepressant rather than switching to another. (LO #1)
   a. True
   b. False

3. Protocols for ketamine infusion in the treatment of major depression still vary widely. A recent systematic review attempted to provide some guidance for use of ketamine. Which intravenous (IV) dose of ketamine was most effective according to this review? (LO #1)

   a. 0.1 mg/kg

   b. 0.5 mg/kg

   c. 2.0 mg/kg

   d. 4.0 mg/kg

4. According to a recent retrospective cohort study of 18,000 patients with bipolar disorder, which medication or class of medications was the most effective in reducing all-cause hospitalization? (LO #1)

   a. Long-acting injectable antipsychotics

   b. Quetiapine

   c. Benzodiazepines

   d. Lithium

ADHD

5. You are treating a 12-year-old boy for ADHD. Reports from his mother and his teachers show he has improved on his current treatment dose of dextroamphetamine/amphetamine, but some lingering problems with attention persist. His mother has concerns about raising the medication dosage and would like to discuss dietary options to aid in her son's treatment. According to recent literature, which of the following supplements has the most robust evidence for the treatment of ADHD symptoms? (LO #2)

   a. Omega-3 fatty acids

   b. Omega-6 fatty acids

   c. Zinc

   d. Magnesium

6. In a recent study of neurofeedback for the treatment of ADHD in adults, there was a significant improvement noted in the Conners' Adult ADHD Rating Scale (CAARS) in which treatment arm? (LO #2)

   a. Neurofeedback

   b. Meta-cognitive group therapy

   c. Sham neurofeedback

   d. All treatment arms

7. In an outpatient practice, you are treating many adolescents with ADHD. For those who don't reach full treatment response with medication, you refer them to cognitive behavioral therapy (CBT) in addition to standard medication management. How many of those adolescents would you expect to meet treatment response with the addition of CBT? (LO #2)

   a. 10%

   b. 25%

   c. 50%

   d. 75%

8. When discussing the effectiveness of modafinil for the treatment of ADHD in children and adolescents, what would be the most accurate description of the effect size of treatment with modafinil compared to placebo? (LO #2)

   a. Small

   b. Medium

   c. Moderate to large

   d. Very large

MEDICATION SIDE EFFECTS

9. Which of the following medications has the lowest mortality and morbidity indexes in an overdose? (LO #3)

   a. Amitriptyline

   b. Clomipramine

   c. Imipramine

   d. Nortriptyline

10. In a recent randomized controlled trial of patients with bipolar II disorder currently in a major depressive episode, there was a significantly higher rate of switching to hypomania when treated with both sertraline and lithium compared to lithium alone. (LO #3)

    a. True

    b. False

11. When starting methylphenidate for the treatment of ADHD, during which time period is the risk of suicide greatest? (LO #3)

    a. There is no increased risk of suicide associated with ADHD treatment

    b. 90 days before starting the prescription

c. 90 days after starting the prescription

d. 90–180 days after starting the prescription

12. More evidence is being released about the risk associated with antidepressant medication use and type 2 diabetes in adults and now in adolescents. For adolescents, which period of antidepressant use is associated with the highest risk of developing type 2 diabetes? (LO #3)

a. First 90 days of use

b. 91–150 days of use

c. 151–210 days of use

d. > 210 days of use

ANTIPSYCHOTICS

13. You are treating a 28-year-old woman with schizophrenia who recently found out she was pregnant with an estimated gestational age of 10 weeks. In the past, when she stopped taking antipsychotic medications, her mental health quickly decompensated, requiring acute psychiatric hospitalization. Which of the following would be the safest medication option for your patient and her unborn child? (LO #4)

a. Risperidone

b. Paliperidone

c. Olanzapine

d. Stop all antipsychotic medications

14. A recent study looked at metformin specifically in children and adolescents with autism spectrum disorder prescribed atypical antipsychotics. How much weight loss would you expect to see in those children prescribed metformin? (LO #4)

a. 2% of body mass index (BMI)

b. 5% of BMI

c. 8% of BMI

d. 12% of BMI

15. You are treating an adult patient for major depressive disorder who has not responded to an adequate dose of an SSRI over a 6-week period. You are considering augmentation with either bupropion or aripiprazole. When thinking over the side effects, which side effect would NOT be more associated with aripiprazole compared to bupropion? (LO #4)

a. Decreased libido

b. Somnolence

c. Akathisia

d. Weight gain

16. For patients with schizophrenia who smoke cannabis, which group has the greatest risk of relapse? (LO #4)

a. Former cannabis users

b. Intermittent cannabis users

c. Continuous users of low-potency cannabis

d. Continuous users of high-potency cannabis

CHILD AND ADOLESCENT PSYCHIATRY

17. In a recent study of using risperidone plus minocycline to treat irritability in children with autism spectrum disorder, about what percentage of children showed at least partial response (> 25% irritability reduction)? (LO #5)

a. 25%

b. 50%

c. 65%

d. 90%

18. SSRIs and SNRIs have the highest effect size when prescribed for treatment of which of the following disorders in children and adolescents? (LO #5)

a. Depressive disorders

b. Obsessive-compulsive disorder

c. Post-traumatic stress disorder

d. Anxiety disorders

19. A recent trial evaluated the use of ER guanfacine for the treatment of ADHD in children diagnosed with autism spectrum disorder. Approximately what proportion of children in the ER guanfacine group were rated as "much improved" or "very much improved" on the Clinical Global Impressions—Improvement (CGI-I) scale? (LO #5)

