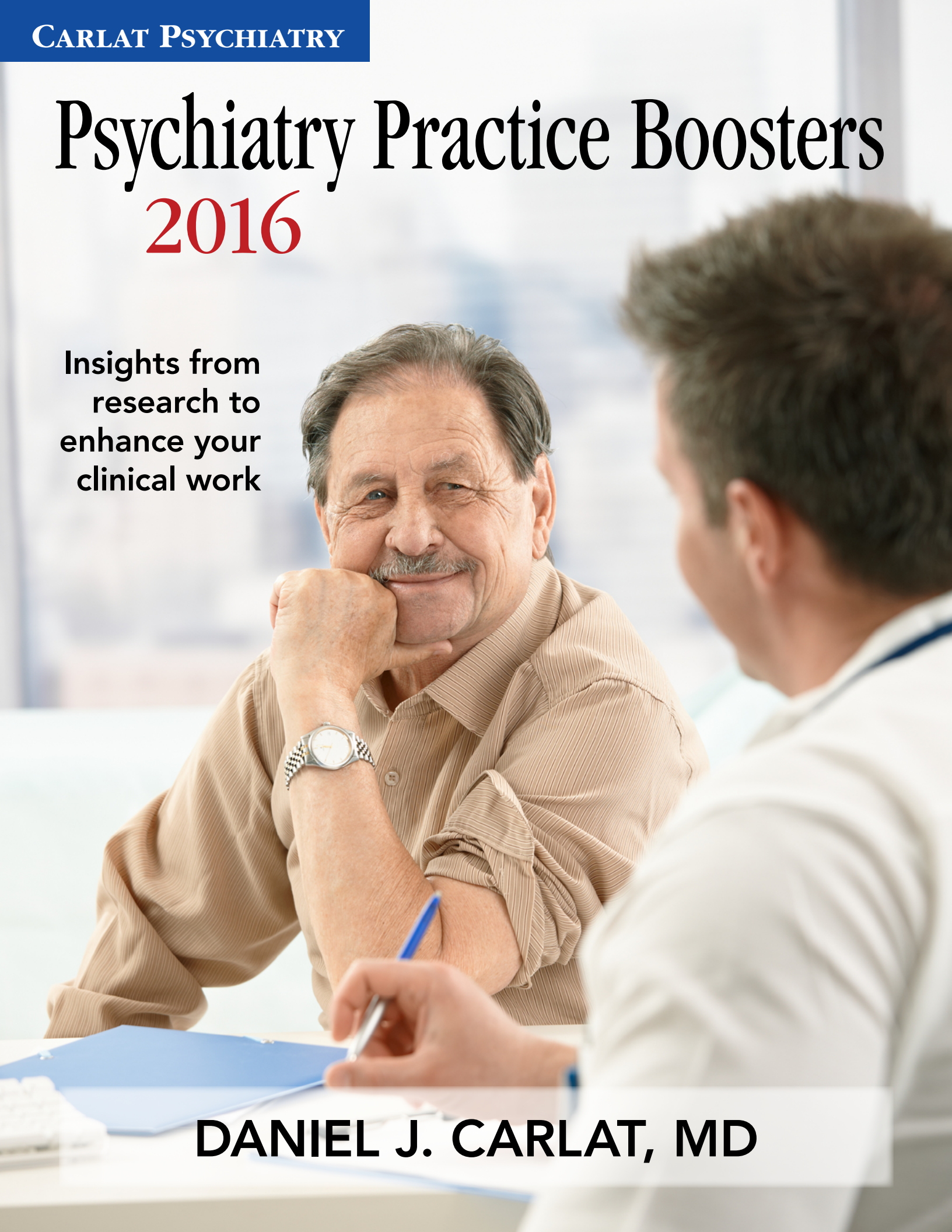
CARLAT PSYCHIATRY

Psychiatry Practice Boosters 2016

Insights from research to enhance your clinical work



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1 2 3 4 5 6 7 8 9 10

Table of Contents

Anxiety disorders

Side effects of medications

Child and adolescent psychiatry

Substance abuse

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Introduction

So many journal articles, so little time. I feel your pain, and over the years we've published hundreds of research updates in the Carlat newsletters. In this CME book, I've curated our most important research updates over the past three years and revised them, adding information to help you better understand how each finding might improve your practice.

For this book, we've generally chosen studies that lead to a bottom line recommendation for how you might change your clinical practice. These studies aren't necessarily the huge manufacturer-funded randomized clinical trials, which we generally cover in our lead articles in the Carlat Reports. Instead, many are smaller studies that introduce intriguing approaches you may not have heard about. For example, you'll read about light therapy for non-seasonal depression, and buprenorphine as a treatment for suicidal ideation. You may or may not choose to give these treatments a test drive, but it's nice to know that there are options in your toolbox beyond the standard rotating list of psychotropics.

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. (I've added an 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, 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 err on the side of recommending a new treatment if one of the following applies: the intervention (usually a medication) doesn't have a lot of bad side effects; and/or there aren't many good treatments for the condition targeted.

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 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. doi:10.1002/14651858.MR000033.pub2). 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 abuse, 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;162:1370–1372).

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 did 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 which compare two active drugs for a condition without including a placebo group. The patients know what they are taking. The doctor knows what he or she is prescribing. 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.

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,* posted on the web at http://www.tufts.edu/~gdallal/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 effects 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.

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

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

MOOD DISORDERS

Light Therapy for Non-Seasonal Depression

REVIEW OF: Lam RW, Levitt AJ, Levitan RD, et al. Efficacy of bright light treatment, fluoxetine, and the combination in patients with nonseasonal major depressive disorder: a randomized clinical trial. *JAMA Psychiatry.* 2016;73(1):56–63. doi:10.1001/jamapsychiatry.2015.2235.

STUDY TYPE: Randomized double-blind placebo-controlled trial

Most of us know that light therapy is effective for seasonal affective disorder (SAD), but does it work for non-seasonal depression?

Recall that SAD is defined as recurrent episodes of depression that occur at a particular time of year (usually winter) and that completely remit at another time (usually the spring). By the way, DSM-5 doesn't use the term SAD, but instead calls it "major depressive disorder with seasonal pattern."

Whether light therapy works for non-seasonal depression is unclear. Systematic reviews have yielded inconclusive results, in part because prior studies have had methodological weaknesses. A new study with a robust design was published in 2016.

Over a 5-year period, researchers recruited 122 adult patients with non-seasonal major depression between the ages of 19 through 60 from three clinics in Canada. The patients were randomized to one of four groups: light therapy alone, fluoxetine 20 mg plus light therapy (combination treatment), fluoxetine 20 mg plus sham negative ion treatment, and double placebo (placebo pills plus negative ion). Light therapy was given with a 10,000-lux fluorescent light box for 30 minutes daily in the early morning. The study lasted 8 weeks, and 106 participants completed it. The primary outcome measure was change in the Montgomery-Åsberg Depression Rating Scale (MADRS); secondary outcomes included response and remission rates.

RESULTS

At study conclusion, both light therapy and combination therapy were superior to placebo; however, combination therapy beat placebo more convincingly. Whereas light therapy alone yielded lower MADRS scores than placebo, combination therapy bested placebo not only on MADRS scores, but also on response rates and remission rates. Surprisingly, fluoxetine was not significantly better than placebo; the authors attributed this to small sample size.

Here are the numbers: Average improvements in MADRS scores were 16.9 (combined fluoxetine and light), 13.4 (light therapy only), 8.8 (fluoxetine and sham light), and 6.5 (placebo). Response rates (defined as ≥ 50% drop in MADRS score) for combined treatment, light, fluoxetine, and placebo were 76%, 50%, 29%, and 33%, respectively. Remission rates (defined as MADRS score ≤ 10) were 59%, 44%, 19%, and 30%.

THE CARLAT TAKE

This is probably the best-designed clinical trial of light therapy for non-seasonal depression to date, and the results endorse both light monotherapy and combination light and fluoxetine, with the combination being possibly more robust. Both combination treatment and light monotherapy beat fluoxetine alone in this trial.

PRACTICE IMPLICATIONS

The bottom line is that, at least for depressed patients in the higher latitudes, we should consider changing our standard practice of prescribing an antidepressant alone. Having patients add light therapy every morning for several weeks may well optimize antidepressant treatment.

Should We Add Stimulants to SSRIs to Treat Geriatric Depression?

REVIEW OF: Lavretsky H, Reinlieb M, St Cyr N, Siddarth P, Ercoli LM, Senturk D. Citalopram, methylphenidate, or their combination in geriatric depression: a randomized, double-blind, placebo-controlled trial. *Am J Psychiatry*. 2015;172(6):561–569. doi:10.1176/appi.ajp.2014.14070889.

STUDY TYPE: Randomized double-blind placebo-controlled trial

We often think about adding a stimulant to an antidepressant for elderly patients with depression. Geriatric depression often presents with apathy, low energy and motivation, and cognitive decline, so theoretically stimulants are a natural choice. Past studies of combining stimulants with antidepressants have been mainly small open trials, with mostly positive results. But we haven't seen the kind of rigorous double-blind methodology we'd like. This study fills that gap.

143 elderly patients (average age 69.7) with major depression and normal Mini-Mental State Examination scores (average 28.7) were randomly assigned to three treatment groups: methylphenidate plus placebo (n = 48), citalopram plus placebo (n = 48), and citalopram plus methylphenidate (n = 47). Patients were seen weekly for the first 4 weeks to titrate the doses and then every 2 weeks thereafter for the remainder of the 16-week study. Daily doses ranged from 20 to 60 mg of citalopram (average of 32–35 mg, depending on the study arm) and 5–40 mg of methylphenidate (average of about 16 mg).

RESULTS

The patients assigned to citalopram plus methylphenidate did the best, with a remission rate of 62% at the end of the trial, significantly better than the remission rates of the citalopram-placebo group (42%) and methylphenidate-placebo group (29%). There was no significant difference among groups in measures of cognitive improvement or side effects. In an analysis of improvement rate, the citalopram-methylphenidate group improved more quickly than the citalopram-placebo group over the first 4 weeks of the trial.

THE CARLAT TAKE

This is the first well-controlled study assessing the value of starting depressed elderly patients on a combination of an SSRI and stimulant vs. SSRI alone. The study wasn't huge, and a replication would be valuable. Nonetheless, it looks like starting with both drugs might be a good idea. Patients receiving citalopram plus methylphenidate improved more quickly and were more likely to be in remission after 4 months. An average dose of 16 mg of methylphenidate was well-tolerated.

PRACTICE IMPLICATIONS

When treating depressed elderly outpatients, consider starting treatment with a combination of an SSRI and a stimulant.

Botox Injections Can Be Effective Antidepressants

REVIEW OF: Magid MM, Reichenberg JS, Poth PE, et al. Treatment of major depressive disorder using botulinum toxin A: a 24-week randomized, double-blind, placebo-controlled study. *J Clin Psychiatry.* 2014;75(8):837–844. doi:10.4088/JCP.13m08845.

STUDY TYPE: Randomized double-blind placebo-controlled trial

Botulinum toxin A, commonly known as Botox, is often used as a cosmetic treatment, especially in the forehead or between the eyebrows. Used in this way, the toxin causes short-term paralysis of these muscles, which minimizes forehead wrinkles and frown lines. Previous small placebo-controlled studies have shown that cosmetic Botox has an antidepressant effect. A new study replicates these findings and shows that the effect is long-lasting.

Researchers from a university-affiliated psychiatric clinic in Austin, Texas, used advertisements to recruit participants. The inclusion criteria were a current major depressive episode as measured by the Hamilton depression scale and moderate to severe frown lines. Those who had previous Botox treatment were excluded. Thirty people were enrolled. Most of the patients (28) were women, the average age was 49 years, the average duration of depressive illness was 18 years, and patients were taking an average of 1.47 antidepressants upon study entry (they were allowed to continue their antidepressants).

Patients were randomly assigned to either a Botox group (Botox injection into the glabellar muscles that cause frown lines) or a placebo group (salt water injections into the same area). The study lasted 24 weeks and had a crossover design: Patients initially assigned to placebo were switched at week 12 to Botox, while patients initially assigned to Botox were switched over to placebo. This design increases the statistical power of a study with a low number of subjects.

Researchers evaluated the participants at weeks 0, 3, 6, 12, 15, 18, and 24 for improvement in depression symptoms; the primary outcome was antidepressant response as defined by a reduction of at least 50% on the Hamilton depression scale.

RESULTS

Patients who received Botox (either at week 0 or at week 12 after crossing over from placebo) had a statistically significant reduction in depression symptoms, compared to those receiving placebo. Six weeks after receiving Botox, response rates were 55% in the group that received the injection at week 0, 24% in the group that received the injection at week 12, and 0% in the placebo group. Partial responses were seen in 73%, 65%, and 5%, respectively. Interestingly, depressive symptoms continued to improve over the 24-week period after a single Botox injection, even though the cosmetic effects wore off in 12 to 16 weeks.

The researchers speculated that Botox's antidepressant effect may be due to its cosmetic effect, more positive social feedback to a happier face, or decreased feedback from the facial muscles to the brain resulting in less activation of the amygdala and other structures involved in depression.

THE CARLAT TAKE

This is the latest study showing that cosmetic Botox injections have an antidepressant effect.

PRACTICE IMPLICATIONS

It's premature to routinely "prescribe" Botox injections as an antidepressant. Yet for some patients, especially women, who are looking for an alternative to medications or therapy, it's not unreasonable to point out that there is pretty good evidence that this simple cosmetic procedure can improve both frowning lines and frowning mood.

Does rTMS Work as Augmentation in Patients With Resistant Depression?

REVIEW OF: Liu B, Zhang Y, Zhang L, Li L. Repetitive transcranial magnetic stimulation as an augmentative strategy for treatment-resistant depression, a meta-analysis of randomized, double-blind and sham-controlled study. *BMC Psychiatry.* 2014;14(1):342–350. doi:10.1186/s12888-014-0342-4.

STUDY TYPE: Meta-analysis of randomized sham-controlled trials

Repetitive transcranial magnetic stimulation (rTMS) is approved by the FDA for treatment resistant depression (TRD) and presumably works by modulating brain circuitry (see the September 2014 issue of *TCPR* for more detail). The FDA approval is specifically for patients who have not responded to prior antidepressants. But it's not clear how we should use the treatment—is it best used as monotherapy, or should we add rTMS to whatever medication the patient is currently taking, even if the medication isn't working?

To answer this question, researchers located seven studies that specifically added TMS to an existing antidepressant regimen. The studies included a total of 279 patients with TRD, which was defined as not responding to at least one antidepressant trial. In all, 171 of these patients were assigned to antidepressant plus rTMS augmentation, while 108 received an antidepressant augmented with sham treatment.

RESULTS

The researchers found that 47% of rTMS plus antidepressant patients responded (defined as a 50% improvement on the Hamilton depression scale), compared to only 22% of sham plus antidepressant patients. The odds ratio was 5.12, meaning rTMS patients were about five times more likely to respond than those receiving sham treatment. The number needed to treat was 3.4, meaning that 3.4 patients would have to be treated with rTMS for one patient to benefit more from rTMS than from sham.

While these results sound impressive, the authors cautioned that the quality of most of the studies was poor. In particular, most studies did a poor job of ensuring patients were truly blinded to which treatment they received. rTMS causes distinct vibrating sensations in the scalp, whereas sham does not. This means it's quite possible that many of the rTMS patients realized they were getting the active treatment, and may have improved more due to hopefulness and positive expectancy.

THE CARLAT TAKE

As in most large meta-analyses of rTMS, this one appears to endorse the treatment—specifically for antidepressant augmentation in patients with TRD. But the glowing numbers are undermined by significant doubts about the integrity of the blinding.

PRACTICE IMPLICATIONS

None. With the methodological limitations of the study, it's not at all clear that we should run out and start encouraging patients on antidepressants to undergo magnetic stimulation therapy.

Buprenorphine for Suicidality? Maybe.

REVIEW OF: Yovell Y, Bar G, Mashiah M, et al. Ultra-low-dose buprenorphine as a time-limited treatment for severe suicidal ideation: a randomized controlled trial. *Am J Psychiatry.* 2016;173(5):491–498. doi:10.1176/appi.ajp.2015.15040535.

