CARLAT PUBLISHING

THIRD EDITION

Psychiatry Practice Boosters

Insights from research to enhance your clinical work

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Carlat Psychiatry

Psychiatry Practice Boosters, Third Edition

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Published by Carlat Publishing, LLC
PO Box 626, Newburyport, MA 01950

Publisher and Editor-in-Chief: Daniel Carlat, MD
Executive Editor: Janice Jutras

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Print ISBN: 978-1-7329522-4-9
eBook ISBN: 978-1-7329522-5-6

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Acknowledgments

For the third edition of *Psychiatry Practice Boosters,* we have included even more reviews of research articles published in the past few years. The Carlat family of newsletters (*The Carlat Psychiatry Report, The Carlat Child Psychiatry Report,* and *The Carlat Addiction Treatment Report*) continues to grow along with the list of contributing authors. The original research updates adapted for this publication were authored by: Chris Aiken, MD, Bachaar Arnaout, MD, Rehan Aziz, MD, Stephanie Fenwick, PharmD, Brian Frankel, MD, Kristen Gardner, PharmD, Jessica Goren, PharmD, BCPP, Adrienne Grzenda, MD, PhD, Edmund S. Higgins, MD, Karen Hoffman, PhD, Thomas Jordan, MD, Jess Levy, MD, Xiaofan Li, MD, Donna Lisi, PharmD, Pavan Madan, MD, Jason Mallo, DO, Randall Moore, MD, Ahsan Nazeer, MD, Michael Posternak, MD, Xavier Preud'homme, MD, Nicholas Rosenlicht, MD, Adam Strassberg, MD, and Christian J. Teter, PharmD, BCPP. Special thanks to the editors reviewing the manuscript: Talia Puzantian, PharmD, BCPP, Chris Aiken, MD, Joshua Feder, MD, Benjamin Oldfield, MD, Osman Ali, MD, James Megna, MD, PhD, DFAPA, Brian McCarthy, MSN, PMHNP-BC, Peter Parry, MBBS, Jonathan Gamze, MD, Travis Lajoie, DO, and Janice Jutras.

Introduction

If you are like most practitioners, you've probably developed a fairly standardized approach to treating patients. Over the years, it can become easy for your knowledge to stagnate. Yet, staying up to date with current literature is critical to providing good care. To help you keep track of recently published papers and avoid feeling overwhelmed, we've chosen recent journal articles that are most impactful for clinical practice. In addition, we've translated each article's statistical language into something easier to understand, allowing you to evaluate what change (if any) you should make to your practice.

The articles in this third edition of *Psychiatry Practice Boosters* are gleaned from the past two years of research updates in the Carlat family of newsletters. We include only a couple of the research updates published in the second edition, chosen because they are particularly helpful in clinical practice (eg, guidance on how to switch a patient from methadone to buprenorphine and the continued importance of lithium in psychiatric practice). The new updates address a wide range of topics on developments in psychopharmacology and psychotherapy, the increasing use of cannabis in the US, and studies relevant to the most common illnesses we treat in our daily practice.

HOW TO READ THESE UPDATES

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

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

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A Quick Primer on Study Design and Statistics

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

HOW TO READ A RESEARCH ARTICLE

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

1. Who funded the study?

If a study is funded by a drug manufacturer, it is more likely to report results favorable to the sponsor's drug than studies funded by other sources (Lundh A et al, *Cochrane Database Syst Rev* 2012;12:MR000033). The reasons for this are not necessarily nefarious. Industry-funded studies are often very well designed, with large numbers of subjects and gold-standard research methods. One reason companies are more likely to get positive results is that they are careful about which drugs they choose to 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 analyses after the fact to make their drug look better. While industry-funded studies can be valuable, you will need to give their conclusions more scrutiny than those funded by more objective sources, such as NIMH or private foundations. That said, not even NIMH researchers are completely free of bias—there's always an incentive to claim a positive result.

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 apply to the patients in your office. For example, antidepressant trials often exclude patients with symptoms that are too mild or too severe, or patients with comorbid substance use, bipolar disorder, psychosis, or suicidality. One study concluded that patients who make it into research trials represent only about 20% of the patients whom real clinicians actually treat (Zimmerman M et al, *Am J Psychiatry* 2005;162(7):1370–1372).

3. What type of study design is it?

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

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 that received the treatment of interest and one that 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. Randomized trials are almost unheard of in pregnancy because of concerns about the possible risk to the fetus. Instead, researchers identify women with depression who happen to have been prescribed an antidepressant and compare them with a group with the same diagnosis who were 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 a single primary outcome, such as percentage 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 outcome does 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 appear by chance alone. The investigators may try to reel in that statistical noise with techniques like the Bonferroni correction, but these corrections are prone to errors of their own.

For this reason, savvy readers will focus on the results of predefined primary outcomes. Secondary results are meant to inform future research, not current practice.

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

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 an antidepressant causes many early dropouts, the LOCF method will tend to drag the final average depression score down, making the medication appear 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?

In casual conversation, "significant" means big, but in research it simply means that the results are likely to be true, even if the results are very small. The larger the study, the more likely it is that the differences it measures are real. So when a study reports that one antidepressant has a "significantly" lower rate of nausea, look closely at the numbers. If the study is large enough, the results could be labeled significant even if the rates of nausea are 45% and 50% for the antidepressants being compared. Clinicians are interested in truth, but we also want to make a difference for our patients, and that's where we look to other measures like effect size and number needed to treat, which tell us how powerful a treatment really is. 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 two 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 to balance the two arms of a study is to randomly assign patients to one group or the other. 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 improve 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, the natural course of the illness, the desire of patients to please you by saying they've improved even if they haven't, etc. All of these nonspecific 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 that 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 the passage of time, the attention of the research team, or other factors. But then a big part of the cure—the effects of the patient's 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 encompasses both the patient and the researcher. 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.

Just as randomization can fail, leaving two unequal groups at the start of a trial, so can blinding. Subjects naturally try to figure out whether they got the placebo or the drug, and they are pretty good at guessing, especially if the drug is highly sedating. Investigators can check the integrity of the blind by asking the patients and their blinded physicians to guess which treatment they got, but this—unfortunately—is rarely done.

Another word for double-blind is "closed-label," in contrast with open-label studies where the patients know exactly what they're getting and researchers know exactly what they're dishing out. We've just said that open-label 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. Nor are they devoid of value. Often an initial uncontrolled, open-label study identifies a drug as having promise for a given diagnosis, leading to a larger controlled study later on.

What about single-blind studies? Usually these are studies that compare two active drugs for a condition without including a placebo group. The patients know what they are taking. The doctor knows what the patients are getting. The only one who is blind is the rater, who is the one assessing the degree of clinical improvement using structured rating scales. This design still leaves plenty of room for the placebo to confound the results. Investigators might convey a tad more enthusiasm about one of those drugs to the subject, especially if the company that makes that drug is funding the study.

Non-pharmacologic trials. Placebos and blinding are relatively straightforward when testing medications. But what about non-pharmacologic clinical trials, such as studies on mindfulness therapy or internet-based CBT? In these cases, using a classic placebo control group is not an option. The control

group can instead be set up with a different psychotherapy intervention, placement on a waitlist, or even a pharmacologic intervention that's already shown efficacy in the disorder being studied. Standardization of treatment intervention is very important, and the study will often mention the training of treatment providers or the use of manual-based therapies. Double-blinding the study is also a problem, as it's often impossible to blind the treatment provider or the patient receiving the therapy intervention, but single-blinding of the researcher administering the rating scales is standard practice.

STATISTICAL SIGNIFICANCE: WHAT DOES IT MEAN?

You won't get very far into any journal before you start reading about statistical significance and its close sibling, 95% confidence intervals (abbreviated as CI throughout this book). 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 out of 100 people on Prozac responded vs only 40 out of 100 people on placebo. 60% is better than 40%, so you've once again proven that Prozac is an effective antidepressant, right? Not necessarily. It's possible that Prozac and placebo are equally effective, but that by pure chance 6 out of 10 people assigned to Prozac got better. An analogy is coin flipping. If you flipped a coin 10 times and got heads 6 times, would you automatically conclude that the coin is rigged—ie, that it is more effective at producing heads than tails? Probably not, because you'd expect that out of 10 coin tosses you might get more heads than tails or vice versa. But what if you tossed the coin 100 times? If you got 60 heads and 40 tails, you'd start to get suspicious that the coin is weighted toward heads. It's pretty unlikely that you'd get 60 heads by chance alone. Not impossible, mind you, but pretty unlikely.

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

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

Look at it this way: Before we accept a finding as scientific fact, we want to be pretty certain that it didn't occur through some coincidence of random factors. But how certain is "pretty certain"? Would 80% certainty ($p = 0.2$) be enough for you? Probably not. Most doctors would not feel comfortable basing important treatment decisions on only an 80% certainty that a treatment is effective. Much better would be 99% certainty ($p = 0.01$), but if that were the required threshold, very few treatments would be shown as significantly better than placebo, and hence we would have very little to offer our patients. It just so happens that 95% certainty has felt right to scientists through the last 50 years or so. Of course it's arbitrary, but if we don't agree on some threshold, we open ourselves up to researchers creating their own threshold values depending on how strongly they want to push acceptance of their data (and some still do this anyway). Because the scientific community has settled upon $p = 0.05$, the term "statistical significance" has a certain, well, significance!

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

WHAT'S AN EFFECT SIZE?

Knowing that the apparent advantage of Prozac over placebo in these patients is statistically significant is all well and good. But how do we get a handle on measuring how strong this advantage is? This is where effect size comes into play. The effect size is the size of a statistically significant difference. To calculate it, you divide the difference between the two treatment groups' outcome measures by the standard deviation. (The standard deviation is how wide the data are spread out; in other words, how much overlap there is between the results of the treatment group and the placebo group.)

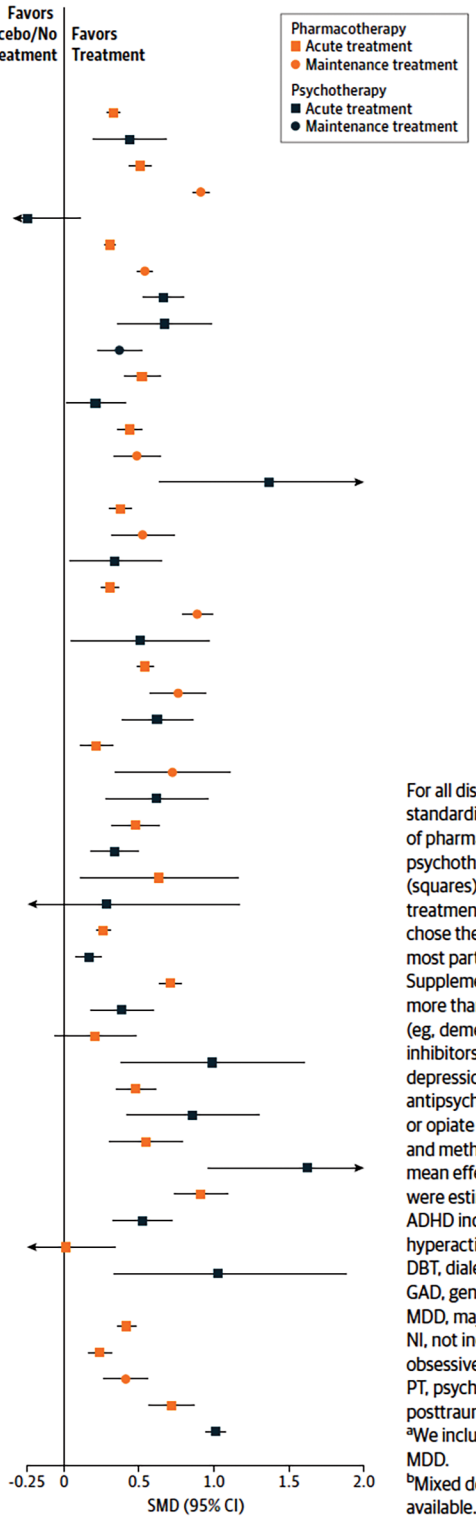
If the effect size is 0, this implies that the mean score for the treatment group was the same as the comparison group, ie, that there was no effect at all. And just as obviously, the higher the effect size, the stronger the effect of treatment. Here are the standard benchmarks: Effect sizes of 0 to 0.2 represent little to no effect, 0.2 to 0.5 a small effect, 0.5 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 6.1 in the Prozac group and 4.4 in the placebo group, and the standard deviation was reported to be 3.9, the calculation for effect size would be: $(6.1 - 4.4) / 3.9 = 0.44$, which is just shy of a moderate effect size in favor of Prozac.

A moderate effect size is considered strong enough to be visible to the casual observer, so it might seem surprising that Prozac falls below that threshold. It's true. SSRIs consistently fall in the small effect range. But what that really means is that the difference between the SSRI and the placebo is too small for the casual observer to detect. The effect size removes the placebo effect, which for SSRIs accounts for about 1/3 of the benefits we see in practice.

Effect sizes for psychiatric treatments range from barely detectable (medications for generalized anxiety disorder are 0.3; PTSD medications are 0.2) to loud and clear (stimulants in ADHD are 0.7 to 0.8; exposure therapy for phobias is 1.0). Across all psychiatric treatments, from psychotherapy to

	SMD (95% CI)
Therapy	
Dementia drug (n = 8069)[18,28,35]	0.33 (0.29 to 0.37)
Dementia PT (n = 270)[60]	0.44 (0.20 to 0.69)
Schizophrenia acute drug (n = 5568)[30]	0.51 (0.44 to 0.58)
Schizophrenia relapse drug (n = 6493)[31]	*0.92 (0.86 to 0.97)*
Schizophrenia psychodynamic therapy (n = 164)[59]	-0.25 (-0.59 to 0.11)
MDD acute drug (n = 12 564)[15]	0.31 (0.27 to 0.80)
MDD relapse drug (n = 9268)[25]	*0.54 (0.49 to 0.59)*
MDD acute PT (n = 3465)[16,a]	0.67 (0.53 to 0.80)
Depression psychodynamic therapy, acute (n = 196)[50,b]	0.69 (0.30 to 1.08)
MDD relapse PT (n = 881)[57]	*0.37 (0.23 to 0.52)*
Dysthymia drug (n = 1454)[32]	*0.52 (0.40 to 0.64)*
Dysthymia PT (n = 275)[49]	0.21 (0.02 to 0.41)
OCD acute drug (n = 3097)[43]	0.44 (0.36 to 0.52)
OCD relapse drug (n = 951)[23]	*0.48 (0.32 to 0.64)*
OCD PT (n = 240)[54]	1.37 (0.64 to 2.24)
Panic acute drug (n = 7725)[37]	0.38 (0.31 to 0.45)
Panic relapse drug (n = 796)[23]	*0.53 (0.32 to 0.74)*
Panic PT (n = 328)[54]	0.35 (0.04 to 0.65)
GAD acute drug (n = 11 427)[38]	0.31 (0.26 to 0.36)
GAD relapse drug (n = 1342)[23]	*0.89 (0.79 to 0.99)*
GAD PT (n = 95)[54]	0.51 (0.05 to 0.97)
Social phobia acute drug (n = 7619)[27]	0.55 (0.49 to 0.60)
Social phobia relapse drug (n = 760)[23]	*0.76 (0.58 to 0.95)*
Social phobia PT (n = 377)[54]	0.62 (0.39 to 0.86)
PTSD acute drug (n = 2507)[44]	0.22 (0.11 to 0.33)
PTSD relapse drug (n = 272)[23]	*0.73 (0.34 to 1.11)*
PTSD PT (n = 266)[54]	0.62 (0.28 to 0.96)
Somatoform disorder drug (n = 832)[24]	0.48 (0.32 to 0.64)
Somatoform disorder PT (n = 1647)[56]	0.35 (0.18 to 0.50)
Borderline personality disorder drug (n = 1151)[47]	*0.63 (0.11 to 1.16)*
Borderline personality disorder DBT (n = 20)[61,c]	0.29 (-0.59 to 1.17)
Alcohol drug (n = 10 605)[40,41]	*0.26 (0.22 to 0.31)*
Alcohol PT (n = 2338)[58,62]	0.17 (0.08 to 0.26)
Opiates drug (n = 4001)[33,34]	*0.71 (0.64 to 0.79)*
Opiates PT (n = 545)[51]	0.39 (0.18 to 0.60)
Anorexia drug (n = 211)[22,29]	0.21 (-0.06 to 0.48)
Anorexia PT (n = 77)[52]	0.99 (0.38 to 1.60)
Binge-eating drug (n = 1254)[39]	*0.48 (0.35 to 0.61)*
Binge-eating PT (n = 90)[53]	0.86 (0.42 to 1.30)
Bulimia drug (n = 824)[17]	*0.55 (0.31 to 0.79)*
Bulimia PT (n = 204)[53]	*1.61 (0.96 to 2.29)*
Primary insomnia drug (n = 566)[26]	0.90 (0.74 to 1.09)
Primary insomnia PT (NI)[55]	0.52 (0.33 to 0.72)
Trichotillomania drug (n = 72)[19]	0.02 (-0.32 to 0.35)
Trichotillomania PT (n = 59)[19]	1.14 (0.38 to 1.89)
Disorders for which only meta-analyses on 1 modality were available	
Bipolar mania acute drug (n = 11 092)[48]	0.42 (0.36 to 0.48)
Bipolar depression acute drug (n = 3770)[42,45]	*0.24 (0.17 to 0.32)*
Bipolar disorder relapse drug (n = 2829)[46]	*0.41 (0.27 to 0.56)*
Adult ADHD drug (n = 1045)[21]	0.73 (0.57 to 0.87)
Specific phobia PT (n = 1217)[63]	1.03 (0.91 to 1.16)