a. 10%

b. 25%

c. 50%

d. 75%

20. When choosing a pharmaceutical intervention for children with major depressive disorder, which of the following best describes treatment with desvenlafaxine? (LO #5)

    a. Little evidence for its use in this context

    b. Augmentation strategy when used with an SSRI

    c. Second-line monotherapy agent

    d. First-line monotherapy agent

21. In a recent study examining the use of atomoxetine in children with ADHD and dyslexia, which group showed statistically significant improvement across a variety of reading skills? (LO #5)

    a. ADHD only

    b. Dyslexia only

    c. ADHD and dyslexia

    d. Both b and c

SUBSTANCE USE

22. A recent randomized controlled trial evaluated the use of N-acetylcysteine (NAC) in veterans diagnosed with post-traumatic stress disorder (PTSD) and a substance use disorder. The treatment group showed improvement in which of the following? (LO #6)

    a. Clinician-Administered PTSD Scale (CAPS)

    b. PTSD Checklist Military (PCL-M)

    c. Self-report of cravings for substances

    d. All of the above

23. Gabapentin was originally thought to have no abuse potential, but recent reports show that about 1% of the general population abuse gabapentin. However, the rate is higher among those who abuse opioids. According to recent data, what percentage of opioid abusers also abuse gabapentin? (LO #6)

    a. 8%

    b. 22%

    c. 34%

    d. 58%

24. Adolescent vaping of which of the following nicotine concentrations may lead to increased daily cigarette smoking after 6 months compared to no nicotine vaping? (LO #6)

    a. 1–6 mg/ml

b. 7–12 mg/ml

c. 12–18 mg/ml

d. 18+ mg/ml

25. Moderate alcohol use (7 to < 14 units of alcohol per week for women or 7 to < 21 units per week for men) may lead to cognitive decline. (LO #6)

a. True

b. False

26. When transitioning patients from methadone to buprenorphine for maintenance treatment of opioid use disorder, methadone is first titrated down, then stopped for at least 24 hours. After these steps, at what point should buprenorphine treatment be started? (LO #6)

a. Before withdrawal symptoms appear

b. When mild withdrawal symptoms appear

c. When moderate withdrawal symptoms appear

d. Wait until severe withdrawal symptoms appear

PSYCHOTHERAPY INTERVENTIONS

27. One of your patients with mild cognitive impairment (MCI) asks you whether he should play video games for cognitive improvement. What method of computerized cognitive training (CCT) has the best evidence for improving cognition? (LO #7)

a. Group CCT led by trained supervisors

b. Group CCT led by peers

c. Individual home-based CCT

d. There is no evidence for CCT improving cognitive performance

28. A recent study evaluated therapy for the treatment of anorexia nervosa in adolescents, comparing traditional family-based therapy (FBT) to parent-focused therapy (PFT). Which of the following best summarizes the findings? (LO #7)

a. It was better to include both the adolescent and parents in the therapy sessions

b. It was better to have therapy sessions with only the parents

c. It was better to have therapy sessions with only the adolescent

d. No difference was seen between the different therapy interventions

29. When treating complicated grief, which of the following options is likely to have the highest response rate? (LO #7)

    a. Placebo

    b. Citalopram

    c. Complicated grief treatment

    d. Combination of complicated grief treatment and citalopram

30. Cognitive behavioral therapy interventions over the internet (ICBT) have recently been evaluated for the treatment of obsessive-compulsive disorder (OCD) in adolescents. Which of the following statements best characterizes the effectiveness of such treatments? (LO #7)

    a. ICBT for adolescent OCD is as effective as ICBT for adult OCD

    b. ICBT for adolescent OCD is as effective as in-person CBT for adolescent OCD

    c. ICBT for adolescent OCD is better than being placed on a therapy waitlist

    d. ICBT for adolescent OCD has no effectiveness

About Carlat Publishing

Carlat Publishing was founded by Daniel Carlat, MD. Its flagship publication is *The Carlat Psychiatry Report.* Dr. Carlat is an associate clinical professor of psychiatry at Tufts University. He is also the author of *Drug Metabolism in Psychiatry: A Clinical Guide, The Psychiatric Interview,* and *Unhinged,* and co-author of *The Medication Fact Book for Psychiatric Practice*.

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Psychiatry Practice Boosters, Second Edition

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EDITORIAL TEAM

Psychiatry Practice Boosters, Second Edition is edited by Thomas Jordan, MD, MPH, and continues in the tradition of the first edition by adapting the research updates published in the Carlat family of newsletters (*The Carlat Psychiatry Report*, *The Carlat Child Psychiatry Report*, and *The Carlat Addiction Treatment Report*). This edition's research update authors include: Ricardo Arechiga, PharmD, Ariana Ayon Verduzco, PharmD, Rehan Aziz, MD, Jean Baker, MS, RD, Daniel Carlat, MD, Candace Good, MD, Bret A. Moore, Psy.D, ABPP, Taylor W. Noriega, PharmD, Kirsten Pickard, BA, Colleen Ryan, MD, Adam Strassberg, MD, and Shirley Y. Tsai, PharmD.

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