STUDY TYPE: Randomized double-blind placebo-controlled trial

When patients become severely suicidal, we have few good treatment options. What we usually do at a minimum is arrange for inpatient admission and close monitoring by staff to prevent self-harm—but that doesn't really constitute treatment. Once patients are in a safe environment, we try intensive supportive psychotherapy, antidepressants (which, while effective, take weeks to work), a variety of medications to treat symptoms such as agitation and insomnia, and more recently, the experimental treatment ketamine (which requires repeated infusions under medical supervision). In addition, lithium reduces suicidality in bipolar disorder, and clozapine does so in schizophrenia—but both work over the long term and are not rapid-acting treatments for suicidal ideation.

Recognizing the need for more options, Israeli researchers studied the use of very low doses of buprenorphine in suicidal patients. Patients with suicidal ideation were recruited from four medical centers. The participants were severely suicidal, with an average score of 19.7 on the Beck Scale for Suicidal Ideation; 64% of them had made at least one suicide attempt. They were randomly assigned to groups receiving either buprenorphine (n = 40) or placebo (n = 22). Buprenorphine was started at 0.1 mg once or twice a day and gradually titrated up to a max dose of 0.8 mg/day (average dose was 0.44 mg/day). No changes to the patient's regular psychiatric treatment were made. Most of the patients from both groups were on medication, including over 70% who were taking antidepressants. The primary outcome measure was change from baseline on the Beck scale, which was assessed weekly for 4 weeks.

RESULTS

After 2 weeks, suicide severity ideation dropped by an average of 4.3 points more in the buprenorphine group than the placebo group, and after 4 weeks, the difference was 7.1 points; both values were statistically significant. Adverse events occurred in 77.2% of the buprenorphine patients and in 54.8% of the placebo patients. The most common buprenorphine-related side effects were fatigue (49.1%), nausea (36.8%), and constipation (26.3%). After 4 weeks, the medication was stopped without a taper, and no patients reported any withdrawal symptoms over the ensuing week, nor was there any exacerbation in suicidality.

THE CARLAT TAKE

This was a small study (62 subjects) and of short duration (4 weeks), but the results were encouraging, and imply that very-low-dose buprenorphine can quickly reduce suicidal ideation. For some perspective on the dosing, the typical buprenorphine dose for maintenance treatment of patients with opiate use disorder is 8 mg to 12 mg per day, over 20 times the average dose in this study, which was 0.44 mg per day.

PRACTICE IMPLICATIONS

If you have a patient with severe suicidal ideation, a reasonable option is to prescribe a brief course of ultra-low-dose buprenorphine. Understand that there is a small chance of fostering opiate addiction in such patients, so keep the dose super low and the time course short (around 4 weeks). Getting access to buprenorphine for this indication will be challenging, but Belbuca is a new buprenorphine buccal strip formulation approved for treating pain that comes in doses ranging from 75 mcg to 900 mcg, which would allow you to prescribe the doses used in this trial.

Psychedelic Mushrooms for Treatment Resistant Depression

REVIEW OF: **Carhart-Harris R, Bolstridge M, Rucker J, et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *Lancet Psychiatry.* 2016;3(7):619–627. doi:10.1016/S2215-0366(16)30065-7.**

STUDY TYPE: **Open-label uncontrolled clinical trial**

Psilocybin is the active ingredient of the most commonly abused psychedelic mushrooms. The compound is a serotonin 2A receptor agonist, which theoretically might imbue it with antidepressant effects. There have been a smattering of small trials showing that patients taking a dose or two of psilocybin benefit in terms of anxiety, depression, and even alcohol abuse. In this new small study, researchers tested the drug for treatment resistant major depression.

As part of an open-label feasibility study, six men and six women with moderate to severe treatment resistant depression (defined as two failed antidepressant trials) were recruited via a clinical research network in London. The patients ranged in age from 30 to 64, they were well-educated (10 of them had either undergraduate or postgraduate degrees), and 5 of them had used psilocybin in the past, mostly many years ago.

The treatment procedure involved administering a 10 mg oral dose of psilocybin and another 25 mg dose one week later. The goal of the first, lower dose was to test safety and tolerability; the second dose was the actual treatment. Researchers then monitored depressive symptoms with the Quick Inventory of Depressive Symptoms (QIDS) 1 week and 3 months post-treatment.

RESULTS

The patients' symptoms of depression, anxiety, and anhedonia all improved substantially from baseline. Scores on the QIDS were 11.8 and 9.2 points lower at 1 week and 3 months post-treatment, respectively. Overall, patients tolerated the psychedelic experience well. Short-term confusion or unclear thinking (n = 9), nausea (n = 4), and headaches (n = 4) were the most common adverse effects. In addition, all patients experienced transient, mild to moderate anxiety shortly after taking the drug. No patients dropped out of treatment because of side effects or the intensity associated with taking a psychedelic drug.

THE CARLAT TAKE

This was a tiny study, so we can't conclude that psilocybin is going to be effective for most patients with treatment resistant depression. The patients in this study were in their 30s, 40s, and 50s and were well-educated, with many having past experiences with psychedelics, so that gives you a feel for what types of patients might benefit from this treatment. The authors wrote that the "logical next step" would be a placebo-controlled randomized trial. Agreed, but good luck getting funding and approval for such a large-scale study of magic mushrooms.

PRACTICE IMPLICATIONS

Well, you can't prescribe psilocybin, which is a Schedule I drug. Perhaps the topic of using hallucinogens will come up in conversation with some of your patients, particularly the aging hippies in your practice. It will be up to them what to do with this information!

Symbyax Helps Kids With Bipolar Depression—But Has Downsides

REVIEW OF: Detke HC, DelBello MP, Landry J, Usher RW. Olanzapine/fluoxetine combination in children and adolescents with bipolar I depression: a randomized, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry.* 2015;54(3):217–224. doi:10.1016/j.jaac.2014.12.012.

STUDY TYPE: Randomized double-blind placebo-controlled trial

There are three FDA-approved medications for bipolar depression in adults (olanzapine/fluoxetine combination [OFC], quetiapine, and lurasidone), but only one for children: OFC, brand name Symbyax. The data underlying FDA's approval of OFC for kids was recently published, and gives us a better sense of the trade-offs we might be making when prescribing it.

The Eli Lilly–sponsored trial included 255 kids between 10 and 17 years old with a moderately severe depressive episode of bipolar illness. Two-thirds of the participants were randomized to receive OFC, and the other third received placebo. The most common dose of OFC used was 12 mg/50 mg/day, the maximum approved dose for kids and adults. Treatment lasted for 8 weeks, and the primary efficacy measure was the Children's Depression Rating Scale-Revised.

RESULTS

Kids on OFC did significantly better than those on placebo as early as the first week and maintained this difference throughout the 8 weeks. And although placebo response was high, response and remission were significantly higher in the OFC group than the placebo group (78% vs. 59% responded and 59% vs. 43% remitted).

In terms of side effects, there were no big surprises: OFC caused significantly more weight gain, increased appetite, sedation, somnolence, and tremor compared with placebo. Kids on OFC gained an average of 11 pounds over 8 weeks, whereas kids taking placebo gained an average of 1 pound. In terms of weight, 52% of OFC kids gained ≥ 7% of baseline body weight (FDA's definition of significant weight gain), compared to 4% of placebo kids. Elevated prolactin occurred significantly more in the OFC group, and 5 of the girls taking OFC were symptomatic with menstrual changes and lactation. QT interval was prolonged more significantly in the OFC group as well, and this was likely due more to the fluoxetine component than the olanzapine.

OFC is currently the only FDA-approved treatment for bipolar depression in kids. For adults, there are more options: Latuda and Seroquel XR are approved, and Lamictal has some positive data to support its use. Of these three, you can eliminate Seroquel as a potential treatment for kids because two controlled trials found it no better than placebo. Latuda data in kids will likely be forthcoming.

THE CARLAT TAKE

OFC is an option for bipolar depression in kids, but its high side effect burden should give us pause before prescribing it.

PRACTICE IMPLICATIONS

We recommend avoiding OFC in pediatric bipolar disorder. Instead, pick and choose an SSRI plus a lower-side-effect atypical antipsychotic, such as lurasidone or aripiprazole.

Pet Therapy for College Students

REVIEW OF: Stewart LA, Dispenza F, Parker L, Chang CY, Cunnien T. A pilot study assessing the effectiveness of an animal-assisted outreach program. *J Creativ Ment Health.* 2014;9(3):332–345. doi:10.1080/15401383.2014.892862.

STUDY TYPE: Open-label uncontrolled clinical trial

Animal-assisted therapy (AAT) is a pretty new technique in which a counselor brings a specially trained pet (usually a dog) into the room with a patient. The patient is encouraged to pet and otherwise interact with the dog, and this is thought to enhance therapy in various ways, such as by relaxing the client, providing a positive bonding experience, and generally breaking the ice between therapist and patient. The few existing studies of this technique have shown that AAT facilitates therapist-patient alliance and rapport.

This pilot study was the first to assess AAT in a college counseling environment. As part of a counseling outreach program at a small arts college in the Southeast (presumably Savannah College of Art and Design in Atlanta), researchers recruited 55 undergraduate students to participate. All students completed the Burns Anxiety Inventory and a couple of other lesser-known psychological surveys both before and after the intervention. The students interacted with one of the college's counseling staff, who is a registered Pet Partners therapy team member, and her therapy dog.

The sessions took place in a group setting at a residence hall lobby on the college campus twice a month for an academic quarter. Students were invited to drop in and interact with the therapy dog (named Sophie May, breed not specified), the registered Pet Partners therapy counselor, and other attendees for a period of two hours. The average attendance at each event was 10–15 students, and participants spent anywhere from five minutes to two hours with the dog. Students were able to pet, hug, feed, brush, draw, photograph, sit near, and play fetch with the dog. The counselor provided information about the college's counseling center, but did not provide counseling services or psychoeducation during the sessions.

RESULTS

Comparing scores before and after pet therapy, the students had a 60% reduction in symptoms of anxiety and loneliness. Most of the students (84%) said interaction with the dog was the most impactful aspect of the intervention; the other 16% said interaction with other students and staff members was most helpful.

THE CARLAT TAKE

Just a few hours of interaction with a friendly dog seems to help allay the anxiety and loneliness that often bedevil college students. Of course, the study has limitations, such as no control group or other gold standard methods. Certainly a double-blind study would have been hard to pull off—maybe they could have used stuffed animals as a "placebo?" At any rate, it's an intriguing study, and as a low-cost, low-side-effect treatment, petting a dog is hard to beat.

PRACTICE IMPLICATIONS

Pet therapy should be added to your list of alternative treatments to recommend to patients with symptoms of anxiety or depression that are not responding well to meds or conventional therapy. Many people toy with the idea of having a pet anyway, and sharing the results of this study might create the impetus they need.

Predicting Suicide Risk: The Effect of Parental Attempts

REVIEW OF: Brent DA, Melhem NM, Oquendo M, et al. Familial pathways to early-onset suicide attempt: a 5.6-year prospective study. *JAMA Psychiatry.* 2015;72(2):160–168. doi:10.1001/jamapsychiatry.2014.2141.

STUDY TYPE: Prospective cohort

We've known for some time that if your patient has a parent with a history of a mood disorder or a suicide attempt, the patient's own risk of a suicide attempt increases. A new study provides the best evidence of this to date and adds some more information that might help us prevent bad outcomes.

From 1997 to 2005, researchers recruited 334 patients with mood disorders who were referred to one of two academic clinics in Pittsburgh and New York City. These patients had an average of 2.1 children each, for a total of 701 offspring. These offspring were then recruited into a long-term study. They were given a battery of standardized psychiatric interviews at baseline, and these evaluations were repeated annually for a mean follow-up of 5.6 years. Researchers assessed for the presence of DSM-IV psychiatric disorders at each time point, and administered a variety of symptom scales to measure symptoms of depression, hopelessness, impulsivity, aggression, and other factors.

RESULTS

Over half of the parents, or 57.2%, had made suicide attempts at some point in their lives. (For perspective, the lifetime prevalence of suicide attempts in the general population is about 5%.) Of the 701 offspring, 73 (10.4%) made a suicide attempt. Offspring of parents who had made suicide attempts were about five times more likely to have made an attempt themselves than offspring of non-attempters. The authors did not mention whether there were any completed suicides. The mean age of an offspring with an attempt was 20.1 years.

The factors that most strongly predicted an offspring suicide attempt were the following:

- The offspring had a mood disorder at the time point just before a suicide attempt—this elevated the risk of an attempt 11-fold compared to those without a mood disorder at that time point
- The offspring had a history of a suicide attempt—a 5.7-fold increased risk
- The parent had a history of a suicide attempt—a 4.8-fold increased risk
- The offspring had a mood disorder at study entry—4.2-fold increased risk

Some of the salient secondary findings included the fact that a parent's suicide attempt conferred a higher risk of an offspring attempt—regardless of whether the offspring had a mood disorder. Also, "impulsive aggression," which was measured with a couple of self-report "hostility inventories," appears to play a role. High impulsive aggression scores in the offspring increased the likelihood of a mood

disorder, which in turn increased the risk of a suicide attempt. Offspring age, sex, or bipolar vs. unipolar disorder had no effect on risk of suicide attempts.

THE CARLAT TAKE

Although this large study doesn't really provide any groundbreaking information, it reinforces conventional wisdom that obtaining family histories is important. If your patient had a parent who attempted suicide, that patient is at nearly five times higher risk for a suicide attempt—and there are other powerful predictors of attempts, such as having a mood disorder and a prior history of an attempt. Finally, probe for a history of impulsive aggression, which may be a red flag for a mood disorder more likely to lead to an attempt. Patients who have any or all of these risk factors should be treated more intensively—for example, more frequent visits, more family involvement, more school involvement, and therapy combined with medications.

PRACTICE IMPLICATIONS

Ask all of your patients the question: "Did your parents ever try to hurt themselves?" A positive answer means that your patient has an elevated risk of an eventual suicide attempt.

Ongoing ECT Does Not Equal Ongoing Cognitive Problems

REVIEW OF: Kirov GG, Owen L, Ballard H, et al. Evaluation of cumulative cognitive deficits from electroconvulsive therapy. *Br J Psychiatry.* 2016;208(3):266–270. doi:10.1192/bjp.bp.114.158261.

STUDY TYPE: Retrospective cohort

Electroconvulsive therapy (ECT) is well known to cause short-term amnesia and disorientation for several hours after treatment. For most of our patients, these cognitive side effects disappear fairly quickly, usually within a few days, and it's appropriate that we provide such reassurance to patients. But what about patients who have longer-term ECT? Some patients with treatment resistant depression resort to multiple courses of ECT over the years, while others undergo maintenance monthly treatments. Does such long-term treatment lead to more long-lasting cognitive impairment? A recent study provides us with some reassuring data.

Cardiff University researchers collected cognitive performance data on 199 ECT patients over a 10-year period. The main goal was to see if repeated or ongoing courses of ECT caused cumulative cognitive problems. The researchers were also interested to know if other factors such as age, days since last ECT session, and depression severity played a role in any cognitive decline (the mean age of the patients was 56.3 years).

Nine cognitive tests measuring recognition, working memory, verbal fluency, processing speed, and mental status were given at three time points: prior to the start of ECT, within 1 week after treatment completion, and at 3 months follow-up. Those who received multiple courses of ECT were tested again at the same intervals. Those who required maintenance ECT (> 50 sessions) were tested yearly. The total number of ECT sessions patients received prior to the testing was also recorded.

RESULTS

The analysis showed that the total number of ECT sessions had no effect on performance on any of the cognitive tests. However, a longer time gap since the last ECT session was associated with improved performance. The factors that did decrease performance were greater age and more severe depression.

THE CARLAT TAKE

Many patients are concerned about the long-term effects of ECT. While this study is not definitive, since it is not a randomized controlled study, it is highly suggestive that long-term ECT, including maintenance treatments, does not significantly impair cognition as measured by objective testing. That said, we all know patients who insist that their memory is in general poorer since they started ECT. Such a subjective feeling can't always be measured with testing, but that doesn't mean it isn't real.

PRACTICE IMPLICATIONS

Reassure patients that multiple courses of ECT, or maintenance ECT, usually don't cause any more long-term memory loss than a single course.

Citalopram Safety Warning Has Unintended Consequences for Patients

REVIEW OF: Rector TS, Adabag S, Cunningham F, Nelson D, Dieperink E. Outcomes of citalopram dosage risk mitigation in a veteran population [published online ahead of print May 10, 2016]. *Am J Psychiatry.* doi:10.1176/appi.ajp.2016.15111444.