For all disorders, we present the standardized mean difference (SMD) of pharmacotherapy (orange) and psychotherapy (blue) in acute (squares) and maintenance (circles) treatment vs placebo. We always chose the efficacy outcome with the most participants as reported in the Supplement (eTable 5). If there was more than 1 treatment for 1 disorder (eg, dementia [acetylcholinesterase inhibitors and memantine], bipolar depression [antidepressants, antipsychotics, and mood stabilizers], or opiate addiction [buprenorphine and methadone]), we presented their mean effect size. Italicized SMDs were estimated from odds ratios. ADHD indicates attention-deficit/hyperactivity disorder; DBT, dialective-behavioral therapy; GAD, generalized anxiety disorder; MDD, major depressive disorder; NI, not indicated; OCD, obsessive-compulsive disorder; PT, psychotherapy; and PTSD, posttraumatic stress disorder.

[a]We included only studies examining MDD.

[b]Mixed depressive disorder was available.

[c]Only 1 study was available.

Source: Huhn M et al, *JAMA Psychiatry* 2014;71(6):706-715

medications, the average effect size weighs in at 0.5. That's fairly decent, but nothing to brag about. In general medicine, the average effect size is 0.45. See table on page 7 for examples of how effect sizes stack up across treatments.

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.

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

MOOD DISORDERS

Does TMS Really Work in Depression?

REVIEW OF: Yesavage JA, Fairchild JK, Mi Z, et al. Effect of repetitive transcranial magnetic stimulation on treatment-resistant major depression in US veterans: A randomized clinical trial. *JAMA Psychiatry*. 2018 Sep 1;75(9):884–893.

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

Repetitive transcranial magnetic stimulation (rTMS) has been FDA approved for treatment-resistant depression (TRD) since 2008. This non-invasive therapy uses an electromagnetic coil to stimulate electrical activity in the frontal cortex. The present study tested its efficacy in a Veterans Affairs (VA) population of TRD patients with complex comorbidities.

This was a double-blind, sham-controlled, randomized trial conducted across nine VA medical centers. In total, 164 subjects were enrolled; the average age was 55, and 81% were men. Treatment resistance was defined as 2 or more failed adequate antidepressant trials. Subjects had high rates of comorbidity, including PTSD (49%), medical comorbidity (49%), and a history of substance abuse (54%). Most were poorly functioning: Only 24% were working, and only 38% were married.

rTMS and sham rTMS were delivered for up to 30 sessions. Both groups came for treatment 5 days a week. Importantly, the sessions included supportive elements such as daily queries of mood and medication adherence and weekly screening for substance use. The primary outcome was remission of depression (≤ 10 on the Hamilton Depression Rating Scale).

RESULTS

rTMS displayed no advantage over sham treatment on the primary measure. Specifically, 41% achieved remission with active treatment, compared to 37% with sham treatment ($p = 0.67$). A sub-analysis suggested that rTMS might be more effective for depressed patients without comorbid PTSD (49% vs 43% remission rates), though this difference did not reach statistical significance either ($p = 0.09$). rTMS was very well tolerated.

THE CARLAT TAKE

Does this mean rTMS does not work? Not exactly, but it offered little benefit in this population of predominantly low-functioning men with complex comorbidities in the VA system. Remission rates were unusually high in both groups, and the fact that 40% recovered with sham treatment speaks to the therapeutic value of behavioral activation, structure, and social interaction in overcoming even the most seemingly refractory depressions.

PRACTICE IMPLICATIONS

When all the current research is considered, ECT is more effective than rTMS and should be the first-line treatment when depression has not responded to traditional pharmacotherapy (Chen JJ, *Behav Brain Res* 2017;320:30–36).

TMS: Deeper Is Not Better

REVIEW OF: Filipčić I, Filipčić IŠ, Milovac Ž, et al. Efficacy of repetitive transcranial magnetic stimulation using a figure-8-coil or an H1-coil in treatment of major depressive disorder: A randomized clinical trial. *J Psychiatr Res.* 2019 Jul;114:113–119.

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

Seven transcranial magnetic stimulation (TMS) devices are FDA approved for depression, but only one—the Brainsway—is distinctly different from the others. Brainsway uses a patented H1 coil that penetrates deeper into the cortex than the standard figure-8 coil. Brainsway's marketing materials suggest that deeper is better, but the two versions of TMS have never been compared head to head—until now.

In this non-industry-sponsored study, 228 patients with moderate major depression were randomized to one of the following arms over 4 weeks: TMS with the H1 coil, TMS with the figure-8 coil, or 2 visits of standard psychopharmacology. All patients were taking an antidepressant and stayed on that medication during the trial. The evaluators were blinded, but the patients knew which treatment they were getting. The primary outcome was remission on the 17-item Hamilton Rating Scale for Depression (HAMD-17). The study was funded by a public psychiatric hospital in Croatia, which is where the treatments were conducted.

RESULTS

The H1 coil and figure-8 coil were not statistically different on the primary outcome of remission, although both were superior to the standard psychopharmacology group. On secondary measures, the H1 coil had a greater response rate on the HAMD-17 than the figure-8 coil, but there were no differences in the total change on the HAMD-17 or quality-of-life measures. Likewise, safety and tolerability were equal for both devices.

THE CARLAT TAKE

This is the first head-to-head study of the two rTMS devices, and its mixed results do not settle the score. Indirect comparisons of the two devices have been equally inconclusive, according to a meta-analysis of 19 trials (Gellersen HM and Kedzoir KK, *BMC Psych* 2019;19(1):139).

PRACTICE IMPLICATIONS

Despite company claims, deeper stimulation with the H1 coil does not work any better than earlier figure-8 coils.

Probiotics for Bipolar Disorder

REVIEW OF: Dickerson F, Adamos M, Katsafanas E, et al. Adjunctive probiotic microorganisms to prevent rehospitalization in patients with acute mania: A randomized controlled trial. *Bipolar Disord.* 2018 Nov;20(7):614–621.

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

Probiotics, the so-called "good" bacteria in the gut flora, have become popular as a natural treatment for various disorders. They are taken as capsules or through food sources like yogurt, vinegar, and fermented foods. Of relevance to psychiatry, some have theorized the existence of a "gut-brain axis," in which probiotics influence mood and behavior through the vagus nerve and the endocrine and immune systems. Probiotics have shown promise in small studies of anxiety, depression, cognition, and weight loss, and this trial tested whether a daily probiotic could lower the rate of rehospitalization after a manic episode.

The authors randomized 66 patients to receive either a probiotic or placebo as an adjunct to their usual medications after discharge from a hospital stay for mania. The probiotic capsule contained two bacterial strains that are found in breast milk and thought to modulate immune function: *Bifidobacterium lactis* BB-12 and *Lactobacillus rhamnosus* GG.

RESULTS

After 6 months, the number of patients with at least 1 rehospitalization was lower in the probiotic group (8 of 33, 24%) compared to those taking placebo (17 of 33, 51%). Three patients in the placebo group had more than 1 rehospitalization during the study period. However, the probiotic had no effect on manic and depressive symptoms (measured monthly using the Young Mania Rating Scale, Brief Psychiatric Rating Scale, and Montgomery–Åsberg Depression Rating Scale; YMRS, BPRS, and MADRS, respectively). No significant side effects were reported in this study.

THE CARLAT TAKE

It's interesting that the probiotic seemed to lead to such a stark reduction in rehospitalization rates, but did not improve patients' actual mood symptoms. Functional outcomes like hospitalization are arguably more important than symptom scales, but the lack of symptomatic improvement raises doubts about these results. A second randomized placebo-controlled trial of probiotics in bipolar disorder came out in 2020, and it noted only a non-significant trend in symptom reduction. If probiotics work in bipolar disorder, they must be addressing some aspect of the illness that isn't captured in our symptom rating scales (Shahrbabaki ME et al, *Iran J Psychiatry* 2020;15(1):10–16).

PRACTICE IMPLICATIONS

Probiotics have potential benefits for medical conditions that often accompany bipolar disorder, like metabolic and irritable bowel syndromes. On the other hand, they may not be safe

for everyone. These "healthy bacteria" should be avoided in people who are pregnant, immunocompromised, or at high risk of infection, where probiotics pose known risks. The specific strains used in this study have a good safety record in humans, and they are available from online retailers as USANA-108 probiotic sticks and Culturelle Baby Grow + Thrive liquid.

Lithium Favored in Treatment Effectiveness Study

REVIEW OF: Lähteenvuo M, Tanskanen A, Taipale H, et al. Real-world effectiveness of pharmacologic treatments for the prevention of rehospitalization in a Finnish nationwide cohort of patients with bipolar disorder. *JAMA Psychiatry*. 2018 Apr 1;75(4):347–355.

STUDY TYPE: Retrospective cohort study

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

RESULTS

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

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

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

THE CARLAT TAKE

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

PRACTICE IMPLICATIONS

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

Suicide Rates in College Students

REVIEW OF: Mortier P, Auerbach RP, Alonso J, et al. Suicidal thoughts and behaviors among first-year college students: Results from the WMH-ICS project. *J Am Acad Child Adolesc Psychiatry*. 2018 Apr;57(4):263–273.e1.

STUDY TYPE: Cross-sectional study

Adolescence is a time of high risk for suicidal thoughts and behaviors (STB), and rates are rising. In those ages 15–29, suicide is the second leading cause of death globally (www.who.int/mental_health/prevention/suicide/suicideprevent/en). A recent article published some interesting survey data, giving us a clearer picture of how common STB is and what some of its causes are. Full-time, freshman college students at 19 colleges in eight countries were surveyed.

RESULTS

The response rate was 45.5%, and the final sample included 13,984 responses (54% female; mean age 19). Approximately one-third of all respondents reported STB at some point during their lifetime. The median age of onset of STB was 14, with 75% of cases starting before age 16. More than half of those with ideation at some point in their life transitioned to a suicide plan, and a quarter of planners attempted suicide.

The strongest correlate for STB and transition from ideation to attempts was non-heterosexual orientation, yet it was notable that students who identified as heterosexual but with same-sex attraction also had a significantly elevated risk of transitioning from suicidal ideation to development of a plan.

THE CARLAT TAKE

Suicidal ideation and behavior are distressingly common among first-year college students worldwide. The transition to adulthood and self-differentiation makes this a particularly vulnerable period. Those with non-heterosexual orientation may be at even higher risk.

PRACTICE IMPLICATIONS

This study tells us to double down on screening our own patients and pressing for more screening efforts. In addition, prevention initiatives and gatekeeper training are effective in decreasing suicidality and increasing help-seeking. Where resources are limited, campus outreach could specifically target high-risk first-year students.

Resilience Networks in Adolescent Females at Risk for Major Depression

REVIEW OF: Fischer AS, Camacho MC, Ho TC, Whitfield-Gabrieli S, Gotlib IH. Neural markers of resilience in adolescent females at familial risk for major depressive disorder. *JAMA Psychiatry*. 2018 May 1;75(5):493–502.

STUDY TYPE: Prospective cohort study

One of our biggest in-office challenges is how to enhance teen resilience, the process of adapting to and recovering from stressful life experiences. Some neuroscientists hypothesize that resilience is related to the limbic system, which plays a vital role in emotion processing, motivation, and learning. According to one theory, when people can exert better modulation of the limbic system, they are at lower risk of depression. A group of researchers recently looked at these neural pathways in adolescent females, and there were some intriguing results.

Fischer and colleagues examined brain pathways of resilience in adolescent females at familial risk for depression. They conducted a longitudinal study at Stanford University from 2003 to 2017. Sixty-five subjects participated: 20 at high risk of MDD in whom depression did not develop (resilient), 20 at high risk in whom depression developed (converted), and 25 at low risk of MDD with no history of psychopathology (control). Outcomes measured via functional MRI scans included connectivity in the limbic, salience, and executive control networks. Participants were imaged once, on average at age 19, 6 years after beginning the study.

RESULTS

The researchers found that resilient adolescent females had greater connectivity between the limbic and executive control systems than did subjects who developed depression or even controls. The strength of the connection was correlated with positive life events.

THE CARLAT TAKE

This study is consistent with the hypothesis that high-risk but resilient adolescent females have greater executive system control over emotions and behavior arising from the limbic system, which perhaps insulates them against depression.

PRACTICE IMPLICATIONS

What are the treatment implications of this small study? Theoretically, since positive life events were correlated with better neural resilience, we might want to focus on therapeutic approaches that have an activity-oriented style and are designed to strengthen adaptive coping and cognitions, thereby helping teens foster positive life experiences.

Optimal Antidepressant Doses in Major Depression

REVIEW OF: Furukawa TA, Cipriani A, Cowen PJ, et al. Optimal dose of selective serotonin reuptake inhibitors, venlafaxine, and mirtazapine in major depression: A systematic review and dose-response meta-analysis. *Lancet Psychiatry*. 2019 Jul;6(7):601–609.

STUDY TYPE: Systematic review and meta-analysis

Most antidepressants do not have a linear response curve. In other words, the benefits level off as the dose goes up. If the dose gets too high, the side effects start to outweigh those diminishing returns. What's not clear is where the "sweet spot" lies for each antidepressant, and this study set out to capture that optimal dose range.