STUDY TYPE: Retrospective cohort

In the summer of 2011, the FDA sent out letters to physicians warning them that citalopram can cause QT prolongation on an EKG at doses of 40 mg/day or higher. We covered this issue at the time (see *TCPR,* November 2011, Vol. 9, Issue 11) and concluded that the FDA data were not all that reliable for the 40 mg dose, because only the 20 mg and 60 mg doses had actually been tested and correlated with EKG findings. At 60 mg, citalopram causes about as much QT prolongation as ziprasidone (Geodon), so we recommended using the higher dose when the benefits outweigh the risks, as is the usual advice regarding ziprasidone.

At any rate, soon after the FDA warning, the Department of Veterans Affairs (VA) informed all its providers about it. Recently, VA researchers published a study detailing the results of this warning on VA prescribing practices and on patient outcomes.

The study authors searched VA national electronic health records and found that in August 2011, shortly after the FDA warning, 35,848 patients had a prescription higher than 40 mg/day of citalopram, with an average dose of 64 mg/day. Although VA clinicians were not required to decrease doses after the warning, many did. Within six months of the warning, 60% of the high-dose patients had been prescribed doses of 40 mg/day or less. The researchers compared rates of hospitalizations and mortality in patients whose dose was decreased vs. those who continued on high-dose citalopram.

RESULTS

Hospitalization or death for any reason was 2.5 times *greater* in the reduced-dose group vs. the maintained-dose group. Depression-related hospitalizations were also higher in the reduced-dose group, as was self-injurious behavior. Interestingly, reducing the dose did not do anything obvious to prevent arrhythmia—there was no drop in hospitalization for cardiac arrhythmias. The researchers concluded that the FDA warning did more harm than good.

THE CARLAT TAKE

If the VA's results can be extrapolated to the general clinical population, the FDA warning may have led to harmful prescribing decisions. Patients whose citalopram doses were lowered were more likely to be hospitalized, were more likely to harm themselves, and realized no clear cardiac benefits.

PRACTICE IMPLICATIONS

If you have patients who are doing well on high-dose citalopram, don't reduce the dose based on the FDA warning alone. Instead, check an EKG, and if there is a wide QT interval, consult with a cardiologist to determine whether the risk of an arrhythmia is high enough to justify slashing the dose of an antidepressant. Judging by the results of this study, you may ultimately decide to stay the course.

Antidepressant Use in Pregnancy and the Risk of Autism

REVIEW OF: Boukhris T, Sheehy O, Mottron L, Bérard A. Antidepressant use during pregnancy and the risk of autism spectrum disorder in children. *JAMA Pediatr.* 2016;170(2):117–124. doi:10.1001/jamapediatrics.2015.3356.

STUDY TYPE: Retrospective cohort

Rates of autism diagnoses are on the rise. While no one knows for sure why, a new study explores whether the increased use of antidepressants during pregnancy might be one of the causes.

The researchers looked at databases from Quebec of nearly 150,000 full-term births and followed the health of the children for up to 10 years. Antidepressant exposure was defined as having at least 1 prescription filled during the mother's pregnancy. Cases of autism spectrum disorders (ASD) in children were identified by looking at ICD codes used in medical service claims. For example, if a pediatrician listed pervasive developmental disorder or Asperger's syndrome as one of the diagnoses during an annual checkup, this would be counted as an ASD case.

Because patients who take antidepressants are expected to differ from those who do not, the researchers attempted to control for things like socioeconomic factors, as well as maternal physical and mental health.

RESULTS

Of the 145,456 infants followed, 1,054 (0.7%) received at least 1 ASD diagnosis—which is about in line with ASD prevalence rates. The mean age at first ASD diagnosis was 4.6 years, and boys outnumbered girls by about 4:1. In total, 4,724 (3.2%) of the infants were exposed to antidepressants in utero. Use of antidepressants during the first trimester was not found to be associated with an increased risk of an ASD. However, antidepressant use in the second and/or third trimester was found to confer an 87% increased risk of an ASD diagnosis—or just under a 2% incidence rate rather than 1%, which is the estimated prevalence of ASDs in the community (*MMWR Surveill Summ* 2012;61(3):1–19). When antidepressant classes were examined, only SSRIs were statistically associated with the increased risk. The researchers concluded that SSRI use in the second and third trimesters increases the risk of an ASD in children.

The findings are concerning, but there is one potentially fatal flaw to the study: The researchers were unable to control for the severity of depression. Most women with only a mild depression would be expected to stop their antidepressant once pregnant. Those with a more severe illness, in contrast, would be much more likely to remain on the antidepressant throughout their pregnancy. Could it be that the increased rates of ASDs are due more to the effects of severe depression, and that antidepressant exposure is not the cause but merely a marker for greater severity? Two pieces of study data support this possibility. First, SNRIs conferred only a 0.4% risk, which was lower than the average rate;

if serotonergic reuptake inhibition is thought to be the mechanism of insult, as the authors postulate, we would expect SNRIs to confer a risk comparable to SSRIs. Second, there were 167 exposures to combined antidepressant therapy. It can be assumed that pregnant women who take 2 or more antidepressants during pregnancy are more severely depressed than those who take only 1. The risk for ASDs in this group was 3%—more than double that of the SSRI group. This finding is also more consistent with depressive severity being the causal link, rather than SSRI exposure.

THE CARLAT TAKE

We are left in the same place after this study as we were before: Untreated depression almost certainly poses a risk to a fetus (Suri R et al, *J Clin Psychiatry* 2014;75(10):e1142–1152), while arguably there is no proven substantial risk to SSRI use during pregnancy (Weisskopf E et al, *Expert Opin Drug Saf* 2015;14(3):413–427; Pearlstein T, *Best Pract Res Clin Obstet Gynaecol* 2015;29(5):754–674). Thus, in deciding whether to remain on their antidepressant, patients must choose between the known risks associated with untreated depression and the unknown risks of antidepressant use.

PRACTICE IMPLICATIONS

If patients ask you about news items implying that SSRIs in pregnancy "cause" autism, reassure them that this study did not demonstrate such. SSRIs are still considered relatively safe in pregnancy.

ANTIPSYCHOTICS

A New Treatment Program Effective for First-Episode Psychosis

REVIEW OF: Kane JM, Robinson DG, Schooler NR, et al. Comprehensive versus usual community care for first-episode psychosis: 2-year outcomes from the NIMH RAISE early treatment program. *Am J Psychiatry.* 2016;173(4):362–372. doi:10.1176/appi.ajp.2015.15050632.

STUDY TYPE: Randomized open-label controlled trial

When a patient presents to you with a first episode of psychosis, you probably start medication and work on refining your diagnosis. Depending on where you practice, the patient may or may not receive therapy or other support services. The question is, should we be doing really intensive treatment with these first-episode patients? Would it make any difference in terms of improving long-term outcomes? A new NIMH-funded study compared a comprehensive treatment program with treatment as usual, and the results were promising.

Researchers enrolled 404 patients with a first episode of psychosis and randomly assigned them to one of two treatment groups. Patients in the experimental arm (n = 223) received a set of intensive treatments called the NAVIGATE package, which included personalized medication management, family psychoeducation, individual therapy focusing on resilience, case management, and employment and education support, for at least 2 years. The control group (n = 181) received treatment as usual, which in community mental health centers is mostly medication.

The study's methods were interesting. Instead of randomly assigning individual *patients* to these treatments, researchers randomly assigned entire *clinics*. Thus, of 34 community mental health centers enrolled, 17 were assigned to NAVIGATE and 17 were assigned to usual care. The advantage is that this confers a real-world flavor to the study. It's more practical to train a clinic's entire staff on providing a comprehensive suite of treatments than it is to pluck individual patients out of the clinic for specialized treatment at an academic center. The disadvantage is that it's harder to make sure patients in the two groups are truly comparable because they aren't randomly assigned individually.

All the patients were between 15 and 40 years of age (mean was 23), with a history of only one episode of psychosis and a diagnosis of schizophrenia, schizoaffective, schizophreniform, or brief psychotic disorder (more than 50% had schizophrenia). Patients in the study had taken no more than 6 months of antipsychotic medications, and the average time between the onset of symptoms and first treatment was 74 weeks—nearly 1.5 years. The patients in the NAVIGATE group were more likely to be male than those in usual care (77% vs. 66%), had worse Positive and Negative Syndrome Scale (PANSS) scores (78 vs. 74), were less likely to have had a prior hospitalization (76% vs. 82%), and were less likely to be in school at baseline (16% vs. 26%). Whether these group differences affected the results of the study is unclear.

So what were the specifics of the NAVIGATE treatment? While the paper didn't get into details, the NAVIGATE website (www.navigateconsultants.org) provides more information. Each patient is

assigned four clinicians: a prescriber, a therapist, a family education clinician, and a "supported employment and education" specialist. There's also an overall case manager. Patients have sessions with one or more team members weekly for the first 6–12 months, then less frequently (usually monthly) during months 12–18.

The website offers free downloads of a detailed manual for each of the treatments. As a psychiatrist who doesn't really specialize in psychosis, but who still sees plenty of psychotic patients, I found scanning these manuals to be quite helpful. I learned useful information on how to do cognitive restructuring with severely ill patients, on what supported employment actually means, and on how family education can be helpful.

RESULTS

Patients were assessed every 6 months over 2 years. Those assigned to NAVIGATE had significantly greater improvement on the primary outcome measure—the Quality of Life Scale score. The largest improvements were seen in interpersonal relations, sense of purpose, motivation, curiosity, emotional engagement, and engagement in activities. A significantly larger proportion of NAVIGATE patients were either working or going to school during the study. In terms of core symptoms, NAVIGATE patients showed more improvement on psychotic and depressive symptoms in the PANSS scale. NAVIGATE patients stayed in treatment significantly longer than the usual treatment patients (median of 23 months vs. 17 months). There was no significant difference in hospitalization rates between the groups (both had relatively low rates of about 3%–4% per month or 34%–37% of patients hospitalized over 2 years).

The researchers also found that the NAVIGATE program was more effective when patients entered treatment earlier in the psychotic process. Patients who had a duration of illness less than 74 weeks had significantly greater improvement in quality of life and psychotic symptoms than those patients who went longer than 74 weeks before getting treated.

THE CARLAT TAKE

A comprehensive care program for first-episode psychosis patients appears to help more than treatment as usual, at least over a 2-year period. The authors said they are continuing their assessments for 5 years and will someday publish those longer-term results. However, it's not clear if the NAVIGATE program produced benefits via its specific therapeutic components or simply by exposing patients to more visits and more time with clinicians. And even if NAVIGATE is as effective as it seems, there is the economic question of whether community mental health centers can afford to implement it. That's not clear either, though the authors were optimistic for two reasons: First, insurance covers many of the NAVIGATE services, such as medications, individual therapy, and family therapy; second, the federal government has allocated money to support programs targeting first-episode psychosis.

PRACTICE IMPLICATIONS

When you see a patient with a first-episode psychosis, don't rely on medications and supportive therapy alone. Let the patient, the family, and your practice setting's director know that according to a federal study, a comprehensive treatment program might yield extra benefits for these patients.

The New Three-Month Version of Injectable Paliperidone: Should You Use It?

REVIEW OF: Berwaerts J, Liu Y, Gopal S, et al. Efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo for relapse prevention of schizophrenia: a randomized clinical trial. *JAMA Psychiatry.* 2015;72(8):830–839. doi:10.1001/jamapsychiatry.2015.0241.

STUDY TYPE: Randomized double-blind placebo-controlled trial

Long-acting injectable antipsychotics (LAI), formerly known as "depot" neuroleptics, are good options for some patients—primarily those who either forget or don't want to take their pills. While studies have not always shown a clear advantage of LAIs over orals, there's no question that they can play a useful role for some. All previously available LAIs (there are 6 options out there) had to be given no less frequently than every 2–4 weeks. Now, a 3-month formulation of paliperidone (Invega Trinza) has been developed and approved by the FDA. What did the pivotal research trial show?

506 patients were recruited from multiple study sites spanning eight countries. For the first 17 weeks, all patients were treated with the standard once-monthly version of injectable paliperidone (Invega Sustenna). After dropouts, 379 patients were left, and all were switched to a 12-week trial of Invega Trinza. After additional dropouts, 305 patients were left, and they were randomly assigned to either continued treatment with Trinza (n = 160) or placebo injectable (n = 145). These patients were followed on average for 6 to 9 months.

RESULTS

The main outcome was percent of patients who relapsed to psychosis. Only 11 patients (7%) relapsed while on Trinza, significantly fewer than the 31 patients (23%) who relapsed on placebo. Because of the large efficacy difference between Trinza and placebo, the study was ended early. Trinza was well-tolerated. The main side effects reported more frequently on Trinza than placebo were headaches (9% vs. 4% on placebo), weight gain (9% vs. 3%), and akathisia (4% vs. 1%). While the study was not designed to compare different doses, patients on the 525 mg dose of paliperidone were more likely to last longer before relapse than those taking the 350 mg dose.

THE CARLAT TAKE

Trinza was more effective than placebo, and the magnitude of the advantage was so large the study was stopped early. Sounds good, but there are a couple of caveats. First, Trinza was contrasted with placebo as opposed to comparable and cheaper active agents, such as oral meds or other LAIs. This means that we don't know whether the new formulation really has an advantage over its competitors.

In fact, the study design inherently favored preparations made with paliperidone. How? The only patients who received Trinza were those who had already done well for 4 months on

paliperidone monthly injectable. This "enriched" sample essentially stacks the deck in favor of Trinza. It would be like doing a consumer taste test of a new version of Coca-Cola, but only including consumers who had been enjoying the older version of Coke. By excluding those who prefer Pepsi from your trial, you'd expect your new version of Coke to be given high marks. Analogously, if you were considering switching a patient from, say, Haldol decanoate to paliperidone, that patient might be less likely to do as well as the patients in this study.

Nonetheless, an antipsychotic preparation that lasts for 3 whole months is a genuine innovation, and we're happy to have another option for patients.

PRACTICE IMPLICATIONS

If you have patients who are noncompliant with oral meds, offer them an LAI, and if insurance will pay, consider going with paliperidone monthly in preparation for an eventual switch to Trinza. If your patient is already on monthly paliperidone, but doesn't like monthly shots, then it's reasonable to try the switch to the 3-month version. But if your patient is stable on any other injectable, we don't know if the switch will be effective.

Second-Generation Antipsychotics Do Not Raise Risk of Major Malformations

REVIEW OF: Cohen LS, Viguera AC, McInerney KA, et al. Reproductive safety of second-generation antipsychotics: current data from the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics. *Am J Psychiatry* 2016;173(3):263–270. doi:10.1176/appi.ajp.2015.15040506.

STUDY TYPE: Prospective cohort

Plenty of women come to us on second-generation antipsychotics (SGA) and ask about their safety in pregnancy. Because of a lack of reported malformations, these medications are widely considered to be relatively safe, but we are in dire need of more evidence to be more confident. Researchers at Massachusetts General Hospital (MGH) have created a national registry to track the safety of SGAs, and in a recent paper they reported their results so far.

Over a 6-year period, 214 women between the ages of 18 and 45 who had been exposed to an SGA during their first trimester were enrolled in the registry. These women were compared to a control group of 89 women who were not exposed to SGAs, but who did have a psychiatric illness during pregnancy. The women were interviewed at multiple time points: 1) at the time of registry enrollment; 2) at 7 months pregnant, and 3) at 3 months postpartum. Medical records were also reviewed. The majority of women (about 60%) in both the exposed and unexposed groups had a primary diagnosis of bipolar disorder, and only a small proportion (about 2%) carried a primary diagnosis of schizophrenia.

RESULTS

In the exposed group, the risk of developing a serious malformation was 1.4% (3 of 214 births); in the unexposed group, the risk was 1.1% (1 of 89 births). The researchers concluded that SGAs are unlikely to be teratogenic, but also mentioned that the study sample was too small to reach a definite conclusion. They pointed out that the MGH registry continues to collect data on this issue, and that as the sample size increases, they will likely be able to estimate the risk with more precision.

THE CARLAT TAKE

SGAs probably do not increase the risk of serious fetal malformations, which is reassuring. It's important to note, though, that the study did not report on less serious effects, such as higher birth weight, neonatal withdrawal, or even gestational diabetes. Prior studies of SGAs have shown possible associations with these outcomes, so counseling pregnant women about these meds remains complicated.

PRACTICE IMPLICATIONS

Tell women that SGAs probably don't cause major malformations—but they may cause less serious problems. Whether women choose to continue the medication during pregnancy will depend on how convinced they are that the SGA is preventing a serious psychiatric relapse.