This dose-response meta-analysis included 77 double-blind, randomized, placebo-controlled trials of fixed-dose SSRIs (except fluvoxamine), venlafaxine, and mirtazapine in major depression (n = 19,365). Median trial length was 8 weeks (range = 4–12 weeks). Primary outcomes were efficacy (treatment response defined as 50% or greater reduction in depressive symptoms), tolerability (dropouts due to adverse effects), and acceptability (dropouts for any reason).

TABLE: Antidepressant Dosages

ANTIDEPRESSANT	OPTIMAL DAILY DOSE
Citalopram	20–40 mg
Escitalopram	10–15 mg
Fluoxetine	20–40 mg
Mirtazapine	15–30 mg
Paroxetine	20–30 mg
Sertraline	50–100 mg
Venlafaxine	75–150 mg

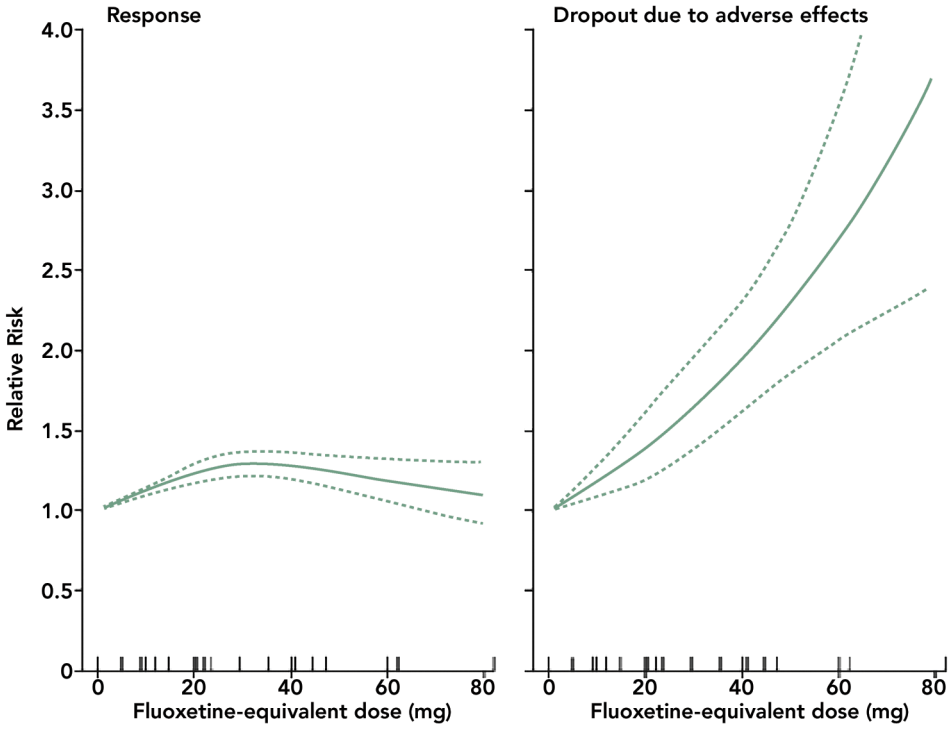
From the Article: "Optimal Antidepressant Doses in Major Depression" *The Carlat Psychiatry Report*, Volume 18, Number 3, March 2020 www.thecarlatreport.com

RESULTS

The best balance of efficacy, tolerability, and acceptability was achieved at low to medium doses of these antidepressants (see table and graph). At higher doses (> 40 mg of fluoxetine equivalents), the benefits plateaued and dropouts from side effects showed steep, linear-to-exponential curves. Venlafaxine was unique in that its efficacy continued to increase up to 375 mg, though it started slowing at doses above 150 mg.

THE CARLAT TAKE

These results show that the low to medium range of antidepressant doses may be most appropriate for patients with depression. It's often helpful to keep charts like this close by when considering a change in medication. After this publication, a second study appeared using the same data but stratified by age. That analysis clarified that the elderly—those over age 60—were particularly vulnerable to the adverse effects of higher doses of antidepressants (Holper L, *EClinicalMedicine* 2020;18:100219).



GRAPH: Relationship of Dose to Response and Adverse Effects for SSRIs Across 99 Treatment Groups (Furukawa TA et al, 2019).

From the Article: "Optimal Antidepressant Doses in Major Depression" *The Carlat Psychiatry Report*, Volume 18, Number 3, March 2020 www.thecarlatreport.com

PRACTICE IMPLICATIONS

When a patient does not recover fully on an antidepressant, it's tempting to keep raising the dose. That strategy may work sometimes, but this study suggests that for many on second-generation antidepressants, an increased dose is more likely to cause side effects than therapeutic gains, particularly for those over age 60. If you go to a higher dose, measure the outcomes, and consider dropping back down if there's no clear improvement.

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PSYCHOSIS MANAGEMENT

Cannabidiol for Schizophrenia

REVIEW OF: McGuire P, Robson P, Cubala WJ, et al. Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: A multicenter randomized controlled trial. *Am J Psychiatry*. 2018 Mar 1;175(3):225–231.

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

Traditional antipsychotic medications leave much to be desired. Their therapeutic response rate for schizophrenia is low, and their side effects are troubling and lead to high rates of noncompliance. Clearly, there is an urgent need for alternative agents. Although patients—including those diagnosed with schizophrenia—have long attested to the benefits of marijuana, only recently have researchers begun taking it seriously as a therapeutic option. In this pilot study, investigators evaluated the benefits of cannabidiol (CBD), which is one of the two main active components of marijuana (the other being tetrahydrocannabinol or THC), for the treatment of schizophrenia.

In this 6-week trial, adult patients diagnosed with schizophrenia or a related psychotic disorder were recruited from sites across Europe. All patients were actively psychotic, though they could not be entirely treatment-resistant (ie, patients had to have displayed at least a partial response to antipsychotic medications). Patients entered the study only after they had been on a stable dosage of antipsychotic medication for at least 4 weeks, and this medication was continued throughout the course of the study. 43 patients were randomized to CBD and 45 to placebo. CBD was dosed at 1,000 mg/day in the form of an oral solution. Active substance use was not grounds for exclusion. The primary efficacy measure used was the Positive and Negative Syndrome Scale (PANSS), while cognition was measured using the Brief Assessment of Cognition in Schizophrenia (BACS) scale.

RESULTS

Positive symptoms (eg, delusions or hallucinations) were significantly reduced at the 6-week endpoint for patients receiving CBD compared to placebo. Improvement in negative symptoms (eg, flat affect) favored CBD, but this difference did not reach statistical significance. Patients receiving CBD also fared better on global assessment of functioning, clinicians' global assessment of improvement, and cognitive measures, though this latter difference fell just short of statistical significance ($p = 0.07$). No major adverse events occurred that were attributed to CBD, and the participants were not able to tell if they were taking CBD or placebo.

THE CARLAT TAKE

CBD's therapeutic potential has received a lot of attention lately. This is the most rigorous study of CBD in schizophrenia to date, and its intriguing findings warrant replication with a larger sample and longer duration. The dose of 1,000 mg/day is also important to recognize. A similar study published a few months later showed no significant effect of CBD at a dose of 600 mg/day for positive or negative symptoms associated with schizophrenia (Boggs DL et al, *Psychopharmacology* 2018;235(7):1923–1932).

PRACTICE IMPLICATIONS

Given the many limitations and pitfalls associated with traditional antipsychotic medications, a novel compound that might be devoid of those pitfalls is a most welcome development. Currently the only prescription CBD product is Epidiolex, which is FDA approved for some forms of childhood epilepsy, though it must be used with caution due to potent induction of multiple CYP450 enzymes. Over-the-counter CBD products can vary widely in quality and may contain THC as well. The current research into medicinal CBD and THC products also varies; in a recent systematic review the dose of CBD ranged between 2.5 and 1,000 mg/day (Sarris J et al, *BMC Psychiatry* 2020;20(1):24). Right now the research is too early for us to recommend a particular product or dose schedule of CBD for treatment of psychiatric disorders.

Is Clozapine the Next Step After a Single Failed Antipsychotic Trial?

REVIEW OF: Kahn RS, van Rossum IW, Leucht S, et al. Amisulpride and olanzapine followed by open-label treatment with clozapine in first-episode schizophrenia and schizophreniform disorder (OPTiMiSE): A three-phase switching study. *Lancet Psychiatry*. 2018 Oct;5(10):797–807.

STUDY TYPE: Sequential trial with open-label and randomized, double-blind comparison phases

Clozapine is often used as a last resort in schizophrenia, even though practice guidelines recommend a trial of this medication after failing 2 antipsychotics. The current study set out to test a treatment algorithm based on those guidelines in patients with first-episode psychosis.

Researchers recruited a total of 446 patients from 27 clinics in various European countries. All patients were in their first psychotic episode and had diagnoses of schizophrenia (51%), schizophreniform disorder (43%), or schizoaffective disorder (6%). To refresh your memory, schizophreniform disorder means that symptoms of schizophrenia have been present for more than a month but less than 6 months. The average age was 26; most were male (70%) and Caucasian (87%). The primary outcome was symptomatic remission on the Positive and Negative Syndrome Scale (PANSS). The trial was funded by the European Commission.

The patients were entered into a three-phase study:

- Phase 1: All 446 patients were prescribed open-label amisulpride, an antipsychotic used outside the US for schizophrenia but approved by the FDA in 2020 for postoperative nausea and vomiting (as Barhemsys injection), for 4 weeks at ≤ 800 mg/day.
- Phase 2: Those patients who did not achieve remission on amisulpride were randomly assigned to a double-blind trial of either continuing amisulpride or switching to olanzapine (≤ 20 mg/day, mean 16 mg/day) for 6 weeks.
- Phase 3: Patients who did not respond to either amisulpride or olanzapine were treated with open-label clozapine (≤ 900 mg/day, mean 490 mg/day) for 12 weeks.

Amisulpride and olanzapine were selected for this algorithm because their effect sizes are second only to clozapine's in schizophrenia.

RESULTS

Just over half (56%) of the patients remitted during the first phase of antipsychotic treatment with amisulpride. Of the 93 patients who started the second phase, about 32% remitted with either amisulpride continuation or olanzapine switch, with no significant differences between these drugs. Finally, 40 patients were left to assign to clozapine; 18 of those completed the 12-week trial, and 5 (28%) achieved remission.

THE CARLAT TAKE

Because switching to olanzapine did not yield better outcomes than continuing the first antipsychotic, the authors suggested that this second-line switch could be skipped and that patients who don't respond to their first antipsychotic might be better served by going straight to clozapine. Studies have continued to support the use of clozapine in severely ill patients despite its significant risks for metabolic syndrome, weight gain, and Type 2 diabetes (Masuda T et al, *JAMA Psychiatry* 2019;76(10):1052–1062).

PRACTICE IMPLICATIONS

Moving clozapine up from step 3 to step 2 in the schizophrenia algorithm is a bold suggestion. We'd like to see that tested out in a more controlled manner before changing practice guidelines. What these results do tell us is that schizophrenia recovery can take time. If patients haven't recovered after 10 weeks, whether with one antipsychotic or two, a trial of clozapine is not unreasonable, but it's not clearly the best option either.

Dose Maintenance or Reduction With Antipsychotics?

REVIEW OF: Zhou Y, Li G, Li D, Cui H, Ning Y. Dose reduction of risperidone and olanzapine can improve cognitive function and negative symptoms in stable schizophrenic patients: A single-blinded, 52-week, randomized controlled study. *J Psychopharmacol*. 2018 May;32(5):524–532.

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

Once patients with schizophrenia are stabilized on an antipsychotic in the acute phase of their treatment, guidelines are unclear on how to continue dosing. Some guidelines recommend lowering the dose, others recommend maintaining the dose, and others give no firm recommendations whatsoever. For fear of relapse, many clinicians never lower the dose, so many patients are simply kept on the higher acute-phase doses. These doses can be associated with more side effects, including extrapyramidal symptoms, metabolic syndrome, and impaired cognitive function.

This 52-week, single-blinded (rater-blinded), randomized controlled study sought data on maintenance and reduction using two frequently prescribed antipsychotics. Relapse was defined as a score of ≥ 4 on the Positive and Negative Syndrome Scale (PANSS) on at least one of the following: delusions, conceptual disorganization, hallucinatory behavior, or suspiciousness.

Researchers studied 75 stabilized schizophrenic patients, who were prescribed either risperidone (≥ 4 mg/day) or olanzapine (≥ 10 mg/day). They were randomly divided into a maintenance group (n = 38) and a dose-reduction group (n = 37). In the maintenance group, the dose of medication remained unchanged. In the dose-reduction group, the dose of antipsychotic was reduced by 25% for the first 4 weeks, then reduced by 50% of the original dose for the remaining 48 weeks. Doses were never lowered below minimum recommendations—ie, below 2 mg/day for risperidone or below 5 mg/day for olanzapine.

RESULTS

Over 52 weeks, relapse rates were not significantly different between the groups, with relapse of only 4 patients in the dose-reduction group and 6 patients in the maintenance group. A 50% dose reduction of antipsychotics did not lead to any worsening of psychotic symptoms. In fact, patients on the lower doses had fewer extrapyramidal symptoms ($p = 0.012$), lower body mass index ($p = 0.005$), improved cognitive function ($p = 0.001$), and improved negative symptoms overall ($p < 0.001$).

THE CARLAT TAKE

It's important to note that this research supports dose reduction, not elimination, of antipsychotic medication for stable patients. Despite a small sample size, using single rather than double blinding, and being limited to only two antipsychotics, this study offers much-needed evidence to guide some important clinical decisions.

PRACTICE IMPLICATIONS

During the maintenance phase for our stabilized patients with schizophrenia, careful antipsychotic dose reduction (by 25% over the first 4 weeks, and then by 50% thereafter) is worth trying. The improvement in side effects and cognitive functioning may be well worth it to our patients.

Steroid-Induced Psychosis in the Pediatric Population

REVIEW OF: Hodgins GE, Saltz SB, Gibbs EP, et al. Steroid-induced psychosis in the pediatric population: A new case and review of the literature. *J Child Adolesc Psychopharmacol*. 2018 Jun;28(5):354–359.

STUDY TYPE: Case report and literature review

Childhood psychosis is a rare disorder, and accurate diagnosis is crucial. Recently, clinicians at the University of Miami Miller School of Medicine reported a case of steroid-induced psychosis in a pediatric patient.

In the case report, a 12-year-old Haitian girl was diagnosed with discoid lupus erythematosus after she presented with fever, fatigue, and anemia. She was started on prednisolone and hydroxychloroquine, and a few days later presented with mutism, drooling, and altered mental status. She was admitted to the PICU, and her symptoms were assumed to be related to her lupus; therefore, she was treated with IV prednisolone. After eight days of admission, the patient remained disoriented, mute, and paranoid. After a negative organic workup, the psychiatry consultation team recommended tapering the steroid and started her on clonazepam 0.25 mg BID and risperidone 0.5 mg BID (later switched to haloperidol). After 12 days, the patient was much improved—she was more verbal and had no hallucinations. Once the steroid was entirely discontinued, she became completely organized and was discharged on haloperidol 5 mg/day and lorazepam 1 mg twice daily.

RESULTS

The authors did a literature review and found 15 other case reports of steroid-induced psychosis in children and adolescents. Asthma was the most common indication for the initiation of steroids. The higher the dose of steroids (> 40–80 mg dose equivalents per day), the more chances of psychiatric manifestations.

THE CARLAT TAKE

This case highlights the need to search for specific causes of psychotic symptoms that can usually be resolved, avoiding unnecessary long-term treatments. Especially in young children, primary psychotic disorders are rare, and any psychotic symptoms should prompt a thorough search for a secondary reason.

PRACTICE IMPLICATIONS

For steroid-induced psychosis, discontinuation of steroids is the gold standard and typically completely resolves the symptoms within a few days to a month. For instances where steroid taper is not possible, a trial of benzodiazepines and antipsychotics can be helpful.

Weight Gain From Aripiprazole Same as Risperidone

REVIEW OF: Schoemakers RJ, van Kesteren C, van Rosmalen J, et al. No differences in weight gain between risperidone and aripiprazole in children and adolescents after 12 months. *J Child Adolesc Psychopharmacol.* 2019 Apr;29(3):192–196.

STUDY TYPE: Retrospective cohort study

Many providers prefer aripiprazole over risperidone for young patients due to observed lower incidence of weight gain. This is supported in studies with follow-up of less than 3 months. However, does aripiprazole fare better with long-term use?

Researchers reviewed records of children and adolescents treated with aripiprazole or risperidone for at least 12 months at a Dutch mental health organization between 2008 and 2015. Only 89 of 874 patients on risperidone and 42 on aripiprazole met the inclusion criteria, as over 80% of the charts had missing baseline and/or follow-up data.

RESULTS

BMI z-scores (age- and sex-adjusted BMI) significantly increased for both medications over 12 months. The increase was marginally lower for aripiprazole (0.30, 95% CI = 0.07–0.53) than for risperidone (0.37, 95% CI = 0.21–0.53), but not statistically significant ($p = 0.97$). Of note, the aripiprazole group had a higher BMI z-score at baseline (0.18) compared to the risperidone group (–0.33), possibly as aripiprazole is preferred over risperidone for overweight kids.

The authors predicted that an 11-year-old boy with a BMI of 16.9 at baseline would have a predicted BMI of 18.2 with aripiprazole use for 12 months and 18.4 with risperidone, whereas that same boy would have a BMI of 17.5 without medications for that year.

THE CARLAT TAKE

In this study, using aripiprazole to avoid weight gain was fruitless, at least in children. Children are much more vulnerable to metabolic side effects than adults, so we can't apply these discouraging results to all patients. The small sample size dampens our confidence in the results, but BMI z-scores offer a more accurate understanding of weight gain.

PRACTICE IMPLICATIONS

If we must use antipsychotics in children, "old-school" measures like packing lunch for school and eating dinner with the family, plus reducing fast food and screen time, can have an enormous positive impact on a child's physical and mental well-being. Periodic assessment of BMI and metabolic profile should be routine, with dietary counseling and CBT where appropriate. Among pharmacological interventions, adjunctive metformin has the best data, followed by topiramate.

Polypharmacy in Schizophrenia

REVIEW OF: Tiihonen J, Taipale H, Mehtälä J, et al. Association of antipsychotic polypharmacy vs monotherapy with psychiatric rehospitalization among adults with schizophrenia. *JAMA Psychiatry*. 2019 May 1;76(5):499–507.

Stroup TS, Gerhard T, Crystal S, et al. Comparative effectiveness of adjunctive psychotropic medications in patients with schizophrenia. *JAMA Psychiatry*. 2019 May 1;76(5):508–515.

Antipsychotic polypharmacy is discouraged in guidelines but common in practice. Up to 30% of patients with schizophrenia are prescribed multiple antipsychotics, and combinations of antipsychotics with other drug classes are even more common. Research on these practices, though, is sparse. Two recent studies, both large retrospective non-randomized controlled trials, attempted to clarify whether polypharmacy brings greater benefits in schizophrenia, or just greater risks.

STUDY ONE: Retrospective cohort study

The first study collected data from a population-wide registry in Finland on 62,250 patients with schizophrenia who were hospitalized and followed between 1996 and 2015 (median age 46; male to female ratio equal).

Hazard ratios (HR) were calculated by comparing patients on one, multiple, or no antipsychotics. Within-individual analysis was used to eliminate selection bias (ie, patients were their own controls). Of the total cohort, 67% used antipsychotic polypharmacy at some point. To exclude switches between antipsychotics, data from the first 90 days of multiple antipsychotic use were censored. The primary outcome was psychiatric rehospitalization, and secondary outcomes were mortality and medical hospitalization.

RESULTS

The risk of psychiatric rehospitalization was 13% lower with polypharmacy than monotherapy (HR 0.87; CI 0.85–0.88). That risk was lowest with the combination of clozapine and aripiprazole: 58% lower than no antipsychotic use (HR 0.42; CI 0.39–0.46) and 14% lower than clozapine alone (HR 0.86; CI 0.79–0.94). Among the top 10 treatments with the lowest risk of rehospitalization, only one was monotherapy: clozapine. Remarkably, polypharmacy was also associated with a lower risk of hospitalization due to medical illness and mortality.

STUDY TWO: Retrospective cohort study

The second study evaluated the effects of adding different drug classes to standard treatment in schizophrenia. Using a Medicaid registry, 81,921 patients with schizophrenia on antipsychotic therapy were followed for 1 year after starting an additional psychotropic (mean age 41; 54% male). Patients who were already on multiple psychiatric medications or who filled their antipsychotic inconsistently were excluded from the sample (n = 241 and 579).

HRs were calculated by comparing patients based on whether they were prescribed antidepressants, benzodiazepines, or mood stabilizers vs additional antipsychotics. Patients in each of the treatment groups were demographically similar. Those who did not start a new psychotropic were not included in the comparisons, as it was thought they represented a group with fewer comorbidities and better prognosis. Dropouts were handled by analyzing data on an intent-to-treat basis. The primary outcome was psychiatric hospitalization, and secondary outcomes included medical hospitalization and mortality.

RESULTS

The risk of psychiatric hospitalization was 16% lower for patients who started an antidepressant (HR 0.84; CI 0.80–0.88). Patients started on benzodiazepines had a higher risk of psychiatric hospitalization (HR 1.08; CI 1.02–1.15), while those started on mood stabilizers had an equal risk (HR 0.98; CI 0.94–1.03). Antidepressants were associated with a lower risk of medical hospitalization (HR 0.87; CI 0.79–0.96), whereas no difference was found for benzodiazepines or mood stabilizers. Mood stabilizers were the only group associated with a statistically higher risk of mortality (HR 1.31; CI 1.04–1.66), and this risk was highest with gabapentin.

THE CARLAT TAKE

Both studies had similar weaknesses. With the lack of randomization, various confounding variables could have been overlooked. Factors not examined include reasons for changing medications, frequency of patient-provider contact, use of psychosocial interventions, and extent of medication adherence. Functioning and symptom severity were also not examined. On the other hand, patients prescribed multiple psychotropics are likely to have lower functioning and greater disease severity, so the fact these patients had favorable outcomes is impressive.

PRACTICE IMPLICATIONS

Polypharmacy is often looked down on, but these results suggest it may be a viable strategy in schizophrenia. In combining antipsychotics, the best outcome was with clozapine and aripiprazole. This suggests prescribing antipsychotics with different receptor profiles may be a useful tactic. In terms of combining antipsychotics with other psychotropics, the results are even less definitive and more likely skewed. That limitation aside, antidepressants appear to have the greatest benefit and least risk. In contrast, mood stabilizers and benzodiazepines should be used with more caution.

An Answer for Psychotic Depression

REVIEW OF: Flint AJ, Meyers BS, Rothschild AJ, et al. Effect of continuing olanzapine vs placebo on relapse among patients with psychotic depression in remission: The STOP-PD II randomized clinical trial. *JAMA*. 2019 Aug 20;322(7):622–631.

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

Psychotic features in depression indicate a more severe form of the disease, with a higher risk of hospitalization and double the rate of disability compared with non-psychotic depression. A combination of an antipsychotic and an antidepressant is the mainstay of treatment, but how long to continue the antipsychotic is an unanswered question.

This study enrolled patients 18–85 years of age with severe major depression and at least 1 delusion; hallucinations were optional. Dementia and unstable medical illness were part of the exclusion criteria, so the patients may not have been as ill as some whom we see in clinical practice. Average age was 55 years.

Researchers first treated 269 patients with open-label olanzapine and sertraline. Next, 162 patients who achieved remission or near-remission entered an open-label 8-week stabilization phase. Of the 147 who remained well after the stabilization, 126 were randomized to continue olanzapine or have the antipsychotic replaced with a placebo for 36 weeks. The design was double-blind, and the antipsychotic taper took place over 4 weeks. All patients remained on sertraline throughout the trial.

RESULTS

The primary outcome was risk of relapse, which included relapses into depression or psychosis as well as psychiatric hospitalization or suicidality. 55% of sertraline-placebo patients relapsed, compared to 20% of sertraline-olanzapine patients. The number needed to treat (NNT) to keep patients well with continued antipsychotic therapy was 2.8, which is a relatively low (favorable) value for depression treatment in general.

Weight gain was the main side effect of continued olanzapine. The placebo group lost weight while the olanzapine group continued to gain, with a difference of 9 pounds between them at the end of the study. Falls were also greater in the olanzapine-continuation group (31% vs 18%).

THE CARLAT TAKE

The majority of the relapses (79%) occurred within the first 20 weeks of the 36-week randomization phase. In a letter to the editor, Klaus Munkholm and colleagues argued that these relapses may have been a withdrawal phenomenon. The authors of the study countered that their criteria for relapse shared little in common with known symptoms of antipsychotic withdrawal.

PRACTICE IMPLICATIONS

When a patient recovers from psychotic depression on an antidepressant and antipsychotic, we should continue both medications for at least 2 months as long as the medication is reasonably tolerable. After 6 months of remission (28 weeks), we might consider a slow taper of the antipsychotic, weighing the severity of the episode, side effects, and the patient's preferences.

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ANXIETY DISORDERS

Pharmacology for GAD: Complex Choices

REVIEW OF: Slee A, Nazareth I, Bondaronek P, et al. Pharmacological treatments for generalised anxiety disorder: A systematic review and network meta-analysis. *Lancet*. 2019 Feb 23;393(10173):768–777.

STUDY TYPE: Network meta-analysis

With over two dozen choices, how do we pick a medication for generalized anxiety disorder (GAD)? The authors of this network meta-analysis sought to answer this question.

Network meta-analysis allows researchers to gauge treatments that haven't been directly compared in head-to-head studies. If drug A works better than drug B and B works better than C, then the network meta-analysis concludes that A is likely to work better than C, even though A and C have never been directly compared.

The investigators selected 89 trials of 25 drugs studied in over 25,000 patients. The primary outcome was change in the Hamilton Rating Scale for Anxiety (HAM-A). Trial length varied from 4 to 26 weeks.

RESULTS

Surprisingly, quetiapine XR was the most efficacious among the medications with large sample sizes. However, its benefit was modest, with a reduction of 3.6 points on the HAM-A compared to placebo (150–300 mg per night, as monotherapy). Quetiapine XR was poorly tolerated with a high discontinuation rate (odds ratio 1.44). The following drugs were well tolerated and are listed in order of efficacy: duloxetine, pregabalin, venlafaxine XR, and escitalopram.

The four benzodiazepines were studied as a class, not as individual drugs. Patients quit benzodiazepines much more often than placebo (odds ratio 1.43), although the reasons for discontinuation were not explored.

Studies were excluded if the patients had psychiatric comorbidities other than depression, which means the subjects might have been significantly less ill than the patients we see in routine practice. One-third of the trials were not placebo controlled, and a fairly large number of them had limited quality. However, a sensitivity analysis concluded that these deficiencies did not significantly distort the results.

THE CARLAT TAKE

Although the meta-analysis did not analyze the data according to the quality of the studies, dose, or duration of treatment, Carlat Publishing has analyzed these issues by drilling down on the appendix and the original studies. The studies of pregabalin were all of lower quality. The studies of duloxetine were of the highest quality, followed by escitalopram and venlafaxine XR. For duloxetine, venlafaxine, and escitalopram, high doses (eg, duloxetine 120 mg) were no more efficacious than medium doses (eg, duloxetine 60 mg). Of these three antidepressants,

only venlafaxine XR was studied for more than 12 weeks, and those studies demonstrated greater efficacy than shorter studies, suggesting that its benefits may build over time.

PRACTICE IMPLICATIONS

In GAD, duloxetine stands out for its efficacy, safety, and the quality of its studies. This antidepressant has FDA approval in childhood GAD as well. It may take a few months to see the full effects of antidepressants in GAD, and medium doses are as likely to work as higher ones. Quetiapine XR is one of the more effective medications for GAD, but it has major safety and tolerability issues that caused the FDA to withhold its approval in 2009.

Is D-Cycloserine Useful for Panic Disorder Treatment Augmentation?

REVIEW OF: Hofmeijer-Sevink MK, Duits P, Rijkeboer MM, et al. No effects of D-cycloserine enhancement in exposure with response prevention therapy in panic disorder with agoraphobia: A double-blind, randomized controlled trial. *J Clin Psychopharmacol.* 2017 Oct;37(5):531–539.

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

The mainstay of current treatment for panic disorder involves SSRIs and psychotherapy, specifically either cognitive behavioral therapy (CBT) or exposure with response prevention (ERP) therapy. D-cycloserine (DCS) is a partial N-methyl-D-aspartate (NMDA) receptor agonist that may enhance extinction learning—the gradual decrease in the panic response during ERP. Several studies have evaluated whether adding DCS to ERP therapy might enhance the effectiveness of the therapy, but there have been mixed results.

Conducted at outpatient clinics at three mental health care institutions in the Netherlands, this study evaluated the effectiveness of adding DCS to panic disorder treatment. Fifty-seven patients with panic disorder and agoraphobia were randomized to one of three treatment arms: DCS before the ERP session, DCS after the ERP session, or placebo.

DCS or placebo was administered orally in a single 125 mg fixed dose, either at the beginning or the end of treatment, depending on the condition. All study participants underwent 12 weekly, 90-minute individual ERP sessions. The primary outcome was the mean score on the "alone" subscale of the Mobility Inventory (MI), which is a self-report tool used to measure agoraphobic avoidance behavior in various situations. Measurements were taken at baseline and during sessions 4, 8, and 12, and then at 3- and 6-month follow-up.

RESULTS

There was no difference in the primary outcome between those who received DCS (either pre- or post-ERP session) and placebo. However, within the two DCS treatment groups, the DCS post-ERP group showed a significant improvement in the primary outcome ($p = 0.009$; effect size = 0.6) measured at 3-month follow-up compared to the DCS pre-ERP group.

THE CARLAT TAKE

DCS augmentation of psychotherapy for anxiety disorders sounds plausible in theory, but many studies, including this one, don't show a significant difference when comparing DCS to placebo. However, the authors mention that this study had many limitations. First, the study may have been too small to show an effect—the researchers' power calculations called for 20 subjects per treatment arm, but only 19 were randomized to each arm. Second, the dosing of

125 mg of DCS may have been too high. This may sound illogical, but the way DCS is thought to work is by activating the NMDA receptor. At higher doses, though, DCS has partial NMDA receptor antagonist effects, which reduces its effect on extinction learning. Also, with higher doses and more administrations, patients are more likely to develop tolerance to DCS.

PRACTICE IMPLICATIONS

It's interesting that this study showed a small signal that DCS might be effective post-ERP treatment, but we'll need larger studies with more robust results before recommending that you start using DCS in your practice.

Prescribing Patterns for Children With Anxiety Disorders

REVIEW OF: Bushnell GA, Compton SN, Dusetzina SB, et al. Treating pediatric anxiety: Initial use of SSRIs and other antianxiety prescription medications. *J Clin Psychiatry*. 2018 Jan/Feb;79(1):16m11415.