Should You Be Monitoring Serum Levels of Atypical Antipsychotics in Kids?

REVIEW OF: **Whitney Z, Boyda HN, Procyshyn RM, et al. Therapeutic drug levels of second generation antipsychotics in youth: a systematic review. *J Child Adolesc Psychopharmacol.* 2015;25(3):234–245. doi:10.1089/cap.2014.0044.**

STUDY TYPE: **Literature Review**

Prescribing antipsychotics for children is an ongoing source of controversy. There are currently three FDA-approved indications: irritability in autism, schizophrenia, and bipolar disorder. But much of the recent increase in prescribing is driven by off-label uses, such as ADHD, OCD, depression, conduct disorder, and impulse control disorders. We don't have a lot of efficacy and safety data in many of these instances, and side effects—primarily weight gain and dystonia—can be significant.

One way to potentially minimize dosing would be to measure levels of antipsychotics in the blood and dose accordingly. In adults, there are some data correlating serum drug levels with clinical response for risperidone and olanzapine. The authors of this paper systematically reviewed the literature to see whether serum level monitoring of atypical antipsychotics in kids would be useful.

RESULTS

The authors performed a systematic literature review for papers published between 2000 and 2013 on the topic of serum drug levels and antipsychotics in kids, and they came up with 21 articles. Here are the highlights of their conclusions:

The atypical with the most robust data was clozapine. There were three studies conducted, one of which was quite large: 484 kids with schizophrenia. Clozapine serum levels in the range of 200 to 400 ng/mL seem to be correlated with dose, clinical response, and adverse effects in children, just as in adults.

For aripiprazole, olanzapine, and risperidone, serum levels were variable and didn't predict response. For example, the mean olanzapine serum level in one study was 46 ng/mL, but the range for all kids was 2 ng/mL to 111 ng/mL. In addition to variability between kids, there is also a lot of variability in individual kids over time. One study suggested that to get an accurate read on a child's blood level, you would need more than 20 repeat samples from that child to account for intra-individual variability. In addition, serum levels of these antipsychotics didn't seem to be correlated with clinical response or side effects.

One small study (n = 17 kids) of quetiapine in conduct disorder suggested that there may be a correlation between blood level and clinical response: kids who had levels > 300 ng/mL were more likely to be responders. But another larger study didn't find an association.

THE CARLAT TAKE

There's still not much evidence endorsing therapeutic drug monitoring for antipsychotics in children.

PRACTICE IMPLICATIONS

Ordering levels of clozapine can be useful in the rare cases of children who are being treated with this hazardous drug. Otherwise, therapeutic drug monitoring of antipsychotics in kids is only helpful in assessing medication adherence, or when you encounter significant side effects at low doses and you want to see if the blood levels are unusually high.

NEUROCOGNITIVE DISORDERS

Do Benzodiazepines Cause Dementia? Latest Study Casts Doubt

REVIEW OF: Gray SL, Dublin S, Yu O, et al. Benzodiazepine use and risk of incident dementia or cognitive decline: prospective population based study. *BMJ.* 2016;352:i90. doi:10.1136/bmj.i90.

STUDY TYPE: Prospective cohort

There are plenty of reasons to avoid prescribing benzodiazepines (BZD) for elderly patients, including the risks of acute confusion, falls, and drug dependence. In addition, over the past few years, there's been a growing body of research suggesting a link between long-term BZD use and dementia, though results to date have been inconsistent (Verdoux H et al, *Psychol Med* 2005;35(3):307–315).

Even if there is a correlation between BZD use and dementia, it would not imply that BZDs actually cause cognitive decline. It's equally possible that the causal chain works the other way around—that is, dementia or pre-dementia lead to patients being prescribed BZDs to alleviate symptoms like anxiety and insomnia caused by cognitive problems. This latest, very large study adds to our knowledge on this issue.

3,434 individuals in the Seattle area aged 65 and over and without dementia at study entry were prospectively followed for an average of 7.3 years. Cognition was assessed at baseline and every 2 years thereafter. The diagnosis of dementia was established clinically by a multidisciplinary team of clinicians. BZD use was ascertained by pharmacy records, and a standardized rate of cumulative BZD exposure was calculated for each individual. After controlling for potential confounding variables such as medical illness and depression, the investigators evaluated whether patterns of BZD use predicted later cognitive impairment or dementia.

RESULTS

There were 797 (23.2%) new cases of dementia, of which 637 (79.9%) were of the Alzheimer's type. There was a slightly elevated risk of dementia for individuals with low to moderate levels of BZD exposure—meaning use for 1 to 4 months total over the 7.3 years of follow-up. However, contrary to the authors' expectations, greater cumulative BZD use (more than 4 months of use) was not related to either dementia or less serious cognitive decline.

THE CARLAT TAKE

This study adds evidence to the argument that BZDs do *not* cause long-term cognitive decline in the elderly. The only statistically significant finding was between low BZD use and dementia. If BZDs caused dementia, we would expect higher cumulative BZD exposure to be associated with higher rates of dementia. These findings are instead most consistent with the notion that low-dose BZDs are being used to treat prodromal symptoms of dementia (such as anxiety and

agitation), but do not cause dementia—a finding other investigators have noted as well (Imfeld P et al, *Drug Saf* 2015;38(10):909–919).

PRACTICE IMPLICATIONS

If an elderly patient (defined generally as 65 or older) presents with significant anxiety, you can certainly try an SSRI, but if that doesn't work, judicious use of BZDs is worthwhile and likely does not increase the risk of later dementia. Nonetheless, try to stick with shorter half-life agents like lorazepam or alprazolam, keep the dose low, and evaluate the need for more prescriptions rather than automatically refilling for years on end.

Anticholinergics and Dementia

REVIEW OF: Gray SL, Anderson ML, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med.* 2015;175(3):401–407. doi:10.1001/jamainternmed.2014.7663.

STUDY TYPE: Prospective cohort

Lots of psychiatric medications have anticholinergic effects, particularly the tricyclic antidepressants, several antipsychotics, and antihistamines, which we sometimes use for either insomnia or anxiety. Anticholinergic side effects can be particularly troublesome for the elderly—they include tachycardia, urinary retention, cognitive impairment, and in extreme cases, delirium. A large, new study provides evidence that anticholinergics may increase the risk of dementia. (If this study sounds a lot like the study you just read on benzodiazepines and dementia, it's not a coincidence—these are the same researchers using the same data set, only focusing on anticholinergics rather than benzodiazepines.)

A total of 3,434 Seattle-area adults over 65 years of age from the National Institute on Aging–funded Adult Changes in Thought study were enrolled. The mean age was 74.4 years, 60% were women, 91% were white, and about two-thirds had some college education. Pharmacy dispensing data were used to determine anticholinergic drug use as far as 10 years prior to study entry. The most common anticholinergic classes used were tricyclic antidepressants, antihistamines, and bladder antimuscarinics, such as oxybutynin (Ditropan).

RESULTS

The researchers found that 23.2% of subjects developed dementia (mostly Alzheimer's disease) after a mean follow-up of 7.3 years. The subjects who were in the highest anticholinergic exposure category had a statistically significant increased risk for dementia compared with those with no anticholinergic use (examples of high exposure include taking of 50 mg/day of Benadryl for 6 months, 10 mg/day of Doxepin for 9 months, and 5 mg/day of Zyprexa for 12 months). Those with less exposure still had a slightly elevated risk for dementia.

One of the more interesting findings was that the timing of heavy anticholinergic use within that 10-year exposure window was not important—those who used anticholinergics cumulatively over a long period in the past had as much risk as those with more recent continuous use of anticholinergics.

THE CARLAT TAKE

This study shows a clear association between anticholinergic use in the elderly and later development of dementia. As with the studies we've already discussed about benzos, correlation does not necessarily imply causation. For example, the elderly who took the most anticholinergics may have developed dementia irrespective of the medications. It's possible that people with "pre-dementia" happen to have other symptoms, such as insomnia or depression, which lead their doctors to prescribe drugs with anticholinergic side effects. Nonetheless, this study

more strongly implies causality because, unlike benzodiazepines, there was a clear dose-response relationship between anticholinergic load and later development of dementia. The study also suggests that dementia risk linked to anticholinergic medications may persist even years after people stop taking these drugs.

PRACTICE IMPLICATIONS

Try to avoid prescribing long-term anticholinergics for the elderly. This is not too hard to do in psychiatry. For antidepressants, avoid tricyclics and paroxetine; for antipsychotics, avoid olanzapine, clozapine, chlorpromazine, thioridazine, and loxapine; and avoid antihistamines like diphenhydramine and hydroxyzine. We've got plenty of other options in our medication toolbox.

Mediterranean Diet to Prevent Cognitive Decline

REVIEW OF: Valis-Pedret C, Sala-Vila A, Serra-Mir M, et al. Mediterranean diet and age-related cognitive decline: a randomized clinical trial. *JAMA Intern Med.* 2015;175(7):1094–1103. doi:10.1001/jamainternmed.2015.1668.

STUDY TYPE: Randomized open label controlled trial

Our aging patients often worry about their memory and ask us if we can prescribe them something to either improve their memory or prevent memory loss in the future. Unfortunately, we don't have much to offer in terms of medications—but what about diet? This study was a randomized clinical trial conducted to determine if a Mediterranean diet (an antioxidant-rich cardioprotective dietary pattern) can delay cognitive decline.

447 cognitively healthy men and women from Barcelona, Spain (mean age 66.9 years) were enrolled in this trial. They all had cardiovascular risk factors, but no actual heart disease (this was part of a larger study about the effects of diet on heart disease). They were randomly assigned to one of three intervention groups: a Mediterranean diet supplemented with extra virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (advised to reduce all dietary fat). Participants were followed for a median of 4.1 years. Everyone had a battery of six neuropsychological tests as well as the Hamilton depression scale both at the beginning of the study and at the end. The primary outcome measures were three composite scores computed from the neuropsychological tests. These composites measured overall memory; frontal functions, such as sustaining attention and working memory; and global cognition, which included scores from all six tests.

RESULTS

A lot of participants dropped out of the study before getting their second neuropsych tests—113, or 25.3% of the group. Those who dropped out had somewhat lower Mini-Mental State Examination scores and were more likely to have the ApoE gene, a risk factor for dementia. This means that the results of the study are more likely to apply to elderly people who are sharper and who don't have the ApoE allele.

Participants assigned to the Mediterranean diet plus olive oil significantly outperformed those on the control diet in two of the three composite scores: frontal cognition and global cognition. Those assigned to the Mediterranean diet plus nuts outperformed control on the memory composite score. Over the study period, 37 people developed mild cognitive impairment, with no significant difference among the diets. The intervention had no effect on depression scores.

THE CARLAT TAKE

The results are intriguing, but there were methodological problems with this study. (1) This was a post-hoc analysis of a subsample of data from a larger clinical trial which was not specifically designed to test the effects of diet on cognition. (2) There was a substantial number of drop-outs, limiting the generalizability of the findings. (3) The subjects were not blinded to their treatments (eg, their diets). (4) The sample size was not big enough to be really confident in the findings. Nonetheless, the researchers did show that randomly assigning people to Mediterranean diets leads to measurable cognitive improvement relative to people asked simply to reduce dietary fat.

PRACTICE IMPLICATIONS

Since the Mediterranean diets have been shown to improve heart health, and given these positive findings on cognitive functioning, go ahead and recommend this diet to your elderly patients. You can find more specifics about the diet from the National Center for Biotechnology Information.

ANXIETY DISORDERS

OCD in Kids: CBT, SSRIs, Then What?

REVIEW OF: **Bloch MH, Storch EA. Assessment and management of treatment-refractory obsessive-compulsive disorder in children. *J Am Acad Child Adolesc Psychiatry.* 2015;54(4):251–262. doi:10.1016/j.jaac.2015.01.011.**

STUDY TYPE: **Literature review**

Between 1% and 3% of children have obsessive-compulsive disorder (OCD). Recently, a good literature review summarized what we know about treating kids with OCD.

The best evidence (from randomized controlled trials in kids) suggests that we should start treatment with cognitive behavioral therapy (CBT), either alone or with SSRIs, when kids are first diagnosed. The CBT/SSRI combination had the largest effect size of 1.7, CBT alone had an effect size of 1.2, and SSRIs alone had an effect size of 0.75.

What about the kids who don't respond to CBT or SSRIs? Here are the authors' recommendations for treatment refractory OCD. An important caveat is that few studies of these treatments have been done specifically on kids, so we've noted the type of evidence published so far.

- **Combine treatments:** If the child is receiving CBT alone or SSRI alone, switch to a combination of both (evidence: standard of care, studies in kids).
- **Maximize CBT:** If the child is already getting combination CBT/SSRI, intensify the CBT, such as with daily sessions for three weeks, adding exposure and response prevention, providing homework, etc. (evidence: standard of care, studies in kids). However, the age at which CBT begins to work well with children is not clear, so this approach may not apply to those under age 11 or 12.
- **Maximize SSRI:** Maximize the SSRI dose, even if you end up prescribing higher than the manufacturer's recommended maximum. One study compared 200 mg/day of sertraline to 400 mg/day in 66 adults with OCD who had only partial response. Those in the higher-dose group had significantly better response than those who continued on 200 mg/day without higher side effect or dropout rates (evidence: extrapolated from studies in adults).
- **Try clomipramine:** The tricyclic antidepressant clomipramine, though effective in kids with OCD, is considered a second- or third-line option because of its side effects. Consider using it in a child who has failed one or two adequate trials of SSRI. Some OCD specialists will combine clomipramine and another SSRI, usually by maximizing the SSRI dose and using a lower clomipramine dose (75 mg/day). But the risk with this combination is potential serotonin syndrome (evidence: monotherapy trial data in kids with non-refractory OCD; combination therapy trial data in adults).
- **Augment with an atypical antipsychotic:** Low doses of risperidone, haloperidol, quetiapine, olanzapine, and aripiprazole are well-studied and effective in adults with refractory OCD, but there are no adequate studies in kids (evidence: trial data in adults).

- **Riluzole:** This glutamatergic drug used for amyotrophic lateral sclerosis showed promise in kids and adults with OCD in uncontrolled trials. But a more recent controlled study in kids didn't show any benefit compared to placebo. Potential side effects include hepatotoxicity and pancreatitis (evidence: uncontrolled and negative controlled trials in kids).
- **Ketamine:** An anesthetic, ketamine may be effective for depression and has been studied in adults with treatment refractory OCD. One small open trial showed only extremely short-lived (first 3 hours after intravenous infusion) benefits, while a second small trial showed benefit during the first week (evidence: extrapolated from adults).
- **Memantine:** Approved for Alzheimer's disease and also an N-Methyl-D-aspartate (NMDA) antagonist, memantine was more effective than placebo as add-on to fluvoxamine in one small controlled study of adults with OCD (evidence: extrapolated from adults).
- **Topiramate:** Of two small controlled trials of this anticonvulsant in adults with refractory OCD, only one suggested efficacy (evidence: extrapolated from trials with adults).
- **N-acetylcysteine (NAC):** An amino acid sold as a dietary supplement was studied in a small trial of adults with refractory OCD. NAC 1,200 mg twice daily was better than placebo as add-on to SSRI. Studies in kids with OCD are underway, but NAC has been used in kids with autism spectrum disorder and trichotillomania (evidence: extrapolated from trials with adults).
- **Benzodiazepines:** Controlled studies in adults with OCD have not shown efficacy. Use is not supported by evidence (evidence: extrapolated from trials with adults).
- **Neurosurgery and neurostimulation:** These are strategies used in adults with severe and refractory OCD, but they should not be considered in children whose OCD may remit over the long term.

THE CARLAT TAKE

This is a well done literature review summarizing the current state of the art for treating kids with OCD.

PRACTICE IMPLICATIONS

For kids with OCD, start with CBT with or without SSRI. For refractory cases, use combination CBT/SSRI and maximize SSRI dose. If that still doesn't help, consider adding a low dose of clomipramine, an atypical antipsychotic, or NAC.

N-acetylcysteine Shows Promise for Skin-Picking Disorder

REVIEW OF: **Grant JE, Chamberlain SR, Redden SA, Leppink EW, Odlaug BL, Kim SW. N-acetylcysteine in the treatment of excoriation disorder: a randomized clinical trial. *JAMA Psychiatry.* 2016;73(5):490–496. doi:10.1001/jamapsychiatry.2016.0060.**

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

If you've ever had a patient with skin-picking disorder (SPD), also known as excoriation disorder, you know how difficult it can be to treat and how frustrating it is for patients. Various forms of cognitive behavioral therapy are the most effective treatments, but some medications can be helpful, such as SSRIs or second-generation antipsychotics. Various lines of evidence imply that this variant of obsessive-compulsive behavior may be related to reduced levels of glutamate in the nucleus accumbens. N-acetylcysteine (NAC) is an inexpensive over-the-counter antioxidant that increases glutamate, and studies have shown that it is effective for excoriation's sister disorder, trichotillomania (hair pulling). These data prompted investigators to try NAC in the treatment of SPD.

Over a 12-week period, 66 adult SPD patients from two Midwestern university-based clinics were randomized in a double-blind study to receive NAC (n = 35) or placebo (n = 31). The NAC group received 1,200 mg/day to start, increasing to 2,400 mg/day by week 3 and 3,000 mg/day by week 6. An excoriation-specific version of the Yale-Brown Obsessive Compulsive Scale (NE-YBOCS) was used to assess picking symptoms over the 3 months. Investigators also used the Clinical Global Impression-Severity scale and other self-report, subjective measures.

RESULTS

NAC seemed to work. Baseline NE-YBOCS scores dropped from 18.9 to 11.5 for the treatment group by the end of 12 weeks. During the same time period, the placebo scores shifted from 17.9 to 14.1. Subjective self-reports by the patients were also strong. Of the 53 patients who completed the study, 47% of the NAC group felt they were "much" or "very much" improved, compared to only 19% of the placebo group. No significant adverse events were noted.

THE CARLAT TAKE

The study was small, but NAC clearly outperformed placebo for the treatment of SPD.

PRACTICE IMPLICATIONS

For patients with SPD, NAC is a good alternative to SSRIs, particularly since no prescription is required and there are rarely any side effects. One disadvantage is that most formulations have an unpleasant rotten-egg odor, but this varies by batch and manufacturer. Start at 600 mg BID and increase up to 1,800 mg BID.

Prescribing Anxiety Meds for Teens May Trigger Later Drug Abuse

REVIEW OF: Boyd CJ, Austic E, Epstein-Ngo Q, Veliz PT, McCabe SE. A prospective study of adolescents' nonmedical use of anxiolytic and sleep medication. *Psychol Addict Behav.* 2015;29(1):184–191. doi:10.1037/adb0000026.

STUDY TYPE: Prospective cohort

Adolescents are commonly prescribed controlled medications for anxiety or insomnia. Both benzodiazepines and non-benzodiazepines (the so called "z-drugs," such as zolpidem) are effective, but we often worry about whether these patients will like the meds so much that they will eventually abuse them. This study sought to answer that important question.

University of Michigan researchers conducted surveys of 2,745 adolescents attending five Detroit-area secondary schools between 2009 and 2012. Of these students, the vast majority (2,508, or 91.4%) had never been prescribed a sleep or anxiety drug. On the other hand, 92 (3.4%) of the kids had been prescribed such a drug at some point in their lives, but not recently, and 145 (5.3%) had been prescribed them over the past three years. The key question was: were adolescents who were legally prescribed these meds more likely to later improperly use them than kids who had never received such prescriptions?

RESULTS

The answer, resoundingly, was "yes." Compared with adolescents never prescribed anxiolytics or sleeping pills, adolescents prescribed these medications recently were 10 times more likely to use them for "sensation-seeking motivations," such as to get high or to experiment. They were also three times more likely to use someone else's prescription to self-treat anxiety or to help them sleep.

What about kids who had received a prescription in the more distant past? These respondents were 12 times more likely to use someone else's anxiety medication, compared with teens never prescribed anxiolytic medications. This association was not found with sleep medications, however.

THE CARLAT TAKE

The results are a cause for concern. Kids who receive legitimate prescriptions for benzos or non-benzos are later more likely to use these nonmedically, to get high. This does not necessarily mean that we are creating little addicts, of course. It's possible that kids receiving such prescriptions are already predisposed to eventually abuse them, regardless of our prescriptions. To really prove that prescribing leads to illegal use, you'd have to do a very different study, randomly assigning patients to either receive prescriptions or placebo and then tracking their behavior through the years. Such a study would be very difficult if not impossible to do, but this cohort study is suggestive.

PRACTICE IMPLICATIONS

Be cautious when prescribing either benzos or non-benzo z-drugs to teens: Once they discover that "Ativan feeling," they may well seek it out in the future, whether they are anxious or not.

SIDE EFFECTS OF MEDICATIONS

Intensive Weight Loss Program for Psychiatric Patients Yields Mediocre Results

REVIEW OF: **Green CA, Yarborough BJ, Leo MC, et al. The STRIDE weight loss and lifestyle intervention for individuals taking antipsychotic medications: a randomized trial. *Am J Psychiatry.* 2015;172(1):71–81. doi:10.1176/appi.ajp.2014.14020173.**

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

We know that several commonly used antipsychotics cause weight gain (yes, we're looking at you, Zyprexa, Risperdal, and Seroquel)—but we don't know much about how to prevent the side effect or how to treat it once it occurs. A recent study tested an intensive weight loss program in a large group of psychiatric patients. The results were . . . well, read on and you can decide whether they were impressive.

The researchers enrolled 181 overweight psychiatric patients from health clinics in the Pacific Northwest. To be included in the study, patients had to be at least 18, had to have been on an antipsychotic for at least 30 days prior to entry, and had to be at least moderately overweight, with a minimum body mass index (BMI) of 27. Most of the patients who enrolled were actually much heavier than "moderately overweight"—their average BMI was 38, and their average weight was nearly 240 pounds. Most patients had a diagnosis of either bipolar disorder/affective psychosis (69%) or schizophrenia spectrum (29%).

Patients were randomly assigned to one of two groups: the STRIDE weight loss program or standard psychiatric care without any specific weight loss focus. In the STRIDE program, participants attended weekly 2-hour group meetings for 6 months, exercised for at least 20 minutes daily, and received nutrition and behavior modification counseling. They were also required to maintain daily food and sleep diaries. After the 6-month intervention phase, patients entered a 6-month maintenance phase that was less intensive, consisting of 1 meeting per month. While the patients knew the group to which they were assigned, the researchers assessing the final outcome measures were blinded to assignment (a single-blind study).

RESULTS

So did STRIDE work? At baseline, the average weight of the STRIDE participants (n = 93) was 238.9 pounds. After 6 months, they lost 9.3 pounds (3.9% of initial weight), to weigh in at 229.6 pounds. The control group (n = 85), by contrast, gained a little weight: they went from 234.5 pounds to 236.6 pounds, for a weight gain of 2.1 pounds (0.9%). The weight difference between intervention and control was statistically significant. Unfortunately, the benefits of STRIDE lessened after another 6 months. While the STRIDE participants basically maintained their lower weight during the maintenance phase, the control group lost some weight, so that 12 months after study entry, there was only a 5.7-pound difference between the two groups—which barely achieved statistical significance.

Researchers also measured various labs, but only one of them—fasting blood glucose—decreased more in the intervention group at 12 months. There were no significant differences between the groups in triglycerides, LDL, HDL, or blood pressure readings.

THE CARLAT TAKE

While any weight loss is better than none, the results of this intervention were somewhat disappointing. In round numbers, markedly obese patients (eg, about 240 pounds) stand to lose about 4% of their body weight after a year if they participate in a highly structured 6-month weight loss program—vs. about 2% of their weight if they simply go to regular doctor appointments. In fairness, as the authors point out, not all patients took the program seriously, and those who attended more sessions and filled out more food logs lost more weight.

PRACTICE IMPLICATIONS

The positive spin on the study is that highly motivated obese patients are likely to lose a bit of weight in a STRIDE-like program. But it's likely that a much more effective strategy is prevention—and we can help by prescribing weight-neutral medications when possible.

Metoclopramide Helps Clozapine-Related Drooling

REVIEW OF: Kreinin A, Miodownik C, Mirkin V, et al. Double-blind, randomized, placebo-controlled trial of metoclopramide for hypersalivation associated with clozapine. *J Clin Psychopharmacol.* 2016;36(3):200–205. doi:10.1097/JCP.0000000000000493.

STUDY TYPE: Randomized double-blind placebo-controlled trial

Clozapine's a great drug for treatment resistant schizophrenia, but it's infamous for a couple of serious side effects—agranulocytosis and rapid weight gain. Unless you prescribe a lot of it, you may not even know about drooling as a clozapine side effect, but for patients it is particularly troubling. CIS (clozapine-induced sialorrhea) occurs in about 30% of patients. It's often worse at night, and waking up with a wet pillow is not a particularly nice way for people to begin their day.

There are various things to try for this problem, including anticholinergics such as Artane and Cogentin, alpha adrenergics like clonidine and guanfacine, and sublingual drops such as atropine or pilocarpine. None of them work consistently, and they all have potential side effects. Recently, Israeli researchers evaluated another potential treatment, metoclopramide (Reglan), which is a drug for nausea and other gastrointestinal problems. Since metoclopramide commonly causes dry mouth, the authors of this paper reasoned that it might work for CIS.

Over a 2-year period, 58 inpatients treated with clozapine and experiencing hypersalivation were randomized to receive metoclopramide (30 patients) or placebo (28 patients). Both groups were tracked over 3 weeks. Metoclopramide was initially dosed at 10 mg at bedtime. If there was no response, a 10 mg dose was added in the morning during week 2, and another 10 mg could be added in the afternoon if needed. Researchers used a variety of subjective and objective measures to assess improvement.

RESULTS

At the end of the study, 66.7% (n = 20) of those who received metoclopramide showed improvement or outright disappearance of drooling, significantly more than the 28.6% (n = 8) of those who took placebo (p = 0.031). No patients in the metoclopramide group reported any adverse reaction.

THE CARLAT TAKE

Drooling can be a deal breaker for patients taking clozapine. While this randomized controlled trial is of short duration and based on a relatively small sample, the results support the use of metoclopramide for this distressing side effect. There is one note of caution, however: Metoclopramide is a dopamine antagonist and can cause tardive dyskinesia and other movement disorders. So monitor patients closely if you choose to add metoclopramide to the mix.

PRACTICE IMPLICATIONS

For patients with clozapine-induced hypersalivation, try metoclopramide, starting with 10 mg at bedtime and increasing up to 10 mg 3 times a day.

Atomoxetine Does Not Increase Risk of Suicide Compared to Stimulants

REVIEW OF: Linden S, Bussing R, Kubilis P, et al. Risk of suicidal events with atomoxetine compared to stimulant treatment: a cohort study. *Pediatrics.* 2016;137(5). doi:10.1542/peds.2015-3199.

STUDY TYPE: Retrospective cohort

In 2004, the FDA issued its famous and controversial black box warning that antidepressants may cause suicidal ideation in children and adolescents. Atomoxetine was not originally included in that rogue's gallery of medications, but since the drug was originally developed as an antidepressant, the FDA later reviewed its safety data. The agency's meta-analysis of placebo-controlled trials indeed revealed an increased risk of suicidal thinking, and so atomoxetine was slapped with the same warning.

The big question is whether the FDA's clinical trials data on suicidality are generalizable to real-world patients we see in our offices. To try to answer this, researchers mined Medicaid data from 1999 to 2006 from 26 U.S. states to see if patients treated with atomoxetine had more suicide attempts than those treated with stimulants. Two groups were included in the analysis: those who received first-line atomoxetine treatment (initial treatment with atomoxetine) and those who received it as a second-line treatment (switched to or added atomoxetine after initial treatment with stimulant). Both groups included children and adolescents ages 5 through 18 and were substantial in size—279,315 and 220,215 individuals, respectively. The study's primary end point was total suicide attempts and completions.

RESULTS

Overall, there was no significant difference between the atomoxetine and stimulant groups regarding suicide events (attempted or completed suicide). There were 140 events in the first-line treatment group. Females attempted suicide more often (60%), whereas a greater proportion of males completed suicide (89%). There were 90 suicidal events in the second-line treatment group. Similar to the first-line group, females accounted for 60% of the attempts, and males comprised 73% of completed suicides. The hazard ratios (probability of a suicide event in the atomoxetine vs. stimulant group) for the first- and second-line groups were 0.95 and 0.71, respectively.

THE CARLAT TAKE

Results from clinical trial data and real-world practice don't always jibe. It appears that atomoxetine is no more likely to lead to suicidal events than stimulants (which have never been implicated as potentially causing suicidal ideation).

PRACTICE IMPLICATIONS

Atomoxetine is typically a second-line medication for ADHD after stimulants. If you've been hesitant to try atomoxetine in children because of the black box warning, this study should allay those concerns.

CHILD AND ADOLESCENT PSYCHIATRY

Exercise Not Only Good for Children's Overall Health, It's Good for Their Brains

REVIEW OF: Hillman CH, Pontifex MB, Castelli DM, et al. Effects of the FITKids randomized controlled trial on executive control and brain function. *Pediatrics.* 2014;134(4):e1063–1071. doi:10.1542/peds.2013-3219.

STUDY TYPE: Randomized open label single-blind controlled trial

As psychiatrists, we often see children with cognitive issues, such as ADHD or learning disabilities, and we commonly prescribe them a psychostimulant. But when was the last time you prescribed exercise? This study hints that it might be worth considering.

To test the hypothesis that exercise could improve cognitive function in kids, researchers randomly assigned 221 healthy children, ages 8 to 9, to either a 9-month after-school physical activity program (n = 109) or to a wait-list control group (n = 112). The active intervention was called the Fitness Improves Thinking in Kids (FITKids) program. Children in this group spent 2 hours every day after school for the entire 9 months of the school year doing various exercise and skills games. These included activities such as jumping jacks, throwing, and catching. All children were evaluated both at the start and end of the year on difference indices of aerobic fitness and cognitive abilities. The researchers measuring outcomes were blinded to group assignment.

RESULTS

Children assigned to FITKids improved more than their wait-list counterparts in both physical conditioning and measures of mental fitness. The FITKids children improved more in terms of attentional inhibition (the ability to restrict distractions or habits to maintain focus) and cognitive flexibility (the ability to multitask). The advantages were not huge, however—between 3.2% and 4.8% better than the wait-list group. Improvements were greater in children who attended the exercise program most often.

THE CARLAT TAKE

We've known for some time that physical exercise can help improve cognition in the elderly, and this interesting study provides evidence of similar improvements in young children.

PRACTICE IMPLICATIONS

Since these children were healthy, it's not clear that the results would generalize to children we see in our offices. Nonetheless, consider sharing the results of this study with your patients' parents and teachers. Increased daily physical activity can't hurt, and it's likely to help your patients both physically and psychologically.

Danish Study Explains Most of Autism's Rise

REVIEW OF: Hansen SN, Schendel DE, Parner ET. Explaining the increase in the prevalence of autism spectrum disorders: the proportion attributable to changes in reporting practices. *JAMA Pediatr.* 2015;169(1):56–62. doi:10.1001/jamapediatrics.2014.1893.

STUDY TYPE: Retrospective cohort

According to the Centers for Disease Control and Prevention, the prevalence of autism spectrum disorder is 1.5%, or 1 in 68 children in the U.S. (2014 figures). This represents a 123% increase since 2002, when the prevalence was reported as 0.66%.

There is disagreement about the cause of this increased prevalence. Debate has focused on whether the rise in cases is an artifact caused by greater diagnosis and reporting, or an actual increase due to some unknown pathogenic factor in the environment. A study out of Denmark provides support for the artifact argument.

Researchers analyzed information from nearly 678,000 children born in Denmark from 1980 to 1991, who were followed until 2011. Of those children, 3,956 were diagnosed with autism, with a sharp increase in diagnoses after 1994. Researchers found that there were only 192 diagnoses reported from 1980 to 1993, but 100 from 1994 to 1995, and an astonishing 3,665 (95% of the total) from 1996 to 2011.

What happened in 1994? That was when ICD-10 was introduced, changing diagnostic criteria in ways that led to more kids meeting them. These changes, which were also reflected in DSM-IV, included recognizing autism as a spectrum of disorders (rather than as a subgroup of schizophrenia in ICD-8, which was the previous version used in Denmark). Another significant change occurred in 1995, in Denmark and other Nordic countries: Previously, autism could be diagnosed only in inpatient settings; after 1995, outpatient diagnoses were allowed.

RESULTS

Using statistical techniques that predicted changes in diagnostic rates based on past trends, the researchers estimated that about 60% of Denmark's increase in autism prevalence could be explained by changes in diagnostic criteria and in reporting practices. This means that 40% of the increase remained unexplained. Researchers suggested that the general growth in autism awareness might contribute, but that further studies are needed to explain the changes.