STUDY TYPE: Retrospective cohort study

Anxiety disorders are some of the most common conditions we encounter in children and adolescents, and clinicians employ a variety of medications to treat them. This study examined prescribing patterns for the initial treatment of pediatric anxiety.

Researchers analyzed a large commercial claims database for information on patients ages 3–17 years who were diagnosed with an ICD-9 anxiety disorder (including OCD and PTSD) and started on an antianxiety medication between 2004 and 2014.

Overall, a majority of the 84,500 medicated patients were older teenagers, with 58% being 14–17, and 58% were female. Half of the patients (50%) were diagnosed with unspecified anxiety disorder. More than half received both a diagnosis and a prescription on the same day (57%). While 41% of patients had attended a psychotherapy session within the 30 days prior to medication initiation, it is unclear if the rest had seen a therapist in the past or were referred to one while being started on medications.

RESULTS

Unsurprisingly, most children were started on an SSRI (70%), while some received benzodiazepines (11%), hydroxyzine, guanfacine/clonidine, an atypical antipsychotic, or an antidepressant/antianxiety medication combination (3%–5% each). Children with OCD and selective mutism were more likely to be given SSRIs (83% and 82% respectively) as compared to those with panic disorder (54% SSRI, 30% benzodiazepine) or PTSD (53% SSRI, 14% atypical antipsychotic). Almost a third of children with no other recent psychiatric comorbidity were prescribed a non-SSRI. When compared to psychiatrists, primary care providers were more likely to prescribe non-SSRIs to kids with panic disorder and social phobia.

In a promising trend, across the decade of the study period, teens ages 14–17 were more likely to be started on SSRIs (55% in 2004 vs 65% in 2014) and less likely to be started on benzodiazepines (20% in 2004 vs 10% in 2014). SSRIs were more likely to be refilled after the first prescription (81%) as well as continued for at least 6 months (55%) as compared to benzodiazepines (25% and 5%) or atypical antipsychotics (71% and 41%). Moreover, almost a quarter of those who were initiated on benzodiazepines or atypical antipsychotics eventually got a prescription for an SSRI within 3 months.

THE CARLAT TAKE

Frequency of prescribing does not imply best practice for everyone. While SSRIs are the most commonly prescribed medications with the lowest discontinuation rates in this study, antipsychotics came second, and both have potentially significant side effects in context of a paucity of evidence-based research independent of manufacturer-sponsored studies, the lack of FDA support notwithstanding. It is good to see reductions in benzodiazepine use, as they have few truly legitimate indications (surgery, catatonia) and their potential short- and long-term risks in children and adolescents almost always outweigh their immediate benefits. Although devoid of FDA approval, medications like propranolol, hydroxyzine, and guanfacine/clonidine have an important role to play in mitigating acute anxiety episodes, as well as anxiety stemming from trauma, while minimizing risk of long-term adverse effects like metabolic syndrome.

PRACTICE IMPLICATIONS

SSRIs play an important role in treatment of childhood anxiety disorders, but as AACAP guidelines note, psychotherapy should be the first-line treatment, with medications considered in cases of moderate to severe anxiety or a lack of response or access to psychotherapy. Unless children and youth are equipped with anxiety management techniques, family and/or school interventions that reduce any relevant stressors, and psychotherapy that deals with underlying anxiety-provoking memories and schemata, then cessation of pharmacotherapy—even if partially or fully effective—is more likely to lead to relapse.

How Effective Are Medications for Pediatric Anxiety?

REVIEW OF: Strawn JR, Mills JA, Sauley BA, Welge JA. The impact of antidepressant dose and class on treatment response in pediatric anxiety disorders: A meta-analysis. *J Am Acad Child Adolesc Psychiatry*. 2018 Apr;57(4):235–244.e2.

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

Antidepressants are part of the first-line treatment for severe childhood anxiety disorders when removal of stressors and psychotherapy are not enough, but are all antidepressants created equal in this situation?

A recent meta-analysis shows that antidepressants have a moderate effect size of 0.56 for treating anxiety disorders in children (Locher C et al, *JAMA Psychiatry* 2017;74(10):1011–1020), but do we have the data to further break that down? Another meta-analysis was recently performed that can further guide us in tailoring our medication choices for pediatric anxiety disorders.

In this meta-analysis, the authors pooled data from nine randomized placebo-controlled trials that compared either an SSRI or an SNRI to placebo for the treatment of social, generalized, and/or separation anxiety disorders. Total sample size was 1,805 children ages 5–17 years, with 53% male. All studies were done in outpatient clinics and had a mix of federal and industry funding sources. The follow-up periods varied from 8 to 16 weeks, with a median of 10 weeks. Four SSRIs (fluoxetine, fluvoxamine, paroxetine, and sertraline) and three SNRIs (atomoxetine, venlafaxine, and duloxetine) were used in the studies. The primary outcomes were the time it took to see improvement, how treatment response differed between SSRIs and SNRIs, and differences in low-dose vs high-dose SSRIs. Rating scales, most commonly the Pediatric Anxiety Rating Scale (PARS), were administered every 2 weeks.

RESULTS

Overall, children improved quickly compared to placebo, with a statistically significant difference in the rating scales by week 2 ($p = 0.005$) and a clinically significant difference seen by week 6 ($p = 0.001$). SSRIs outperformed SNRIs over the entire treatment course, with a statistically significant difference emerging by week 2 ($p = 0.021$), but both classes of medications resulted in significant improvement compared to placebo by week 2. For the high-dose vs low-dose SSRI comparison, high-dose was considered > 1.5 fluoxetine equivalents (> 49.5 mg) per day. High-dose SSRI treatment resulted in earlier improvement (week 2), while low-dose treatment resulted in later improvement (week 6). However, over time, there was no significant difference between high-dose and low-dose treatment ($p = 0.638$), but the variance was greater for the low-dose group ($p < 0.001$).

THE CARLAT TAKE

This meta-analysis found that, overall, SSRIs resulted in greater improvement in childhood anxiety disorders than SNRIs, and that high-dose SSRIs led to earlier improvement. The authors postulate that the differences may be due to an underdeveloped noradrenergic system in children compared to the serotonergic system, or due to anxiety disorders themselves being caused by more dysfunction in the serotonergic system.

PRACTICE IMPLICATIONS

When making medication decisions, the more information we have, the better. This study confirms that both SSRIs and SNRIs are effective in treating pediatric anxiety disorders. And, all other things being equal, SSRIs may give better results. Unless you have a reason to avoid SSRIs, using them as the first-line medication choice makes sense. High-dose SSRIs may give faster results but may come at a cost of increased side effects. Always be on the lookout for activation (which is generally more common with SSRIs than SNRIs) and other side effects.

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ADHD

Risk of Psychosis With Stimulants in ADHD Patients

REVIEW OF: **Moran LV, Ongur D, Hsu J, et al. Psychosis with methylphenidate or amphetamine in patients with ADHD. *N Engl J Med*. 2019 Mar 21;380(12):1128–1138.**

STUDY TYPE: **Retrospective cohort study**

In 2007, the FDA required stimulant manufacturers to warn of possible psychosis with stimulants. But what is the real incidence of stimulant-induced psychosis? This study set out to discern if there is a difference between methylphenidate and amphetamine classes of medications in causing this potential adverse effect.

Drawing from two large commercial insurance databases, researchers looked at over 333,000 patients with ADHD ages 13–25 years who were prescribed a stimulant between 2004 and 2015, matching 110,923 methylphenidate users with an equal number of amphetamine users. The authors excluded patients with confounding variables (eg, glucocorticoid prescription) and adjusted for unmeasured confounders (eg, cannabis use). They defined "stimulant-induced psychosis" as a new psychotic illness within the follow-up period (median 4–5 months) along with a prescription for an antipsychotic within 60 days of that diagnosis.

RESULTS

Over the years 2005 to 2014, prescription of amphetamine salts increased 3.8 times, while that of methylphenidates increased only 1.6 times. It was notable that internists and family practice doctors tended to use amphetamines most often, prescribing amphetamines in 72.5% of stimulant prescriptions, with psychiatrists at 62.7% and pediatricians 51.6%.

The overall risk of psychosis was 1 in 660, with onset of psychotic symptoms occurring after a median 128 days. The risk in the amphetamine group was double compared to the methylphenidate group (237 episodes or 0.21% vs 106 episodes or 0.10%).

Amphetamine-related psychosis occurred more in younger children and those treated by non-psychiatrists (about 80% of patients). In the hands of internists and family practice doctors, the hazard ratio was 1.78, for pediatricians it was 1.7, and for psychiatrists it was 1.38.

THE CARLAT TAKE

Amphetamines, such as Adderall and Vyvanse, are more likely to lead to psychosis than methylphenidate, though the actual prevalence is quite low. Those children and young adults who were treated by psychiatrists had a lower rate of stimulant-induced psychosis.

PRACTICE IMPLICATIONS

We recommend extra caution in the use of stimulants (especially amphetamines) in those with other risk factors for psychosis (eg, family history of psychosis, cognitive or behavioral signs of prodromal psychosis, or concurrent cannabis use). In the broader picture, methylphenidate is usually better tolerated in any case and probably a better first-line medication.

How Helpful Is Computerized Testing for ADHD?

REVIEW OF: Hollis C, Hall CL, Guo B, et al. The impact of a computerised test of attention and activity (QbTest) on diagnostic decision-making in children and young people with suspected attention deficit hyperactivity disorder: Single-blind randomised controlled trial. *J Child Psychol Psychiatry*. 2018 Dec;59(12):1298–1308.

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

With busy clinic schedules and the ever-burgeoning load of documentation, computerized diagnostic aids are in more demand than ever. For ADHD, the gold standard is still a clinical assessment with information from parents and teachers, but those reports are difficult to obtain and time-consuming to go through. In these situations, computerized testing may help boost clinical decision-making.

One common testing procedure is continuous performance testing (CPT), which involves a subject's ability to quickly respond to a given stimulus while not responding to distracting stimuli. QbTest is a specific testing method that combines computerized CPT and an infrared camera measuring how much the patient moves around during the 20-minute test. In 2014, the FDA cleared QbTest as a tool to supplement a clinical assessment for ADHD, meaning that it reached the diagnostic sensitivity and specificity thresholds required by the FDA. However, like all such tests, it is not meant to be a standalone diagnostic test. This study attempted to see how useful QbTest is for clinicians.

The randomized controlled trial analyzed data from 250 youth ages 6–17 years referred for an ADHD assessment. Funding came from the National Institute for Health Research in the UK, but equipment and training were provided directly from Qbtech Ltd (the makers of QbTest). The device's website (www.qbtech.com/qbtest) has descriptions of the testing equipment: an infrared camera, a reflector that fits on the patient's forehead, and the computer software. The sample, drawn from UK outpatient clinics, was nearly 80% male and 90% white. All participants took the QbTest at the beginning of the study period, then were divided into two groups. The QbOpen group had the results revealed to the clinician immediately, while the QbBlind group withheld the results. The primary outcome was the number of appointments it took to rule in or out an ADHD diagnosis, with secondary outcomes including appointment duration and clinician's confidence in the diagnosis.

RESULTS

At the end of 6 months, the youth in the QbOpen group were 44% more likely (hazard ratio = 1.44; $p = 0.029$) to have reached a diagnostic decision than those in the QbBlind group. However, over 30% of the entire sample had still not reached a diagnostic decision at 6 months. Interestingly, ADHD was excluded at double the rate when clinicians had access to the QbTest report ($p = 0.049$), and they were more confident in their decision overall ($p = 0.022$). The appointment duration for the QbOpen group

was reduced by about 15% ($p = 0.001$). The authors also did a cost analysis concluding that QbTest was largely cost-neutral to the health care system.

THE CARLAT TAKE

As clinicians, we need to maintain diagnostic pre-eminence over supplemental tests for ADHD. While QbTest may increase the expediency of diagnosis and boost diagnostic confidence for clinicians, we need to be careful that it is neither masking other reasons for symptoms nor ruling them out when, for instance, the child being tested is inattentive but not overactive. It would also be interesting to see more comparison studies with more established measures such as the TOVA, GDS, IVA, or Connors CPT.

PRACTICE IMPLICATIONS

Computerized testing does not replace clinical assessments and collateral information from parents and teachers. While QbTest can provide some interesting information and more data points on which to base a diagnosis, it won't be putting anyone out of business.

Would Treating Kids With ADHD Help Their Mothers?

REVIEW OF: Gokcen C, Coskun S, Kutuk MO. Comparison of depression and burnout levels of mothers of children with attention-deficit hyperactivity disorder before and after treatment. *J Child Adolesc Psychopharmacol.* 2018 Jun;28(5):350–353.

STUDY TYPE: Prospective cohort study

Parenting a child with ADHD can be challenging. Parents often report feeling stressed, burned out, or depressed while caring for their children with ADHD. When ADHD medications lead to significant improvements in a child's behavior, can that alleviate symptoms in parents? A recently published study tried to examine that.

Investigators enrolled 40 children ages 4–10 years with ADHD at an outpatient clinic in Turkey. Twenty-one children completed the 8-week study and were prescribed methylphenidate (15), atomoxetine (3), or, surprisingly, risperidone (3). Researchers assessed the kids with a parent rating scale based on the DSM-IV criteria for ADHD, oppositional defiant disorder (ODD), and conduct disorder (CD) (Turgay-DSM-IV-S). They simultaneously assessed the kids' mothers for depression and burnout symptoms using Beck's Depression Inventory and the Maslach Burnout Inventory.

RESULTS

At the follow-up visit, the researchers found that children showed improvement in their scores of inattention (14.8±6.9 vs 11±8), hyperactivity (18±6.5 vs 10.5±8), ODD (11.6±6.4 vs 7.6±6.3), and CD (4.9±6.2 vs 2±3.7) symptoms. Moreover, their mothers also showed improvement in depression (14.5±7.7 vs 10.4±6.5) and burnout (18.3±10.6 vs 13±9.5). Interestingly, the improvement in mothers' burnout symptoms correlated with kids' ODD and CD symptoms ($r = 0.5$ and $p = 0.02$ for both), and improvement in mothers' depression symptoms correlated with CD symptoms in kids ($r = 0.47$; $p = 0.03$). Changes in mothers' symptoms did not correlate with the changes in children's inattention and hyperactivity symptoms.

THE CARLAT TAKE

This study suggests that improvement in ODD and CD symptoms in children with ADHD is associated with a decrease in burnout and depression symptoms in mothers. However, the findings of this study are difficult to generalize due to small sample size (40), high dropout rate (47.5%), lack of a control group, and an unclear separation between the pre-treatment and post-treatment scores. Furthermore, the authors did not disclose the rationale or dosage for the medications selected; they also did not disclose the psychiatric treatment status of the mothers.

PRACTICE IMPLICATIONS

When evaluating a child for ADHD symptoms, comorbid disorders like ODD and CD must be assessed and addressed appropriately. Whether or not this study proves causation, it makes sense that improvement in ODD and CD domains in children with ADHD can lead to all-around healthier families and communities.

Amphetamine Extended-Release Oral Suspension for ADHD

REVIEW OF: Childress AC, Wigal SB, Brams MN, et al. Efficacy and safety of amphetamine extended-release oral suspension in children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2018 Jun;28(5):306–313.

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

In 2015, the FDA approved Dyanavel XR (amphetamine extended-release oral suspension), which was the first long-acting liquid version of amphetamine on the market. To provide some context, Quillivant XR, a long-acting liquid methylphenidate formulation, was approved in 2012 and appears to be fairly popular for kids who can't or won't swallow pills. Seeing a market opportunity, Tris Pharmaceuticals developed Dyanavel XR and funded a placebo-controlled trial that was successful enough to gain FDA approval. Recently, this study was published, and some readers might be curious to look at the quality of the data.