THE CARLAT TAKE

In Denmark, much of the apparent increase in autism rates is explainable by a broadening of diagnostic criteria. It's likely that the increase in the U.S. has the same explanation. By the way,

you may wonder why so many valuable epidemiological studies come out of Denmark. The reason is that the Danish government has long kept detailed health records of all its citizens. This means Denmark can answer interesting health questions more accurately than we can; instead of selecting a representative sample of the population to study, they can literally study their *entire* population. They don't have to worry about whether their results are generalizable to everybody, since everybody is part of the sample.

PRACTICE IMPLICATIONS

Nothing in these data suggest a need to change your clinical practice, but this is an important piece of information when you are discussing autism with concerned parents who may have read about other theories to explain autism's rise, from vaccines (completely discredited) to environmental toxins (still awaiting convincing evidence). Still, it is important to note that criteria changes accounted for much, but far from all, of the reported increase.

SUBSTANCE ABUSE

Smoking Cessation Drug Side Effects Not as Common as Feared

REVIEW OF: Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet.* 2016;387(10037):2507–2520. doi:10.1016/S0140-6736(16)30272-0.

STUDY TYPE: Randomized double-blind placebo-controlled trial

Both varenicline (Chantix) and bupropion (Zyban) are effective antismoking agents, but over the years we've heard about potential neuropsychiatric side effects, especially related to varenicline. These include depression, suicidal thoughts, psychosis, and nightmares. Because of this, many psychiatrists are reluctant to prescribe varenicline to their patients. Until now, there has been no large randomized study testing whether varenicline is dangerous in patients with psychiatric disorders. The FDA required both Pfizer (maker of Chantix) and GlaxoSmithKline (maker of Zyban) to conduct a post-marketing safety study addressing potential side effects. The results of this study are reassuring.

Between late 2011 and early 2015, 8,144 smokers (defined as smoking 10 or more cigarettes daily) spanning 16 countries were randomized to four treatments: varenicline 1 mg twice daily, bupropion SR 150 mg twice daily, nicotine patch 21 mg/day, or placebo. Smokers were categorized into two groups: those with psychiatric disorders (the psychiatric cohort, n = 4,074) and those without (the nonpsychiatric cohort, n = 3,984).

The psychiatric cohort included almost all major DSM-IV Axis I disorders as well as borderline personality disorder; 34% of participants had a history of suicidal ideation, and 13% had a history of suicidal behavior. However, no acutely suicidal patients were allowed in the study, and only psychiatrically "stable" patients were included (meaning they were on a stable treatment regimen and were in remission). Treatment lasted 12 weeks, and patients were followed for an additional 12 weeks after treatment. The two primary outcomes were the presence of moderate and severe psychiatric adverse events, and continued abstinence from smoking for at least 1 month after 2 months of treatment.

RESULTS

Across all four treatments, the psychiatric cohort was about 3 times more likely to experience psychiatric side effects than the nonpsychiatric cohort (5.8% vs. 2.1%). However, none of the active treatments produced more psychiatric side effects than placebo in either group. Rates of suicidal ideation or suicidal behavior ranged from 0.2% to 0.5%. There were no completed suicides in the psychiatric cohort; there was 1 suicide in the nonpsychiatric cohort in a patient assigned to placebo. The most frequent side effects of any type in each treatment group were nausea (varenicline, 25%), insomnia (bupropion, 12%), abnormal dreams (nicotine patch, 12%), and headache (placebo, 10%). In terms of efficacy, varenicline produced the highest quit rate overall (33.5%); bupropion and patch were equally effective (22.6% and 23.4%, respectively), and all the other treatments beat placebo (12.5%). Psychiatric patients

had nearly the same quit rate as nonpsychiatric patients, challenging the widely held belief that mental illness is a barrier to kicking the habit.

THE CARLAT TAKE

In psychiatrically stable patients, varenicline does not cause more moderate to severe psychiatric side effects than bupropion, the nicotine patch, or placebo. It's unclear how generalizable this is to a typical psychiatric practice, though. How many of your patients are truly stable at any given point in time? That varies with the practice. But for the common patient who comes to us needing a lot of help, these otherwise reassuring safety findings might not be so comforting.

PRACTICE IMPLICATIONS

For your patients who are psychiatrically stable, you should feel quite comfortable prescribing varenicline or other antismoking agents. But for others, warn them about possible side effects such as suicidality, anxiety, and disturbing nightmares.

Is Varenicline the Treatment of Choice for Women Who Smoke?

REVIEW OF: **McKee SA, Smith PH, Kaufman M, Mazure CM, Weinberger AH. Sex differences in varenicline efficacy for smoking cessation: a meta-analysis. *Nicotine Tob Res.* 2016;18(5):1002–1011. doi:10.1093/ntr/ntv207.**

STUDY TYPE: **Meta-analysis of placebo-controlled trials**

Although women in general are less likely to be smokers than men (16.5% of U.S. women vs. 21.6% of men), they are more likely than men to suffer serious tobacco-related health effects and are less successful at quitting. Therefore, it is important to find smoking cessation options that are particularly effective in women. Varenicline (Chantix) is probably the single most effective medication for smoking cessation. Some studies have looked at possible sex differences in its efficacy, but none of significance have been demonstrated. These researchers suspected that the individual studies weren't large enough to be statistically powerful, so they did a meta-analysis of all varenicline studies to further explore the possibility of sex difference outcomes.

Researchers found 16 high-quality, randomized, and double-blinded studies comparing varenicline to placebo. The studies included 6,710 patients, of whom 34% were women. They analyzed data for both men and women, and extracted abstinence rates at 12, 24, and 52 weeks.

RESULTS

Varenicline increased the odds of smoking abstinence more for women than for men, both at the 12-week and 24-week time periods. For example, the drug increased the odds of quitting in women by almost 5 times compared to almost 3.5 times in men by the end of 12 weeks of treatment, which amounted to 46% greater effectiveness for women. However, using 52-week outcomes, varenicline was equally effective in men and women.

THE CARLAT TAKE

This study provides strong evidence that, at least over 3 months of treatment, varenicline is particularly effective in the short term for women. Combined with prior data showing that women are less likely than men to respond to either bupropion or nicotine replacement therapy (Perkins KA et al, *Nicotine Tob Res* 2008;10(7):1245–1251), these data imply that varenicline is the first-choice treatment for female smokers.

PRACTICE IMPLICATIONS

For your female patients who want to quit smoking, explain that the research shows women have a harder time quitting than men, and that varenicline seems to be the best way to reduce this effectiveness gap.

Monetary Incentives for Smoking Cessation: Which Techniques Are Best?

REVIEW OF: Halpern SD, French B, Small DS, et al. Randomized trial of four financial-incentive programs for smoking cessation. *N Engl J Med.* 2015;372(22):2108–2117. doi:10.1056/NEJMoa1414293.

STUDY TYPE: Randomized open label controlled trial

Quitting smoking requires a lot of motivation—something our patients don't always have. Since money is a great motivator, various programs that pay patients to quit have been tried over the years. But how well does this technique work? And how should such programs be designed?

This study compared the effectiveness of four incentive programs. Participants were employees and family members of CVS Caremark who smoked 5 or more cigarettes per day. They were randomly assigned to one of five treatment arms: (1) "treatment as usual," meaning they could seek any treatment that would normally be available to them; (2) "reward," where they could earn up to $800 for 6 months of smoking abstinence; (3) "collaborative reward," in which they could earn up to $800, but would join a small group of 5 other smokers and get paid based on how many people in the group quit; (4) "advance deposit," where they could earn up to $800, but had to pay a $150 deposit in advance, which would be returned only if they successfully quit; (5) "competitive advance deposit," a more complicated program involving a deposit and rewards.

Originally 2,538 subjects were enrolled, but more than half dropped out once they found out which group they were being assigned to (only 1,060 stayed in the study). Very few wanted to be in the deposit programs—only 13% of these participants stayed in the study, as compared to 90% of participants who were assigned to either of the reward conditions. The primary outcome, smoking abstinence, was confirmed by saliva samples at 3 time points: 14 days, 30 days, and 6 months.

RESULTS

All of the incentive programs worked better than usual care, with 6-month abstinence rates ranging from 9.4% to 16%, as compared to 6% in the usual care group. There was no difference between the individual and group-based programs. Reward programs were more effective than deposit programs—because they are so much more acceptable. However, an analysis of those few participants who willingly accepted the deposit programs showed that they actually had a much higher abstinence rate than those in the reward programs—52.3% vs. 17.1%.

THE CARLAT TAKE

Rewards for quitting smoking are effective, and the design of the reward system needn't be complex—a simple payment to an individual was as effective as the more elaborate schemes.

Requiring an up-front payment with the promise of getting it back if you're successful is something that most people loathe, but it works quite well for those who are willing to do it.

PRACTICE IMPLICATIONS

Practically speaking, you can't pay your patients to quit, and it is unlikely your patients will be able to find anyone else who will. Nor can you ethically ask your patients for a deposit—but you can suggest they use the deposit technique with a friend. For example, give them instructions such as: "Write out a $150 check to a cause you hate and give it to a friend, with the understanding that if you are still smoking after three months, your friend will send the check out." While this doesn't entail a potential reward beyond getting your deposit back, this study implies that people who are willing to risk their money in this way might have a high chance of quitting.

Do Electronic Cigarettes Help Smokers Quit?

REVIEW OF: **McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. *Cochrane Database Syst Rev.* 2014;(12):CD010216. doi:10.1002/14651858.CD010216.pub2.**

STUDY TYPE: **Literature review**

More and more smokers are trying out electronic cigarettes (e-cigarettes) in the hopes of quitting smoking. Is this an effective tool for smoking cessation, and should you be recommending it to patients?

E-cigarettes, electronic devices invented by a Chinese pharmacist and inventor, were first imported into the U.S. in 2006. E-cigarettes have a battery-powered heating element which heats a liquid in the device into a smoke-like aerosol, commonly referred to as vapor, which users inhale. The liquid, which is stored in disposable or refillable cartridges or a reservoir, usually contains propylene glycol and glycerol, with or without nicotine and flavors. While the vapor may contain nicotine, it typically does not have the toxins that conventional smokers inhale with cigarette smoke. E-cigarettes have become popular with smokers because they mimic the sensations of cigarette smoking, providing a nicotine "hit." Little is known about how effective they are at helping smokers quit or about their safety.

A new review by the Cochrane Collaboration found only two randomized controlled trials with data from 662 smokers to determine the effect of e-cigarettes on smoking quit rates and on the number of people who cut smoking by at least half. The studies compared the use of e-cigarettes with placebo, in this case a non-nicotine e-cigarette. In one trial, smokers received minimal telephone support to help them quit. The other study recruited smokers not intending to quit smoking. In both cases, the smokers used early e-cigarette models with low nicotine content.

RESULTS

In terms of quitting smoking altogether, researchers found that about 9% of smokers who used e-cigarettes were able to stop smoking for at least 6 months, compared with about 4% of smokers who used the placebo devices. For those who did not quit, 36% of e-cigarette users managed to cut in half the number of conventional cigarettes they smoked, compared with 28% who received placebo devices. The researchers found no evidence of serious side effects in e-cigarette users and said there is no evidence that short-term use creates a health risk.

One of the studies also compared e-cigarettes to the use of a nicotine patch. There was no significant difference between the two in smoking cessation, but a higher number were able to halve their smoking through e-cigarettes vs. the patch (61% vs. 44%).

THE CARLAT TAKE

These encouraging results suggest e-cigarettes may help smokers quit or reduce smoking—though the data is preliminary and limited by a small number of trials. As of August 2016, the FDA will start regulating e-cigarettes, which should encourage companies to fund large studies evaluating them as smoking cessation aids. So stay tuned for much more data over the next few years.

PRACTICE IMPLICATIONS

Tell patients who are trying to quit that in addition to the FDA-approved treatments, there is early evidence that using e-cigarettes might help them cut down on regular cigarettes.

Daily Marijuana Use by Teens Leads to Poor Outcomes

REVIEW OF: Silins E, Horwood LJ, Patton GC, et al. Young adult sequelae of adolescent cannabis use: an integrative analysis. *Lancet Psychiatry.* 2014;1(4):286–293. doi:10.1016/S2215-0366(14)70307-4.

STUDY TYPE: Meta-analysis of longitudinal cohort studies

There's no question that marijuana has at least short-term effects on the mind. Along with its sought-after intoxicating effects, it impairs cognition for several hours after ingestion, causing poorer working memory and impaired executive functioning. The question is whether this transient effect extends to more permanent cognitive impairment with chronic and long-term use. Several studies have attempted to assess the long-term effects of cannabis use, and recently a meta-analysis of three very large studies was published.

Researchers combined data from three longitudinal studies (conducted in Australia or New Zealand), each of which measured the association between marijuana use and a variety of negative outcomes. Specifically, the studies measured frequency of use before 17 years of age (never, less than monthly, monthly or more, weekly or more, or daily). The participants were followed longitudinally over the years, and seven potential outcomes were measured: completion of high school, receiving a university degree, dependence on marijuana, use of other illicit drugs, suicide attempts, development of depression, and dependence on welfare.

Across the three studies, there were about 4,000 participants, and the researchers did a "subject level" meta-analysis. This means that instead of combining the results of the three studies, they ascertained the data of all the individuals in the studies and performed their own statistical analysis. In this way, the researchers were able to gain more statistical power, because they had higher numbers of subjects than any of the individual studies.

RESULTS

The researchers found that in comparison with teens who never used marijuana, those who smoked daily before age 17 were about 3 times more likely to eventually drop out of high school and to never obtain a college degree, 18 times more likely to become dependent on cannabis, 7 times more likely to use other illicit drugs, and 7 times more likely to attempt suicide. In addition, they found a dose-response relationship with poor outcomes (the heavier the marijuana use, the stronger the associations).

The researchers controlled for many factors that could confound these results—in other words, to have confidence that the pot smoking was responsible for the bad outcomes, they made sure other extraneous factors were not actually responsible. Such factors could include low socio-economic status, poor early school performance, depression, and many others. The researchers identified a total of 53 potential confounding factors (or "covariates" in statistical parlance) and adjusted for all of them in their

final statistical analyses. Even after this adjustment, they still found a strong, independent association between pot use and poor outcomes.

THE CARLAT TAKE

This meta-analysis shows a strong association between consumption of cannabis as a teenager and poor life outcomes. Although many confounding factors were controlled for, it's still not possible to declare with certainty that pot use caused all these problems. The researchers themselves said that "reverse causality" (meaning, for example, that dropping out of high school caused the pot use, rather than the other way around) was still plausible, though unlikely. So while not definitive, this is the most compelling evidence yet that daily pot smoking is bad for teens in the long term.

PRACTICE IMPLICATIONS

In your conversations with teens and their parents, you should summarize the results of this study. Tell them that heavy pot use is associated with a much lower chance of graduating from high school or college, and a much higher chance of eventually becoming addicted to pot and other drugs and becoming suicidal. Such pronouncements might still go in one ear and out the other in teens, but the more they hear about real data, the more likely they will eventually connect the dots with their own use.

High-Potency Cannabis Increases Risk of First-Episode Psychosis

REVIEW OF: Di Forti M, Marconi A, Carra E, et al. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. *Lancet Psychiatry.* 2015;2(3):233–238. doi:10.1016/S2215-0366(14)00117-5.

STUDY TYPE: Retrospective case control

In this age of marijuana, tracking the latest strains and variations to hit the streets is a full-time job, and is not required for most psychiatrists. But there is one pot megatrend that you should be aware of, and that is the rise of "skunk." Over the last 20 years or so, growers have cultivated a very potent plant with an odor reminiscent of smelly skunk spray. While all marijuana contains some combination of THC (tetrahydrocannabinol) and CBD (cannabidiol), it is the THC component that gets people high. In general, normal marijuana strains contain no more than 5% THC, while high-potency cannabis is higher than 15%, with 25%–30% considered extremely potent.

U.K. researchers noted that South London has one of the highest rates of psychosis in the world, and that skunk had become the most popular form of marijuana. To see if there was an association between skunk use and psychosis, they interviewed 410 adults who had been admitted to London psychiatric hospitals with a first episode of psychosis between 2005 and 2011. They obtained detailed histories of their cannabis use using the Cannabis Experience Questionnaire, which asks about frequency of use and potency of marijuana consumed. To serve as a control group, they also interviewed 370 people from the same area of south London who had never had psychosis, and gave them the same questionnaire. The controls were matched so that ethnicity, education, and employment status were similar in both groups. The key question was whether the patients with psychosis had a history of greater marijuana consumption than those without psychosis.