The study took place at five investigational sites in the US. A total of 108 boys and girls with ADHD (ages 6–12) were initially enrolled in a 5-week open-label phase in which all patients were given Dyanavel XR, starting at 2.5–5 mg and titrated up to a target dose of 10–20 mg/day. Nine children dropped out of this first phase, and 99 continued on to the placebo-controlled phase of the study. Participants were randomly assigned to either Dyanavel XR (51 patients, mean dose 17.3 mg) or placebo (48 patients). After 1 week on the medication, the children's ADHD symptoms were evaluated with a teacher-rated instrument called the SKAMP (for the Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale).

RESULTS

The primary outcome variable was improvement in SKAMP scores from pre-dose to post-dose of medication. Dyanavel XR was more effective than placebo beginning 1 hour after the dose and continuing for 13 hours. The effect size was a very robust 1.8, in line with effect sizes reported in similar trials of other long-acting stimulants. In terms of side effects, patients on Dyanavel XR reported decreased appetite (26%), insomnia (13%), and affect lability (9%), with no substantial differences in blood pressure or pulse between the treatment and control group.

THE CARLAT TAKE

Not too surprisingly, Dyanavel XR is an effective stimulant treatment for ADHD. This study was not huge but was well designed, and the results were judged to be robust enough to merit FDA approval.

PRACTICE IMPLICATIONS

Dyanavel XR is another arrow in our ever-expanding quiver of stimulant options, and this liquid formulation will likely be just as popular as methylphenidate's liquid XR: Quillivant, first approved in 2012 for ADHD treatment. Being a brand-name option, its cost is high. For families that want cheaper liquid stimulants, go with either generic ProCentra (short-acting dextroamphetamine) or Methylin oral solution (short-acting methylphenidate).

Amphetamines Stand Out in ADHD

REVIEW OF: Cortese S, Adamo N, Del Giovane C, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: A systematic review and network meta-analysis. *Lancet Psychiatry*. 2018 Sep;5(9):727–738.

STUDY TYPE: Meta-analysis of randomized controlled trials

With so many medications available to treat ADHD, wouldn't it be nice to know if some are better than others? In this comprehensive meta-analysis, researchers sought to compare the relative efficacy and tolerability of both stimulant (methylphenidate and amphetamines) and non-stimulant (atomoxetine, bupropion, modafinil, clonidine, and guanfacine) medications for ADHD in children and adults.

The investigators combed through published and unpublished databases and located 82 double-blind, randomized controlled trials in children and adolescents, and 52 such trials in adults. Together, they included over 10,000 children and adolescents, and over 8,000 adults. The primary outcome was change in clinician-rated ADHD symptoms, while teacher ratings were also evaluated for children. "Tolerability" was defined as the percentage who dropped out because of side effects, while the broader term "acceptability" referred to those who dropped out for any reason. Outcomes were evaluated through 12 weeks of treatment.

RESULTS

In children and adolescents, all medications were superior to placebo. Amphetamines emerged as the most effective ADHD medication, superior to modafinil, guanfacine, atomoxetine, and methylphenidate. Methylphenidate was superior to atomoxetine. Based on teacher ratings, only methylphenidate and modafinil separated from placebo (none of the amphetamine trials included teacher ratings). With respect to tolerability, amphetamines and guanfacine both displayed significantly more adverse effects than placebo; amphetamines also significantly increased diastolic blood pressure. Methylphenidate was better tolerated than the amphetamines, and it was the only medication with better acceptability than placebo.

In adults, amphetamines emerged not only as the most efficacious agents but also the only ones with better acceptability than placebo. Methylphenidate, atomoxetine, and bupropion all had similar effect sizes. Modafinil was ineffective in adults, despite having positive results in children. At the time of this analysis, there were no trials of the alpha-2A agonists (clonidine ER and guanfacine ER) in adults, but a more recent randomized placebo-controlled trial did find favorable results for guanfacine ER in 108 adult patients with ADHD (Iwanami A et al, *J Clin Psychiatry* 2020;81(3):19m12979).

Tolerability was similar among the agents. In contrast to their effects on children, amphetamines did not increase diastolic blood pressure in adults. Overall, ADHD medications were less efficacious and less well tolerated in adults than in children and adolescents.

THE CARLAT TAKE

This meta-analysis seems to give us more reason to prescribe amphetamines, but there was a dearth of head-to-head trials, so these comparisons could only be made indirectly. The dropout rate was used as a proxy for acceptability, and this is a rough estimate. Finally, while the large sample sizes instill greater confidence in the results, they also risk finding significant differences that may not necessarily be clinically meaningful.

PRACTICE IMPLICATIONS

One medication rarely stands out in its class, but the amphetamines clearly emerged as the most effective option in both children and adults. That does not mean they should always be first choice, though. Methylphenidate was a more tolerable option in children, and there will always be patients who respond better to the methylphenidate varieties. Non-stimulant options take longer to work, but they performed fairly well in this meta-analysis, sometimes rivaling methylphenidate's benefits. The only failure was modafinil, which worked in children but not adults.

Can Stimulants Prevent Crime?

REVIEW OF: Mohr-Jensen C, Bisgaard CM, Boldsen SK, Steinhausen HC. Attention-deficit/hyperactivity disorder in childhood and adolescence and the risk of crime in young adulthood in a Danish nationwide study. *J Am Acad Child Adolesc Psychiatry.* 2019 Apr;58(4):443–452.

STUDY TYPE: Retrospective case-control series

ADHD has long been linked to antisocial behavior leading to arrests and incarcerations. Children and young adults with ADHD are more likely to be charged with anything from traffic violations to violent crimes. However, these associations do not prove causality. Is the ADHD causing these antisocial behaviors, or are there other psychosocial factors that would explain the findings? And if ADHD is indeed an independent risk factor for criminal behavior, can that risk be decreased through stimulant medication?

These big questions require population-based studies. Researchers evaluated data from Danish national medical and prescription registries and matched 4,231 children diagnosed with ADHD from 1995 to 2005, with controls based on sex and age. Follow-up data from an average of 22 years were obtained regarding arrests, incarcerations, substance abuse, time on stimulant medications, and other psychosocial factors. Nearly all (98%) of stimulant prescriptions were for methylphenidate, and most of the children (85%) were male.

RESULTS

After controlling for confounders such as psychiatric comorbidity, socioeconomic status, parental psychopathology, and other psychosocial factors, males with ADHD were 60% more likely (hazard ratio [HR] = 1.6) to be convicted of a crime and 70% more likely (HR = 1.7) to be incarcerated. For females, the effect was even more profound—they were 120% more likely (HR = 2.2) to be convicted and 190% more likely (HR = 2.9) to be incarcerated. However, when looking at times of active treatment with stimulant medication, the risk of conviction dropped significantly by 40% (HR = 0.6) for both males and females compared to time periods off medication. Incarceration risk also dropped by 40% (HR = 0.6) for males but did not drop significantly for females.

THE CARLAT TAKE

This study takes a mile-high view of a given population, looking for large trends over time. While population-based studies do not apply to every individual patient, knowing that appropriate treatment of ADHD may prevent criminal behavior is very encouraging.

PRACTICE IMPLICATIONS

The data for more severe consequences of ADHD in females are particularly interesting, though they may stem from underrecognized mild ADHD in girls. For all cases, early recognition of the complex needs (related to poverty, trauma, etc.) of children with ADHD and supporting psychosocial treatment with medication can change lives.

Methylphenidate Max Dosing

REVIEW OF: Ching C, Eslick GD, Poulton AS. Evaluation of methylphenidate safety and maximum-dose titration rationale in attention-deficit/hyperactivity disorder: A meta-analysis. *JAMA Pediatr*. 2019 Jul 1;173(7):630–639.

STUDY TYPE: Meta-analysis of randomized controlled trials

Methylphenidate was one of the first stimulants prescribed for the treatment of ADHD in children, adolescents, and adults. Its efficacy is clear, and its availability in immediate release, sustained release, osmotic-release oral system (OROS, brand name Concerta), and transdermal patch keeps it a popular choice. The typical dosing strategy in children and adolescents is to start low and go slow, but if symptoms remain and side effects are tolerable, at what dose should we stop titrating?

The standard FDA dosing information recommends a maximum dose of 60 mg per day in children and adolescents ages 6–17 for both immediate-release and sustained-release methylphenidate. For the OROS formulation, the dose is capped at 54 mg per day for children ages 6–12 and 72 mg per day in adolescents ages 13–17. These guidelines are backed by a few randomized controlled trials, and various organizations have slightly different maximum dose guidelines, but does the rest of the literature support these limits?

RESULTS

This meta-analysis reviewed data from 11 randomized controlled trials (1,304 participants) and 38 cohort studies (5,524 participants) examining methylphenidate dosing strategies. Some studies cited guidelines or previous studies for their maximum doses, but several of the studies capped themselves at a lower maximum dose than the source they were citing recommended. Most studies listed maximum doses far lower than the common guidelines. Only one cohort study went higher—90 mg per day of OROS for ages 6–13. Overall adverse effects were common at a rate of 66% in the cohort studies. The most common side effects were decreased appetite (33%), insomnia (15%), and headaches (14%). Serious adverse events were exceedingly rare, with transient psychosis reported in just 5 cohort study participants and hypertension in 7.

THE CARLAT TAKE

There is ample evidence of efficacy for many patients at dosages lower than the suggested maximums, yet evidence for a true maximum dose for methylphenidate is lacking. The variability in each patient's pharmacokinetics argues for an individualized dosing scheme that may lead to a lower or higher dose as needed (Childress AC et al, *Expert Opin Drug Metab Toxicol* 2019;15(11):937–974).

PRACTICE IMPLICATIONS

If a patient's ADHD symptoms remain on a given dose, and a review of the differential diagnosis yields no other intercurrent conditions, we do not have evidence that would preclude continued careful upward titration of stimulant medications while monitoring for side effects.

CHILD AND ADOLESCENT PSYCHIATRY

Melatonin for Insomnia in Patients With Autism

REVIEW OF: Maras A, Schroder CM, Malow BA, et al. Long-term efficacy and safety of pediatric prolonged-release melatonin for insomnia in children with autism spectrum disorder. *J Child Adolesc Psychopharmacol*. 2018 Dec;28(10):699–710.

STUDY TYPE: Open-label extension of a randomized placebo-controlled trial

Treating sleep problems in youth with autism spectrum disorder (ASD) is tricky at best. One promising treatment is pediatric prolonged-release melatonin (PedPRM) sold under the name Slenyto. In 2017, a randomized controlled trial (funded by the manufacturer) assigned 119 children with ASD and insomnia to either PedPRM (n = 58) or placebo (n = 61). PedPRM outperformed placebo: 68.9% of patients taking the medication had improved sleep outcomes vs only 39.3% of those assigned to placebo (p = 0.001).

Now a new article has been published to determine whether PedPRM maintains its effectiveness over the long term. A total of 95 patients entered this open-label phase, and 84% (n = 80) completed the phase. The average age of the patients was 9 years, and 75% were male. Youths previously randomized to placebo were switched to PedPRM and titrated to a maximum dose of 10 mg/day. Average dose was 8.3 mg for adolescents and 5.6 mg for younger children.

RESULTS

After 37 weeks, children originally randomized to and maintained on PedPRM showed sustained improvements: shorter sleep latency, greater length of sleep, fewer awakenings, and better sleep quality. In addition, those who previously received placebo showed improvement in sleep length and onset after switching to PedPRM. Caregivers' quality of life improved as well, with 49% of caregivers experiencing an improvement on the quality-of-life scale used in the study.

The most common side effect of PedPRM was daytime fatigue, which occurred in 18% of the patients. There were no serious adverse events attributed to the medication, including aggression.

THE CARLAT TAKE

This industry-funded study reports compelling results, which begs us to presume bias despite what appears to be sound methodology. It would be helpful to see a head-to-head study vs over-the-counter melatonin, which is cheaper albeit with more pill-to-pill variability. A more recent study from the same group in 2020 again reported efficacy of prolonged-release melatonin in children with ASD without significant impacts on growth and pubertal development (Malow BA et al, *J Am Acad Child Adolesc Psychiatry* 2020;S0890-8567(20)30034-4).

PRACTICE IMPLICATIONS

Despite the possible industry bias, PedPRM may be a viable treatment option for children with autism and insomnia. However, first-line treatment is still a comprehensive sleep hygiene approach including attention to sensory issues, daily exercise, and psychotherapy, all of which might be effective for insomnia in this population.

Rapid-Onset Gender Dysphoria in Adolescents and Young Adults

REVIEW OF: Littman L. Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria. *PLoS One*. 2018 Aug 16;13(8):e0202330.

STUDY TYPE: Cross-sectional study

Rapid-onset gender dysphoria (ROGD) is a newly coined but non-standardized characterization of gender dysphoria (GD). In this conceptualization, GD begins abruptly during or after puberty in adolescents or young adults (AYAs) with no prior symptoms of GD. Clusters of GD outbreaks have been noted by parents. These outbreaks have occurred in preexisting friend groups in which members became GD or identified as transgender. ROGD is often preceded by an immersion in social media.

Littman studied this phenomenon further. She placed a link to a 90-question survey, consisting of multiple-choice, Likert-type, and open-ended questions, on three websites where parents had reported ROGD. These websites were all notable in that they questioned the medicalization of gender-atypical youth. Data were collected anonymously via SurveyMonkey.

RESULTS

Overall, 256 parents completed questionnaires meeting study criteria. The sample of AYAs was predominantly white, academically gifted, and female sex at birth (82.8%) with a mean age of 16.4 years. Data collected included:

- Many AYAs (62.5%) were diagnosed with at least 1 mental health disorder prior to the onset of GD. Anxiety (63.4%) and depression (58.8%) were the most common. Nearly half of the group had engaged in self-harm.
- Several had experienced a family stressor (44.2%) or sex-/gender-related trauma (30%) prior to the onset of GD.
- 30% of AYAs were not willing to work on their mental health needs before seeking gender treatment.
- For parents who knew the content of their child's GD evaluation, alarmingly, 71.6% reported that the clinician did not explore issues of mental health, previous trauma, or alternative contributors to GD before continuing. 70.0% reported the clinician did not request any medical records.

THE CARLAT TAKE

It is encouraging that individuals who previously might have been underdiagnosed and undertreated are now gaining visibility. It can take tremendous courage to come out as transgender. Still, this study is controversial; *PLoS One* even engaged in a year-long second peer review period prior to this publication. These findings are important to take in context, including the potential for bias in the sampling of parent views, not teens, and specific

websites that carry a cause, as well as the usual caveat that such data cannot be seen as causative per se. This study had quite a few responses that questioned the parent-only interviews and prompted a re-publication in 2019 emphasizing the observational nature of the study (Littman L, *PLoS One* 2019;14(3):e0214157). Littman states that the study had no comparison group and wasn't meant to test a hypothesis but to generate possible hypotheses regarding gender dysphoria in AYAs.

PRACTICE IMPLICATIONS

As clinicians, we need to identify trauma and psychopathology, and we need to manage those difficulties before addressing the AYA's decision regarding sex reassignment or gender transition. Online content and friend groups may influence susceptible AYAs to believe that other psychological distress should be understood as GD. Some AYAs are engaged in online interactions where they are coached in what to say to clinicians, perhaps misrepresenting symptoms, in order to obtain their desired treatment. As a result, it is vital to gather information from collateral informants, including parents, pediatricians, and therapists, and to consider the role of such things as peer interactions, media influences, abuse, family dynamics, and psychodynamic processes.

We would do well to encourage AYAs and parents to allow time for the process to unfold. It may then become clearer whether the symptoms are stable versus an expression of other clinical distress.

Effects of *13 Reasons Why* on Teens

REVIEW OF: Bridge JA, Greenhouse JB, Ruch D, et al. Association between the release of Netflix's *13 Reasons Why* and suicide rates in the United States: An interrupted time series analysis. *J Am Acad Child Adolesc Psychiatry.* 2020 Feb;59(2):236–243.

STUDY TYPE: Cross-sectional study

Netflix's *13 Reasons Why* (*13RW*) continues to generate controversy that it may do more harm than good amid the backdrop of an already increasing teen suicide rate. In previous research updates we reported an increased suicide rate in 10- to 19-year-old females during the 3 months following the show's 2017 premiere (Niederkrotenthaler T et al, *JAMA Psychiatry* 2019;76(9):933–940). Let's look at a second, similarly designed study.

Investigators examined CDC-collected suicide and homicide data before and after the show's release in April 2017. Data were assessed across 5 years (2013–2017) and these age groups: 10–17 years, 18–29 years, and 30–64 years.

RESULTS

Among the show's target audience (ages 10–17), suicide counts were 28.9% higher than expected in the first month following the series premiere. No excess suicide mortality was found in other age groups or in the control outcome, homicide counts. Overall, there were an additional 195 suicide deaths among 10- to 17-year-olds in the 9 months following the premiere. Suicides beyond expected rates were higher in boys than in girls. (Of note, season 1 depicts a male adolescent character making a serious suicide attempt by firearm.) Further, the authors used data showing suicide completion: Adolescent girls are 3 times more likely to attempt suicide than boys, but boys are 4 times more likely to complete suicide.

THE CARLAT TAKE

We now have two epidemiological studies that found associations between the release of *13RW* and increased youth suicides: the 2019 *JAMA Psychiatry* study finding a higher rate in girls, this study finding a higher rate in boys. Each study supports potential suicide contagion by media, at least for season 1, based on timing and age specificity. Netflix has since taken measures to try to reduce risk such as adding content warnings, removing the season 1 suicide scene, and publishing an online toolkit for clinicians, parents, youth, educators, and media professionals (www.13reasonswhytoolkit.org). The toolkit summarizes research outcomes from *13RW,* counsels that at-risk youth should not watch the series, and cautions against teen binge-watching. It also recommends that if teens watch the show, they should do so with a parent or trusted adult and engage in discussions around viewing risk and how to recognize and seek help for negative reactions, if they occur. This is crucial given the recent release of the series' fourth and final season.

PRACTICE IMPLICATIONS

Based on this growing research, it seems apparent that *13RW* may be particularly problematic for at-risk youths. As mental health providers, we need to be aware of this association and provide psychoeducation to youth and families. Our role includes urging parental engagement and advocating for treatment for at-risk youth, while admonishing the media to value life over profits. Mental health provider criticisms about the show's content and associated risk led to Netflix's aforementioned changes, demonstrating the impact of our collective voices. The situation warrants continued surveillance on suicide rates in association with viewing the series, particularly as a fourth season was released in June 2020.

Simvastatin as Adjunctive Therapy for Irritability in Autism

REVIEW OF: Moazen-Zadeh E, Shirzad F, Karkhaneh-Yousefi MA, et al. Simvastatin as an adjunctive therapy to risperidone in treatment of autism: A randomized, double-blind, placebo-controlled clinical trial. *J Child Adolesc Psychopharmacol*. 2018 Feb;28(1):82–89.

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

Disorders of lipid metabolism—specifically inefficient metabolism of lipids—have been implicated as part of the metabolic complexity in children with autism spectrum disorder. Research points to the neuroprotective effects of simvastatin over other statins, due to its greater ability to cross the blood-brain barrier. But does that neuroprotection translate to differences in behavior? This trial compared simvastatin to placebo as adjunctive treatment to risperidone for irritability in children meeting criteria for DSM-IV-TR autistic disorder (AD).

All participants scored ≥ 12 on the Aberrant Behavior Checklist-Community (ABC-C) irritability subscale, and therefore met criteria for treatment of irritability with medications. The ABC-C scale rates children on 58 items arranged in five behavioral abnormality subscales. In total, 66 children ages 4–12 years completed the trial and were randomized to receive risperidone and either simvastatin or placebo. Risperidone target dose was 1 mg/day if < 20 kg and 2 mg/day if ≥ 20 kg. Simvastatin was started concurrently with risperidone and was dosed at 20 mg/day for children < 10 years old and 40 mg/day if ≥ 10 years old. The ABC-C rating scale was assessed at baseline, week 5, and week 10.

RESULTS

The primary outcome was change in the ABC-C irritability subscale, which showed a significant difference in favor of the simvastatin arm at week 10 (−3.45; p = 0.001). Secondary outcomes were the other four subscales, for which there was a significant improvement in the simvastatin group over placebo only in the hyperactivity/noncompliance subscale (−4.27; p = 0.001).

The other subscales that represent the core deficits of AD (lethargy/social withdrawal, stereotypic behavior, and inappropriate speech) showed no significant differences. There was also no significant difference in any adverse events between the groups. The more common side effects across both groups were increased appetite (25.8%), myalgia (13.6%), nausea (12.1%), and headache (12.1%).

THE CARLAT TAKE

The results of this study are promising, but it is only the first of its kind to evaluate simvastatin treatment in this clinical setting. Anti-inflammatory treatments are showing promise in a wide range of psychiatric illnesses, but the core symptoms of autism remain difficult to treat with any type of therapy.

PRACTICE IMPLICATIONS

Since long-term benefits or adverse effects have not been established, it's too early to recommend using simvastatin as a treatment of autism. As in studies of anti-inflammatory interventions, behavioral symptoms may be improved, but the core symptoms of autism remain unchanged.

Azithromycin for Acute-Onset Obsessive-Compulsive Disorder in Children

REVIEW OF: Murphy TK, Brennan EM, Johnco C, et al. A double-blind randomized placebo-controlled pilot study of azithromycin in youth with acute-onset obsessive-compulsive disorder. *J Child Adolesc Psychopharmacol.* 2017 Sep;27(7):640–651.

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

Pediatric acute-onset neuropsychiatric syndrome (PANS) and pediatric autoimmune neuropsychiatric syndrome associated with streptococcus (PANDAS) have been the subject of many debates in the field. From obsessions, compulsions, and tics, to personality changes and oppositional behavior, the symptoms of PANS are wide ranging. PANDAS is considered a subset of PANS that is temporally associated with a Group A streptococcal (GAS) infection.

Due to the link to an infectious cause, antibiotics are being assessed as a treatment for PANS. This study specifically evaluated the tolerability and efficacy of azithromycin in treating children with acute onset of OCD who met criteria for PANS.

Conducted with 31 children ages 4–14, the study compared treatment with azithromycin (10 mg/kg, up to 500 mg per day) to placebo for children with an acute onset of moderate or worse OCD symptoms and neuropsychiatric symptoms. The primary outcomes were changes in the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), and in the Clinical Global Impression—Severity (CGI-S) scale. Several secondary outcomes were measured, including other scales for tic severity, affective lability, and anxiety. Outcome measurements were taken at baseline and then weekly for 4 weeks over the study period.

RESULTS

The results of the trial were split. The azithromycin group had a significantly greater reduction in OCD severity as measured by the CGI-S ($p = 0.003$) at week 4, but there was no significant difference between the treatment and control groups in the CY-BOCS scores ($p = 0.203$). Interestingly, the children in the azithromycin group with greater tic severity at baseline showed the most improvement in the CGI-S. For the secondary outcome measures, the only significant effect was a reduction in the Clinical Global Impression—Improvement Mood subscale ($p = 0.006$) in the azithromycin group.

As for side effects, the azithromycin group had significantly more loose stools (53% of treatment group vs 7% of placebo group), and the placebo group reported more constipation (36% of placebo group vs 0% of treatment group). Electrocardiograms were monitored at baseline and at week 4, showing a significant increase in the QTc ($p = 0.007$) for children in the azithromycin group. Four participants in the azithromycin group had a borderline QTc of 440–460 at week 4 versus 1 participant in the placebo group.

THE CARLAT TAKE

This study, along with other past trials of antibiotics for PANS, gives us mixed results. The authors postulate that the CY-BOCS may not have been the best rating tool for the younger children in this trial, leading to the less robust results compared to the CGI-S outcome. Better response to antibiotic treatment was mediated by baseline tic severity, which will need further exploration.

PRACTICE IMPLICATIONS

This small study is best viewed as a pilot that may lead to larger trials in the future. If you consider using azithromycin for acute-onset OCD, weigh this against the potential for promoting antibiotic resistance and for severe potential side effects such as pseudomembranous colitis, and if you proceed with treatment, you may want to obtain baseline and follow-up electrocardiograms to watch for QTc changes.

Engage Those Infants: Maternal Interaction and Autism

REVIEW OF: Schwichtenberg AJ, Kellerman AM, Young GS, Miller M, Ozonoff S. Mothers of children with autism spectrum disorders: Play behaviors with infant siblings and social responsiveness. *Autism*. 2019 May;23(4):821–833.

STUDY TYPE: Prospective cohort study

Mother-infant interactions are a cornerstone of early development, supporting social and language development of children with or without autism spectrum disorder (ASD). Research on the impact of maternal behaviors on these interactions offers helpful guidance in clinical work with infants with ASD.

This study looked at the interactions between mothers and infants in families where at least one other child in the family had ASD. These infants are considered to have high risk for ASD. It was a prospective study, having partners rate the mothers using a well-standardized instrument, the Social Responsiveness Scale (SRS), and having trained coders rate videotaped interactions of mothers with the infant. The control group consisted of mothers and infants with no family history of ASD. These control infants are considered to be at low risk for having ASD.

The SRS differentiates well between typically developing (TD), at-risk, and ASD populations. And for the video measure, maternal social behavior in context (during play) was assessed by looking at face, vocalization, and positive affect. All of the infants were assessed using a common autism instrument, the Autism Diagnostic Observation Scale (ADOS), at 36 months of age and classified as ASD, TD, or non-TD.

RESULTS

In both the high- and low-risk infants, mothers had similar responsiveness, not significantly different ($p = 0.40$), both falling within normal range of reciprocal social behavior (t-scores < 60). These findings held at 6, 9, and 12 months of age. Mothers in the high-risk group used slightly fewer responses than the low-risk group at 9 and 12 months, but these differences were neither statistically nor clinically significant—although in both groups, mothers with boys and mothers from higher-income families tended to talk more to their babies. On the ADOS, all the infants increased their frequency of social behavior responses to their mothers over time, which was good news.

And here's the key finding: In both groups, when mothers had positive emotional tone and tried to find more ways to connect with their children, the infants also had more positive emotions, vocalized more, looked at their mothers more, responded more, and very importantly, initiated more interactions. This pattern was most consistent when infants were 12 months of age.

THE CARLAT TAKE

This study has several clinically relevant findings. The severity of an infant's difficulties did not dissuade the mother's efforts to communicate, infants generally improved with time, and mothers' positive affect and efforts to engage and interact were associated with improved social communication in their infants no matter the severity of the condition.

PRACTICE IMPLICATIONS

These findings underline the importance of encouraging mothers to persist in attempting to engage infants with autism and related challenges. All infants need positive, face-to-face interactions with their mothers—their efforts are likely to bear fruit.

Heart Rate Changes Linked to Emotional Dysregulation

REVIEW OF: Deutz MHF, Woltering S, Vossen HGM, et al. Underlying psychophysiology of dysregulation: Resting heart rate and heart rate reactivity in relation to childhood dysregulation. *J Am Acad Child Adolesc Psychiatry*. 2019 Jun;58(6):589–599.

STUDY TYPE: Cross-sectional study

Can we use heart rate to assess and track psychopathology? Child psychiatrists associate lower resting heart rate (HR-rest) and heart rate reactivity (HR-reactivity) with externalizing behaviors such as disruptive behaviors and aggression ("under-arousal") and elevations with internalizing problems such as anxiety ("over-arousal"). The transdiagnostic approach of the NIH Research Diagnostic Criteria (RDoC) offers research linking heart rate with emotional dysregulation. This study bridges these ideas to clinical practice.

In this Canadian study, the authors explored how HR-rest and HR-reactivity relate to dysregulation: 182 clinically referred children (75.8% boys) ages 8–12 years underwent heart rate monitoring at rest and during a computerized go/no-go task. 24.2% of children were on psychotropic medications, mostly stimulants. Dysregulation was measured from subscale scores on the clinically ubiquitous Child Behavior Checklist, specifically the Dysregulation Profile (CBCL-DP), which itself is intricately related to the CBCL Anxious/Depressed, Aggression, and Attention Problems subscales.

RESULTS

These researchers found that higher resting heart rate correlated to higher scores on the dysregulation and aggression subscales, but not to anxiety/depression or attention problems. Heart rate reactivity was not correlated to any of these scales. Although males were more likely to have elevated dysregulation and aggression scores, there was no link between gender and resting heart rate and reactivity.

The researchers also used a person-centered approach, in which subgroups with similar profiles were identified. This approach found that patients tended to sort into three symptom-profile groups: normative (n = 92), predominantly aggressive (n = 69), and dysregulated (n = 14). The dysregulated group had the highest scores (more symptomatic) for anxiety/depression, aggression, and attention problems. When the researchers mapped heart rate parameters onto these profiles, they found that youth in the predominantly aggressive group had higher HR-rest. In contrast, youth in the dysregulated group did not have elevated HR-rest but did have elevated HR-reactivity.

THE CARLAT TAKE

Given the variability among people and confounding variables such as past trauma, it is difficult to apply these findings directly to individual patients. Still, with most of the heart rate literature

focused on callous unemotional traits, this study reinforces the importance of looking beyond the categorical descriptors of the DSM and toward a more biologically informed approach.

PRACTICE IMPLICATIONS

One day, perhaps we will be able to use simple physiological measures to help differentiate categories of diagnoses as well as alert us to patients who may have more propensity for aggression. In the future we could be integrating heart rate data into the biopsychosocial model of formulating our patients' diagnoses.

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EFFECTS OF CANNABIS

Is There a Case for Cannabis in the Treatment of Pain?

REVIEW OF: De Vita MJ, Moskal D, Maisto SA, Ansell EB. Association of cannabinoid administration with experimental pain in healthy adults: A systematic review and meta-analysis. *JAMA Psychiatry*. 2018 Nov 1;75(11):1118–1127.

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

In the midst of the opioid epidemic, researchers are looking for new ways to treat acute and chronic pain. Interestingly, states that have legalized medical marijuana have fewer opioid prescriptions but no clear reduction in mortality over time (Shover CL et al, *Proc Natl Acad Sci USA* 2019;116(26):12624–12626). Opioid users who smoke marijuana are less likely to drop out of maintenance treatment programs, while benzodiazepine use predicts worse outcomes in this population (Powell D et al, *J Health Econ* 2018;58:29–42; Socías ME et al, *Addiction* 2018;113(12):2250–2258). Could marijuana have direct benefits in the treatment of pain?