RESULTS

Both groups had similar rates of having ever used cannabis (about two-thirds in both groups had). The people who mostly used low-potency cannabis, whether occasionally, on weekends, or daily, had a similar risk of psychosis as those who never used cannabis. However, those who mostly used high-potency cannabis ("skunk") were about twice as likely to experience psychosis if they used it less than once weekly, almost 3 times as likely if they used it on weekends, and more than 5 times as likely if they used it every day. Those who started using before the age of 15 had a significantly increased risk (by about 1.5 times) of psychotic episodes compared to those who never used.

THE CARLAT TAKE

People who frequently use very-high-potency cannabis are at unusually high risk of becoming psychotic. This is an association, and the study cannot prove causality—though the researchers did try to eliminate other possible confounding causes by using a case control design.

PRACTICE IMPLICATIONS

When taking your substance abuse history, ask patients, "How potent is the pot that you use? Is it called 'skunk'?" If they are smoking high-potency marijuana regularly, inform them that this may be putting them at high risk for developing a psychotic disorder.

Another Treatment for Cannabis Dependence Bites the Dust

REVIEW OF: **Levin FR, Mariani JJ, Pavlicova M, et al. Dronabinol and lofexidine for cannabis use disorder: A randomized, double-blind, placebo-controlled trial. *Drug Alcohol Depend.* 2016;159:53–60. doi:10.1016/j.drugalcdep.2015.11.025.**

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

Second only to alcohol, marijuana is the most common reason people enter substance abuse treatment. And unlike alcohol, there are virtually no effective medications available for those addicted to it—though it's not from a lack of trying. A recent review of 14 drug studies for cannabis dependence revealed little benefit from antidepressants, anticonvulsants, or anxiolytics. The only glimmer of hope came from studies using THC (tetrahydrocannabinol)-based concoctions, which are effective in some studies that use it as substitution treatment, similar to how buprenorphine and methadone are used in opiate use disorder.

The latest potential treatment, studied by researchers from Columbia University, is a combination of dronabinol, a synthetic form of THC, and lofexidine. Lofexidine is an alpha 2 agonist, structurally similar to clonidine, that is available in the United Kingdom, where it is used both for hypertension and opiate withdrawal symptoms.

One hundred twenty-two cannabis-dependent adults were randomized to receive dronabinol + lofexidine or placebo. Patients had used an average of 1.65 g of cannabis daily over the past month, which is roughly the equivalent of smoking 2 joints per day—an average joint contains 0.5 g to 1 g of marijuana. In addition to medications, all patients received weekly cognitive behavioral therapy (CBT) related to their cannabis use, focused on motivational enhancement and relapse prevention. Medications were gradually increased during the first 2 weeks of the study to an average dose of 55.6 mg/day for dronabinol and 1.28 mg/day for lofexidine. Once a stable dose was reached, patients were followed on the medications for an additional 6 weeks.

RESULTS

After an average of 6 weeks of treatment at a stable dose, there were no differences between groups with regard to achieving 3 weeks of abstinence (27.9% abstinence rate for the medication group and 29.5% for the placebo group). About half of patients in both groups decreased cannabis use by 50% or more. The authors attributed this improvement to CBT, which all subjects received. This is not surprising, as CBT has been shown to be effective for cannabis use disorder (Copeland J et al, *Journal of Substance Abuse Treatment* 2001;21:55–64).

THE CARLAT TAKE

It's surprising that this combination of potent medications was no better than placebo at treating cannabis dependence. On the other hand, cognitive behavioral therapy appeared to be quite helpful for these patients—though the study was not designed to test this treatment.

PRACTICE IMPLICATIONS

We're still in the trial and error phase of treating cannabis use disorder. If patients come to you, focus your meds on whatever treatable comorbid psychiatric issues they may have, and use CBT to help them get motivated to cut down their smoking.

When Physicians Become Addicted: How Well Do Treatment Programs Work?

REVIEW OF: Merlo LJ, Campbell MD, Skipper GE, Shea CL, DuPont RL. Outcomes for physicians with opioid dependence treated without agonist pharmacotherapy in physician health programs. *J Subst Abuse Treat.* 2016;64:47–54. doi:10.1016/j.jsat.2016.02.004.

STUDY TYPE: Retrospective cohort

When physicians are diagnosed with opioid or other drug dependence, they are required to receive treatment from special physician health programs (PHP) if they want to keep their medical licenses. Unlike treatment programs for the general population, PHPs do not use opiate agonists, such as methadone or buprenorphine. The rationale is that physician use of such agents would put their patients at risk. Therefore, PHPs rely on psychosocial treatments such as individual and group therapy. How well do such programs work?

Researchers reviewed 5 years of charts for 702 physicians admitted to 16 different PHPs. None of the programs offered opiate agonist treatment. Instead, the physicians were required to attend a psychosocial-based abstinence program, usually consisting of psychoeducation; individual, group, family, and recreational therapy; and 12-step programs. They were also required to abstain from the use of mood-altering substances, submit to urine drug screens, and agree to a 5-year monitoring period. The physicians fell into one of three substance use categories: alcohol use only (n = 204), opioid use with or without alcohol (n = 339), and non-opioid drug use with or without alcohol (n = 159).

RESULTS

These programs worked well. For example, among the opiate users, over three-fourths of physicians remained opioid-free during the monitoring period, which lasted an average of slightly over 4 years. Only about 1 in 10 physicians lost their license (or were not licensed for some unknown reason) to practice medicine. The three addiction categories did not differ in number of positive drug screens or completion of treatment contracts.

THE CARLAT TAKE

Abstinence-based treatment programs can work remarkably well, at least for addicted physicians who are highly motivated to succeed in treatment, at the risk of losing their livelihoods. It's not clear how well such programs would work for nonphysicians.

PRACTICE IMPLICATIONS

When evaluating and formulating a treatment plan for opiate-addicted patients, consider mimicking the methods of physician health programs. The bottom line is that regular drug testing combined with automatic severe negative consequences of relapsing seems to work quite well.

Is LSD Bad for Your Mental Health?

REVIEW OF: Johansen PØ, Krebs TS. Psychedelics not linked to mental health problems or suicidal behavior: a population study. *J Psychopharmacol.* 2015;29(3):270–279. doi:10.1177/0269881114568039.

STUDY TYPE: Retrospective cohort

Lysergic acid diethylamide (LSD) and other psychedelic drugs such as psilocybin and mescaline are DEA Schedule I substances and as such cannot be used legally under almost any circumstances. Yet these drugs have long had their champions in the psychiatric community. Studies of LSD have found it potentially helpful for both depression and alcohol use disorder. Regardless, we're likely very far from being able to prescribe LSD for our patients, in part because of long-standing concerns about psychiatric side effects, such as psychosis and severe anxiety.

A group of Norwegian researchers who are on the board of a nonprofit organization seeking to increase access to these drugs has published a study implying that psychedelics are less dangerous than we often think. The authors used data from the U.S. annual National Survey on Drug Use and Health, which collects information on substance use and mental health from a random sample of the population. They pooled data from 135,095 adults surveyed between 2008 and 2011; in that sample, there were 19,299 people who reported lifetime use of psychedelics. Researchers compared users of psychedelics to nonusers on an array of self-reported mental health indicators. They adjusted for demographic variables including gender, race, income, education, marital status, other drug use, and history of childhood depression.

RESULTS

The authors found that psychedelic users were more likely to be younger, male, white, and unmarried; to have used other drugs; to like doing risky things; and to have somewhat more education and income. They were also more likely than nonusers to report a history of childhood depression. However, when looking for an association between any lifetime use of psychedelics and mental health indicators for the past year, the researchers found no association. Specifically, use of psychedelics was not correlated with outpatient or inpatient mental health treatment, suicidality, depression, or anxiety. In fact, when they analyzed certain sub-segments of the population, they found significant protective effects of psychedelic use. Among people age 26 or older, psychedelic use was associated with a lower likelihood (odds ratio of 0.8) of past-year inpatient mental health treatment than nonusers.

THE CARLAT TAKE

This study is intriguing and provides some degree of confidence that psychedelics are not particularly dangerous in terms of causing significant psychiatric problems. However, methodological limitations prevent us from drawing firm conclusions about the risks or potential benefits of psychedelic drug use. For example, the study's retrospective design made it very

difficult to control for confounding factors. The fact that the authors are partisans of legalizing psychedelic drugs also give us pause, though their statistical analysis appeared robust.

PRACTICE IMPLICATIONS

There are few concrete practice implications because prescribing LSD is prohibited outside of research trials. But if you have a patient who tells you that he or she has used psychedelics, being aware of this data might make you less likely to be concerned.

Drinking Heavily Does Not Imply Alcohol Dependence

REVIEW OF: Esser MB, Hedden SL, Kanny D, Brewer RD, Gfroerer JC, Naimi TS. Prevalence of alcohol dependence among US adult drinkers, 2009-2011. *Prev Chronic Dis.* 2014;11:E206. doi:10.5888/pcd11.140329.

STUDY TYPE: Retrospective cohort

We all have some patients who consume lots of alcohol but who claim they don't have an alcohol "problem." Chances are that we each have our own level of skepticism in such cases. The best thing to do is to carefully evaluate how patients' alcohol use is affecting their lives, since the number of drinks per se is not part of the criteria for alcohol use disorder. This point was driven home recently by a study from the Centers for Disease Control and Prevention, in collaboration with the Substance Abuse and Mental Health Services Administration.

A total of 138,100 adults participated in the National Survey on Drug Use and Health in 2009, 2010, and 2011. They were asked about their current drinking habits and patterns (over the last 30 days), as well as any indicators of alcohol dependence. "Excessive drinking" was defined as meeting criteria for either "binge drinking" and/or "heavy drinking." Binge drinking was defined as ≥ 4 drinks for women and ≥ 5 drinks for men *in a single occasion,* while heavy drinking was defined as ≥ 8 drinks for women or ≥ 15 drinks for men *per week*. In addition, any alcohol consumption by those younger than 21 or by pregnant women qualified for excessive drinking status.

RESULTS

About 29% of participants met the definition for excessive drinking. Of the excessive drinkers, only 10.2% met DSM-IV criteria for alcohol dependence—ie, meeting at least three of the following seven criteria: tolerance, withdrawal, impaired control, unsuccessful attempts to cut down or stop drinking, continued use despite problems, neglect of activities, and time spent in alcohol-related activity. (The study was conducted before DSM-5; alcohol dependence in DSM-IV is equivalent to "severe alcohol use disorder" in DSM-5.)

Zeroing in on binge drinking, the authors found that the more frequently folks had binge drinking episodes, the higher the prevalence of alcohol dependence—only about 4% of those who reported binge drinking once or twice in the past month were alcohol-dependent, compared to nearly 30% of those who binged 10 or more times in the past month.

THE CARLAT TAKE

The take-home message from this study is that the vast majority of people who drink excessively are not "alcoholics" in the clinical sense of the term. This is probably especially true of occasional binge drinkers. This doesn't mean that their drinking isn't a problem to some

degree, though: Excessive drinkers are more likely to graduate to problem drinking eventually, and while a level of drinking might not quite meet DSM criteria, that doesn't mean it isn't causing some life problems.

PRACTICE IMPLICATIONS

When you see patients who drink excessively, don't assume that they need treatment for an alcohol use disorder. Do your evaluation, and if applicable, just call it what it is—excessive drinking—and help patients understand whether it's causing them problems and whether they want to cut down.

Ask Two Questions to Screen for Addiction

REVIEW OF: Saitz R, Cheng DM, Allensworth-Davies D, Winter MR, Smith PC. The ability of single screening questions for unhealthy alcohol and other drug use to identify substance dependence in primary care. *J Stud Alcohol Drugs.* 2014;75(1):153–157.

STUDY TYPE: Cross-sectional study

Substance use disorders are relatively common in primary care settings. Can busy physicians accurately detect them with just one question?

Researchers at Boston University recruited 303 patients sitting in the waiting room of a primary care clinic. They explored alcohol and drug use in those patients using the Alcohol Use Disorders Identification Test (AUDIT), Drug Abuse Screening Test (DAST), and Composite International Diagnostic Interview (CIDI). AUDIT and DAST are often used to screen for addiction, while CIDI served as the study's gold standard and determined the presence or absence of substance dependence.

Single-question screeners were also deployed. For alcohol, patients were first asked, "Do you sometimes drink alcoholic beverages?" and if the response was positive, asked "How many times in the past year have you had X or more drinks in a day?" The National Institute on Alcohol Abuse and Alcoholism's binge drinking definitions were used, where X = 5 for men and X = 4 for women. For other drugs, patients were asked, "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical purposes?"

Nine percent and 12% of patients met criteria for alcohol and drug dependence, respectively. Data for the single-question screeners were then analyzed to find the best balance between sensitivity and specificity for detecting addiction. For alcohol, the cutoff was binge drinking 8 or more times in the preceding year. For other drugs, the corresponding cutoff was drug use 3 or more times in the past year.

RESULTS

Researchers then determined the positive predictive value (PPV) of these cutoff values. (PPV is the percentage of patients with a positive test who actually have the disorder.) For alcohol, patients with a score above cutoff had addiction 35% of the time. For other drugs, a score greater than the cutoff represented addiction in 38% of cases.

On face value, these numbers don't seem very impressive. After all, the majority of positive screens were false positives. But the single-question screeners outperformed AUDIT (PPV = 23%) and compared favorably with DAST (PPV = 46%), which are longer, more time-consuming instruments.

More importantly, the single-question screeners had high negative predictive value (NPV) for ruling out addiction. (NPV is the percentage of patients with a negative test who do not have the disorder.) They effectively excluded addiction when scores were below the cutoff values.

THE CARLAT TAKE

Many patients seek primary care for health problems related to addiction. Detecting substance use disorders can be challenging, as diagnosis is entirely clinical and largely depends on

patient self-report. These single-question screeners, when negative, effectively rule out addiction. Positive findings, while wrong more often than not, are about as accurate or possibly more reliable than standard multi-question inventories.

PRACTICE IMPLICATIONS

This study is more relevant for primary care practitioners, since they tend to screen for psychiatric conditions, then refer patients to us for a full evaluation. Nonetheless, if you have a very busy practice, you might find the two screening questions discussed in this article quite helpful.

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 their four (4) ABPN Self-Assessment Maintenance of Certification credits and/or their eight (8) Category 1 CME Credits™. Pre-tests and post-tests can only be submitted online to receive certificate of credit. Faxed/mailed copies cannot be processed.

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LEARNING OBJECTIVES:

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

1. Mood disorders
2. Antipsychotics
3. Neurocognitive disorders
4. Anxiety disorders
5. Side effects of medications
6. Child and adolescent psychiatry
7. Substance abuse

I. MOOD DISORDERS

1. A 40-year-old woman comes to your office, situated in a major northern U.S. city, with symptoms of depression, including lassitude, hypersomnia, lack of motivation, hopelessness, and passive suicidal ideation. Her symptoms began around February and have continued unabated through June. She has had such symptoms in the past, and she denies that they follow any seasonal pattern. Given a recent clinical trial of light therapy for non-seasonal depression, your most reasonable next step is: (LO #1)

   a. Recommend that she purchase a light box and use it for 30 minutes every morning, and defer antidepressant medication treatment

   b. Start fluoxetine or an alternate SSRI immediately, and recommend that she supplement this with light therapy for 30 minutes every morning

   c. Start an SSRI alone, given that she does not have seasonal affective disorder

   d. Recommend light therapy alone, but increase her exposure beyond the usual 30 minutes to 90 minutes daily

2. A new meta-analysis reported that repetitive transcranial magnetic stimulation as augmentation of antidepressants was effective for patients with treatment resistant depression. But the following was a major flaw of most studies analyzed: (LO #1)

   a. There was no control group

   b. There was no sham treatment

   c. The patients were probably not truly blinded to the treatment

   d. The number needed to treat was higher than 10

3. What duration is recommended for suicidal patients taking low-dose buprenorphine to avoid potential opioid addiction issues? (LO #1)

   a. 4 weeks

   b. 8 weeks

   c. 12 weeks

   d. 24 weeks

4. A small study on the use of psilocybin for treatment resistant depression reported the following: (LO #1)

   a. Patients taking psilocybin improved more than those taking a placebo

   b. Psilocybin was effective but was not tolerable due to intense flashbacks

   c. Psilocybin proved to cause a worsening of depressive symptoms

   d. Psilocybin improved depressive symptoms at 1 week and 3 months post-treatment

5. A study on the use of Symbyax (olanzapine/fluoxetine combination or OFC) in children with bipolar I depression showed which of the following results? (LO #1)

   a. Children on OFC initially did significantly better than those on placebo, but did not maintain the difference throughout the 8-week trial

   b. Children on OFC did significantly better than those on placebo, both initially and throughout the 8-week trial

   c. Children on placebo did the same as those on OFC

   d. Children on placebo responded better than those on OFC

6. You are referred a 71-year-old man who presents with symptoms of depression, including prominent poor energy and motivation. You plan to prescribe him an SSRI, but then decide to add methylphenidate at the same time. What is your rationale for combining these two medications? (LO #1)

a. Several small case series have reported that the SSRI/stimulant combination is helpful for depression

b. A large retrospective chart review reported that 88 elderly patients given stimulants did well at a large medical center over the years

c. A placebo-controlled trial found that the SSRI/stimulant combination outperformed both SSRI/placebo and stimulant/placebo in 143 elderly patients

d. Several of your colleagues have had good success with this combination

7. A study of an animal-assisted therapy outreach program for college students found which of the following was true? (LO #1)

a. Animal contact decreased the percentage of subjects meeting criteria for major depressive disorder

b. The therapy enhanced attention and concentration

c. The program reduced symptoms of anxiety and loneliness in the students by 60%, but there was no measure of DSM-5 diagnoses

d. Visits to the college counseling center increased following the intervention

8. Researchers found that when Botox is injected between the eyebrows, it has no antidepressant effect. (LO #1)

a. True

b. False

9. Which of the following was the one of the results from the Lam et al study of light therapy for non-seasonal depression? (LO #1)

a. Light therapy was not superior to placebo

b. Combination light and fluoxetine therapy was not superior to placebo

c. Fluoxetine therapy was not significantly better than placebo

d. Results were inconclusive

10. You diagnose a 10-year-old female with depression and determine that she has bipolar disorder. The parents are requesting that you prescribe Symbyax (olanzapine/fluoxetine combination or OFC) because they heard that it is the only medication approved for bipolar depression in children. You are reluctant to prescribe based on what data from the major clinical trial? (LO #1)

a. Children on OFC gained an average of 11 pounds over 8 weeks, vs. a gain of 1 pound on placebo

b. About 20% of children on OFC developed diabetes mellitus

c. The OFC trial did not include a placebo control

d. The OFC response rate was under 50%

11. The 2011 FDA warning concerning dangers of high-dose citalopram (Celexa) led to many Veterans Affairs patients being prescribed a lower dose of that antidepressant. A recent study found that patients switched to lower doses experienced which of the following? (LO #1)

    a. Higher rates of antidepressant discontinuation syndrome

    b. Higher rates of hospitalization for depression

    c. Decrease in hospitalization for cardiac arrhythmias

    d. Increase in hospitalization for cardiac arrhythmias

12. In a recent study of buprenorphine in suicidal patients, which was the most common buprenorphine-related side effect? (LO #1)

    a. Constipation

    b. Dry mouth

    c. Fatigue

    d. Blurry vision

13. According to a recent study, which of the following factors negatively affected performance on cognitive tests given to patients who had received multiple courses of electroconvulsive therapy (ECT)? (LO #1)

    a. Longer time gap between sessions

    b. Less severe depression

    c. Greater age

    d. Age of diagnosis

14. According to a recent study on the use of antidepressants during pregnancy and risk of autism spectrum disorders (ASD), how did the risk associated with SNRI use during pregnancy compare to the risk in the average population? (LO #1)

    a. No change

    b. Higher risk than average

    c. Lower risk than average

    d. Same risk as SSRI use

15. A colleague is closing her practice, and you "inherit" a 54-year-old man with a long history of depression in remission. He has been taking citalopram 60 mg/day for 12 years. Because of the FDA warning that citalopram doses above 40 mg/day are potentially dangerous, you should do the following: (LO #1)

    a. Taper the dose of citalopram down to 40 mg/day over 1 week

    b. Taper the dose of citalopram down to 20 mg/day over 4 weeks

    c. Maintain the current dose for the time being and refer to a cardiologist to assess whether the citalopram may be causing QT prolongation

    d. Maintain the current dose with no further evaluation needed

16. During the family and social history, a 38-year-old female with major depression tells you that her mother attempted suicide several years ago. Based on the results of a recent prospective cohort study, you conclude that: (LO #1)

    a. Your patient has a 50% chance of making a suicide attempt in her lifetime

    b. Your patient is more likely to have bipolar depression than unipolar depression

    c. Your patient is 5 times more likely to make a suicide attempt than a patient with no family history of suicide attempts

    d. There is no increase or decrease in suicide risk based on this information

17. A 48-year-old man is a long-term patient who suffers chronic depression and anxiety. You have tried multiple medications with only partial success, and he is very sensitive to side effects. He is seeing a good local therapist. He reports that since his children left for college, his loneliness has worsened. A novel but reasonable treatment recommendation is: (LO #1)

    a. Add bupropion to the high-dose sertraline that he is taking

    b. Add lithium

    c. Recommend that he get a pet

    d. Recommend a new wardrobe

18. A 50-year-old patient with recurrent depression improved dramatically after a course of electroconvulsive therapy (ECT) and had transient memory loss for about an hour after each treatment. You recommend maintenance ECT, and based on the results of a recent study, you tell that patient the following: (LO #1)

    a. Maintenance ECT is effective but may lead to permanent loss of memory of remote events

    b. Maintenance ECT is not more effective than sham treatment

    c. Maintenance ECT does not cause any more long-term memory loss than a single course of treatment

    d. Maintenance ECT improves memory significantly

19. A long-term patient of yours has had recurrent episodes of mild to moderate depression, and she has always responded well to sertraline. She now comes to your office announcing that she is three months pregnant and just read in the newspaper that SSRIs taken in pregnancy may cause infants to develop autism. You quickly read the study in question, and afterwards counsel your patient to: (LO #1)

    a. Continue taking sertraline but decrease to the lowest dose possible in order to prevent autism

    b. Immediately taper off sertraline in order to prevent autism

    c. Continue sertraline at the current dose, advising her that there is absolutely no effect on the fetus

    d. Continue sertraline, because the study did not control for severity of depression, and it may be that depression severity was the causative factor rather than the SSRI

II. ANTIPSYCHOTICS

20. Paliperidone palmitate (Invega Trinza) was recently approved by the FDA for treatment of psychosis. According to a pivotal study, which patients are most likely to benefit from the new formulation? (LO #2)

    a. Patients who were stable on risperidone injectable

    b. Patients who were stable on paliperidone monthly injectable

    c. Patients who were stable on any oral atypical antipsychotic

    d. Patients who were stable on haloperidol decanoate

    e. Feedback: For more information, see Berwaerts J et al, *JAMA Psychiatry* 2015;72(8):830–839.

21. A large federally funded study found that a comprehensive treatment program called NAVIGATE was more effective for first-episode psychosis than treatment as usual. The NAVIGATE program includes the following components: (LO #2)

    a. A prescribing psychiatrist and a cognitive behavioral therapist

    b. A prescriber, a therapist, a family education clinician, and a supported employment specialist

    c. A prescriber and extensive group therapy focusing on supported employment

    d. A prescriber who meets with the patient much more frequently than usual

22. Prior studies of second-generation antipsychotics in pregnancy have shown possible association between the meds and which outcome? (LO #2)

    a. Lower birth weight

    b. Neonatal toxicity

    c. Gestational diabetes

d. Cardiac malformations

23. A literature review of studies evaluating the usefulness of monitoring antipsychotic serum levels in children concluded that which of the following drugs has the best data? (LO #2)

    a. Clozapine

    b. Aripiprazole

    c. Olanzapine

    d. Risperidone

24. Before the approval of the paliperidone 3-month injectable, how many forms of long-acting injectable antipsychotics (LAI) were available? (LO #2)

    a. 6

    b. 10

    c. 12

    d. 15

25. According to a national registry of second-generation antipsychotics (SGA) in pregnancy, women exposed to these medications are more likely to deliver babies with major malformations than unexposed women. (LO #2)

    a. True

    b. False

III. NEUROCOGNITIVE DISORDERS

26. According to a recent study on benzodiazepine use and dementia, what was the effect of greater cumulative use of benzodiazepines as related to either dementia or to less serious cognitive decline? (LO #3)

    a. 10% elevated risk

    b. 20% elevated risk

    c. No effect

    d. Inconclusive

27. A large prospective study of over 3,400 adults found that anticholinergic drugs were associated with the development of dementia, with a dose-response relationship. Common anticholinergics used in psychiatry include: (LO #3)

    a. Paroxetine, tricyclics, olanzapine, and diphenhydramine

b. Fluoxetine, venlafaxine, and risperidone

c. Benzodiazepines, sertraline, and lurasidone

d. Citalopram, duloxetine, and aripiprazole

28. In a recent study, a Mediterranean diet was found to be psychologically helpful in the following way: (LO #3)

a. A Mediterranean diet with nuts and minimal olive oil was most helpful for preserving frontal functions

b. A Mediterranean diet with olive oil was most helpful for preserving frontal functions and global cognition

c. A Mediterranean diet with olive oil and nuts prevented depressive symptoms

d. A Mediterranean diet without olive oil or nuts was the most effective globally

29. A recent study's findings that low-dose benzodiazepines are associated with dementia implies that these drugs cause dementia. (LO #3)

a. True

b. False

IV. ANXIETY DISORDERS

30. A study of more than 2,700 teens in Detroit found which of the following was true for adolescents who had been prescribed anti-anxiety or sleep medications (versus those who had never been prescribed such medications)? (LO #4)

a. They were no more likely to use someone else's prescription for nonmedical use

b. They were more than 10 times more likely to use these meds to get high

c. They were 10 times more likely to use someone else's prescription to self-treat anxiety

d. They were more likely to develop depression

31. A recent meta-analysis that looked at the evidence for treating refractory obsessive-compulsive disorder (OCD) found which of the following was true? (LO #4)

a. Cognitive behavioral therapy (CBT) alone was most effective

b. SSRIs alone were most effective

c. CBT/SSRI combination had the largest effect size

d. Atypical antipsychotics were well-studied and found effective in children with refractory OCD

32. N-acetylcysteine (NAC) is an over-the-counter antioxidant which has shown effectiveness for the following condition: (LO #4)

    a. Insomnia

    b. Bipolar disorder

    c. Skin-picking disorder

    d. Bulimia nervosa

33. Adolescents who had been prescribed anti-anxiety or sleep medications in the more distant past are more likely to use someone's else prescription in which of the following categories? (LO #4)

    a. Sleep medication

    b. Anxiety medication

    c. Stimulants

    d. Pain medication

V. SIDE EFFECTS OF MEDICATIONS

34. What was the result of the STRIDE study in which psychiatric patients participated in an intensive weight loss program? (LO #5)

    a. Patients in the weight loss program gained weight during the first 6 months of the program

    b. Patients lost weight during the first 6 months of the program

    c. Patients continued to lose weight during the maintenance phase of the study

    d. People in the control group, who did not participate in the exercise program, gained weight during the first 6 months and the maintenance phase of the study

35. In a recent study, what percentage of patients with clozapine-related drooling found relief with metoclopramide treatment? (LO #5)

    a. Approximately 28%

    b. Approximately 43%

    c. Approximately 56%

    d. Approximately 67%

36. According to a recent study on atomoxetine use and suicide, what was the difference in suicide rates between the group of patients taking atomoxetine vs. stimulants? (LO #5)

    a. There was a higher rate of suicide in patients taking atomoxetine

    b. There was a lower rate of suicide in patients taking atomoxetine

    c. There was no significant difference in suicide rates between the two groups

    d. Both atomoxetine and stimulants were protective against suicide

VI. CHILD AND ADOLESCENT PSYCHIATRY

37. A study by Hillman CH et al found that while participation in an after-school physical education program had a positive effect on physical fitness, it had no effect on children's cognitive functioning. (LO #6)

    a. True

    b. False

38. A Danish study attributed most of the rising autism rates in that country to which of the following? (LO #6)

    a. Environmental factors

    b. Greater awareness of ADHD among teachers

    c. A link to childhood vaccinations

    d. Changes in how autism is reported

VII. SUBSTANCE ABUSE

39. A randomized placebo-controlled trial found that varenicline (Chantix) was no more likely than placebo to cause psychiatric side effects in psychiatric patients. Which of the following was an aspect of the study methods that renders these results *less* generalizable to typical psychiatric patients? (LO #7)

    a. Varenicline was compared with placebo but not with other active antismoking agents

    b. Only patients who had already tolerated varenicline were recruited

    c. Psychiatric patients were included only if they were either in remission or on a stable medication regimen

    d. Psychiatric patients were excluded if they were acutely suicidal

40. You are evaluating a new patient, and you determine that he binge drinks about 10 times every month. According to recent data from the CDC, what is the likelihood that this patient is alcohol-dependent? (LO #7)

    a. 5%

    b. 30%

    c. 50%

    d. 70%

41. A study by researchers in Australia and New Zealand found which of the following was true for teens who use marijuana daily before the age of 17? (LO #7)

    a. They are less likely to use other drugs than those who never used marijuana

    b. They are less likely to get a high school diploma

    c. They are less likely to become dependent on marijuana

    d. They are less likely to attempt suicide

42. In a recent smoking cessation study, it was found that which of the following had the best rate of success? (LO #7)

    a. Treatment as usual

    b. A $150 buy-in to participate, paid back if the patient quits

    c. An $800 payout for quitting smoking

    d. A competitive environment comparing each patient's success in quitting

43. In a recent study comparing dronabinol/lofexidine plus cognitive behavioral therapy (CBT) with placebo plus CBT, half of patients in both groups decreased cannabis use by 50% or more after an average of 6 weeks of treatment. What did the authors of the study attribute this improvement to? (LO #7)

    a. A combination of dronabinol and lofexidine

    b. Dronabinol alone

    c. Lofexidine alone

    d. Weekly CBT

44. A study found that a small percentage (9%) of e-cigarette users were able to quit smoking entirely. Of those who did not quit, what proportion was able to cut their smoking in half? (LO #7)

    a. 10%

    b. 22%

    c. 36%

    d. 59%

45. Physician health programs (PHP) do not offer opiate addicted physicians substitution treatment, but instead rely on abstinence plus therapy. A retrospective study found that after 4 years, what percentage of such patients remained opiate-free? (LO #7)

    a. 25%

    b. 50%

    c. 75%

    d. 90%

46. Analyzing data from the U.S. annual National Survey on Drug Use and Health, researchers compared users of LSD with nonusers. They found that: (LO #7)

    a. LSD users were more likely to become psychotic

    b. LSD users were more likely to visit an emergency room due to drug use

    c. LSD users and nonusers had equal rates of cardiac illness

    d. LSD users and nonusers had equal rates of mental illness and of mental health treatment

47. According to recent alcohol use data from the Centers for Disease Control and Prevention, about what percentage of Americans who drink excessively have alcohol dependence? (LO #7)

    a. 10%

    b. 30%

    c. 50%

    d. 70%

48. Women are in general less likely to respond to smoking cessation therapy than men. But in a meta-analysis of placebo-controlled trials of varenicline reported that: (LO #7)

    a. Varenicline increased the odds of quitting equally in men and women

    b. After 12 weeks, varenicline increased the odds of quitting in women 46% more than it increased the odds for men

    c. After 52 weeks, varenicline increased the odds of quitting in women by almost 25% compared to men

    d. Varenicline was surprisingly ineffective in men, but effective in women

49. Researchers at Boston University tested two simple questions to screen for alcoholism and illicit drug use. What was most useful about these questions? (LO #7)

    a. When answers were negative, they effectively ruled out addiction

    b. When answers were positive, they accurately established a diagnosis of addiction

    c. When answers were positive, they were not as effective as standard multi-question inventories

    d. They were more time-consuming than standard inventories

50. A London study found which of the following is true about the use of high-potency cannabis, also known as "skunk" weed? (LO #7)

    a. Users of high-potency cannabis are 3 times more likely to experience a psychotic episode than those who never use cannabis

    b. The risk of a psychotic episode was no different if patients used high- or low-potency cannabis

    c. The risk of a psychotic episode was no greater if patients used high-potency cannabis daily

    d. Users of high-potency cannabis are less likely to experience a psychotic episode than those who never use cannabis

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