To address this question, researchers analyzed 18 placebo-controlled trials of cannabinoids as a treatment for mechanically induced pain in otherwise healthy subjects. For this study of acute pain threshold and tolerance, those with chronic pain were excluded. A total of 442 participants were included. Mean age was 27 with equal numbers of men and women. Two-thirds of the studies involved synthetic tetrahydrocannabinol (THC), the cannabinoid responsible for the "high" in marijuana, or controlled prescription-only analogues of THC, such as dronabinol (C-III) and nabilone (C-II). The other third used plant-based cannabis. The majority (89%) used a crossover design where subjects received both cannabinoids and placebo with a washout period between the doses.

RESULTS

Compared to placebo, cannabinoid administration was associated with a small increase in pain threshold and a small-to-medium increase in pain tolerance. However, it did not change overall pain intensity. Cannabinoids made people better able to withstand a greater pain burden, but only to a certain point. They also made the experience of pain less unpleasant (small-to-medium effect size), and this effect was strongest with plant-based cannabis. *Unpleasantness* is important because it may influence the progression from chronic pain to depression. No significant association was found between cannabinoid administration and hypersensitivity to pain. Gender did not significantly impact any of the outcomes.

THE CARLAT TAKE

The biggest limitation to the study is the lack of blinding as most subjects could probably guess whether or not they were "high." Furthermore, it is unclear how well mechanically induced pain approximates real, chronic pain. Lastly, cannabidiol (CBD) was not included in the study. CBD is often praised by enthusiasts for its properties and was recently approved as

prescription Epidiolex for intractable seizures. Unlike THC, CBD produces no "high" and may have added antipsychotic effects.

PRACTICE IMPLICATIONS

Despite the widespread use of THC for a variety of ailments, little data exist to support its many claimed benefits. Additionally, the risks, including psychosis, are too large to recommend it to patients as an alternative analgesic.

Is Cannabis Bad for Cognition?

REVIEW OF: Scott JC, Slomiak ST, Jones JD, et al. Association of cannabis with cognitive functioning in adolescents and young adults: A systematic review and meta-analysis. *JAMA Psychiatry*. 2018 Jun 1;75(6):585–595.

STUDY TYPE: Meta-analysis of observational studies

Our patients typically tell us that, according to the internet, weed is perfectly safe and does not affect their ability to think or function. At least 30 states and the District of Columbia have laws legalizing cannabis, supporting the notion that people have begun to think of marijuana as relatively harmless. Rates of marijuana use in young adults are rising (Hasin DS, *Neuropsychopharmacology* 2018;43(1):195–212). Moreover, a recent study reported that cannabidiol (CBD), a "non-psychoactive" component of marijuana, may reduce psychotic symptoms (Arain M et al, *Neuropsychiatr Dis Treat* 2013;9:449–461).

Given that the brain continues to develop into a person's mid-20s, how dangerous is marijuana use in adolescence and young adulthood? And what do we tell our young patients who are regular users? A new meta-analysis attempts to answer part of that question as it relates to the impact of cannabis use on cognitive function in adolescents and young adults.

RESULTS

The meta-analysis assessed cognitive effects in young adults and adolescents whose primary clinical problem was cannabis use. The analysis included 69 studies of 2,152 regular cannabis users and 6,575 people with minimal use of cannabis. After combining the results from all of these studies, the authors concluded that cannabis does have a mild negative correlation with various aspects of cognition. Specifically, studies showed that use of the drug is negatively associated with executive functioning, speed of information processing, delayed memory, working memory, and attention. But in the aggregate, effect sizes range from −0.21 to −0.33, indicating minimal impact on cognition. Verbal language, visuospatial functioning, and motor functioning were relatively spared. Studies that required at least 72 hours of cannabis abstinence before testing reported no significant effect on cognitive function.

THE CARLAT TAKE

At first glance, these results may seem reassuring. Cognition was minimally impacted, and the effects did not extend beyond active use. However, many of the studies were small, measurement of cannabis use and potency varied, and significant publication bias was noted. Also, the meta-analysis focused solely on neurocognitive effects and ignored other clinically pertinent outcomes.

PRACTICE IMPLICATIONS

Another study looking at 3,826 seventh graders found neurotoxic effects of cannabis on memory and inhibitory control (Morin JG et al, *Am J Psychiatry* 2019;176(2):98–106). Moreover, we

have ample evidence that marijuana use is associated with poor academic and social function, that the tetrahydrocannabinol (THC) component of marijuana is associated with an overall doubling of psychosis risk in youth, and that this increased psychosis risk is dose dependent. So, however you interpret this analysis, THC is clearly not off the hook.

Effects of Cannabis Use on Smoking Cessation

REVIEW OF: Weinberger AH, Platt J, Copeland J, Goodwin RD. Is cannabis use associated with increased risk of cigarette smoking initiation, persistence, and relapse? Longitudinal data from a representative sample of US adults. *J Clin Psychiatry*. 2018 Mar/Apr;79(2):17m11522.

STUDY TYPE: Prospective cohort study

When counseling your patients to quit smoking, you may also want to consider asking them about their past marijuana use. Results from a recent study suggest that there may be a correlation between cannabis and tobacco smoking.

Analysis of longitudinal data of almost 35,000 adult study participants, gathered during two "waves" (2001–2002 and 2004–2005) of the US National Epidemiologic Survey on Alcohol and Related Conditions, found that past cannabis use was associated with an increase in cigarette smoking initiation, persistence, and relapse.

RESULTS

In the study, cannabis use was associated with a 2.9-fold and 4.4-fold increased risk of new cigarette use on either a daily or non-daily basis, respectively, compared to those without exposure to cannabis in the previous year. Among former smokers, past cannabis use was associated with increased relapse rate: 4.18 times more ex-smokers returned to daily smoking and 5.24 times more ex-smokers returned to smoking on a non-daily basis compared to those who had not used cannabinoids in the past 12 months.

Past cannabis use was also associated with difficulty quitting tobacco: Among daily cigarette smokers, past cannabinoid use was associated with decreased odds of smoking cessation by 43% compared with non-cannabis users. Even when demographics and a history of psychiatric disorders were taken into consideration, associations of cannabis use remained significant for the initiation of daily smoking among prior nonsmokers; relapsing to a daily use pattern among former ex-smokers; and difficulty quitting among daily smokers.

THE CARLAT TAKE

This study provides some interesting data showing that people who use cannabis are more likely to start smoking tobacco. Cannabis use was also associated in more difficulty quitting smoking and more likely return to smoking for ex-smokers.

PRACTICE IMPLICATIONS

Tell your patients that if they've used cannabis in the past, quitting tobacco may be more of a challenge than usual. This will set the stage for a discussion of the various smoking cessation agents available, and it might increase your patients' motivation to accept treatment.

Can Computerized Interventions Reduce Cannabis Use?

REVIEW OF: Olmos A, Tirado-Muñoz J, Farré M, Torrens M. The efficacy of computerized interventions to reduce cannabis use: A systematic review and meta-analysis. *Addict Behav*. 2018 Apr;79:52–60.

STUDY TYPE: Systematic review and meta-analysis

As medical and recreational marijuana become legalized in more states, more emphasis is being placed on treatment of those with cannabis use disorders. But with our clinics already at capacity, how can we find the most efficient way of providing therapy? Computerized interventions are already available for nicotine and alcohol use, but what about for cannabis?

This meta-analysis included nine randomized controlled trials evaluating the efficacy of web-based treatments designed to reduce the frequency of cannabis use. The primary outcome was reduction in cannabis use, and the secondary outcome was reduction in other substance use. A total of 2,963 participants were included in the studies—1,724 in the intervention groups and 1,239 in the control groups. All the interventions were computer based, and the control conditions varied from study to study—from no intervention to psychoeducation.

RESULTS

So, how did the computer-based interventions fare? Those who participated in the computerized interventions had a significant reduction in cannabis use when compared to the control groups (SMD: −0.19; 95% CI: −0.26 to −0.11), with no significant heterogeneity among the studies (I2 = 0%). Only three of the nine trials collected data on the secondary outcome of reduction in other substance use, but there was again a significant reduction in those studies compared to the control condition (SMD: −0.27; 95% CI: −0.46 to −0.08), with low heterogeneity (I2 = 26%). Several sub-group analyses were performed, but the only significant result was in the number of sessions—interventions with ≥ 5 sessions performed better than those with < 5 sessions (SMD: −0.21; 95% CI −0.29 to −0.12).

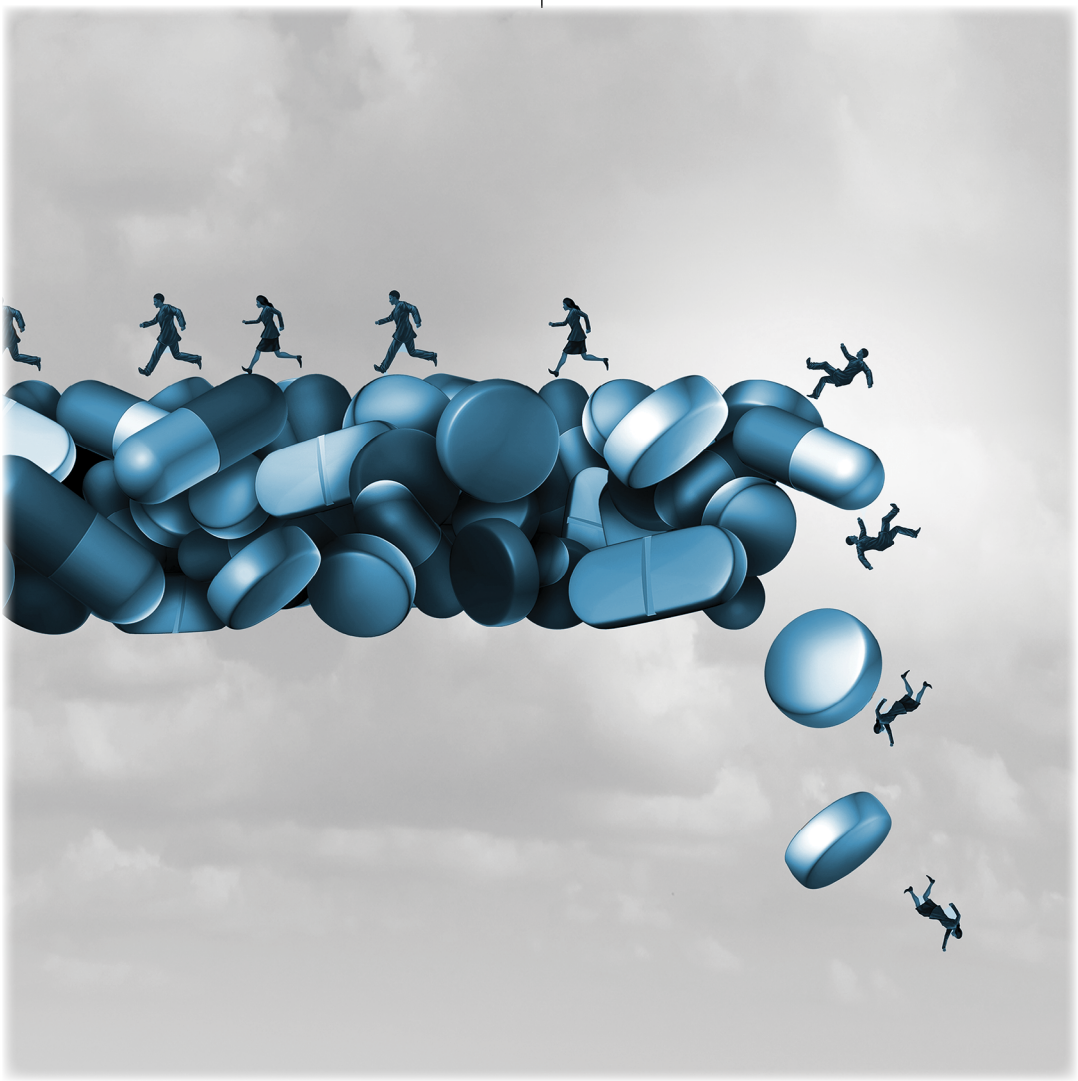
THE CARLAT TAKE

With more people seeking treatment for substance use disorders, we need more options to give them effective care. This analysis shows that computerized interventions can work to help patients reduce cannabis use, along with other substance use. But the verdict is still out on web-based interventions. A more recent Swedish study showed no effect on cannabis use for a web-based treatment program with therapist guidance versus a waitlist control group (Sinadinovic K et al, *Addict Sci Clin Pract* 2020;15(1):9).

PRACTICE IMPLICATIONS

When considering computer-based interventions, it's also important to note what the study doesn't show: There was no comparison to a live therapist intervention. Sessions with an in-person therapist are still recommended, but when that's not available, offering a computer-based intervention may be a good option.

OPIOID USE DISORDER



Oral vs Extended-Release Naltrexone for Opioid Use Disorder

REVIEW OF: Sullivan M, Bisaga A, Pavlicova M, et al. Long-acting injectable naltrexone induction: A randomized trial of outpatient opioid detoxification with naltrexone versus buprenorphine. *Am J Psychiatry*. 2017 May 1;174(5):459–467.

STUDY TYPE: Randomized, open-label trial

Extended-release (XR) naltrexone (Vivitrol) is FDA approved for opioid use disorder (OUD) and has shown efficacy in several trials. It works best for patients who have already successfully detoxed from opioids and who are highly motivated to abstain. But what about oral naltrexone? While it is effective for alcohol use disorder, studies for OUD have shown limited utility. The reason is obvious—patients who are experiencing high cravings can simply skip a dose of the naltrexone pill in order to achieve an opioid high, whereas the XR formulation forces a long delay, during which patients might reconsider their decision to use. Oddly enough, though, no study has been done comparing oral to XR naltrexone, until now.

Researchers randomized 60 adults with OUD (DSM-IV opioid dependence) to either oral or XR naltrexone. The study was a 6-month open-label trial, excluding people with unstable medical or psychiatric disorders, physical dependence on alcohol or sedative-hypnotics, treatment with opioids or psychotropic medications, and history of opioid overdose in the prior 3 years. The primary outcome measure was retention in treatment.

The study didn't quite mimic real-world treatment, as study participants in both groups were asked to attend behavioral therapy sessions twice weekly, and those randomized to oral naltrexone either had to have a responsible adult as an involved medication monitor at home or go to the clinic 3 times weekly to have it administered. Vouchers were used to reinforce attendance. Participants were mostly white (63.3%), male (83.3%), and in their late 30s (mean age 39.5, SD = 11.1).

RESULTS

At the end of 6 months, the retention rate in the XR naltrexone group was significantly higher than the oral naltrexone group (57.1% and 28.1%, respectively). There was no significant difference in the percentage of opioid-positive urine tests between the groups, though that was not the primary outcome, and missed urine tests were not counted as positive. Overall, the treatment was well tolerated, and most adverse events reflected opioid withdrawal and gradually improved.

THE CARLAT TAKE

The results confirm that XR naltrexone is more effective than oral naltrexone for OUD, even when rigorous strategies are used to ensure adherence with the oral formulation. However, oral naltrexone still has its place in treating alcohol use disorder.

PRACTICE IMPLICATIONS

When treating OUD, use oral naltrexone to test tolerance and sensitivity before transitioning to XR naltrexone. We still recommend reserving XR naltrexone for patients who cannot be on buprenorphine or methadone—medications for which we have even more robust data.

Does Extended-Release Naltrexone Worsen Psychiatric Symptoms?

REVIEW OF: Latif ZEH, Benth JŠ, Solli KK, et al. Anxiety, depression, and insomnia among adults with opioid dependence treated with extended-release naltrexone vs buprenorphine-naloxone: A randomized clinical trial and follow-up study. *JAMA Psychiatry*. 2019 Feb 1;76(2):127–134.

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

Extended-release (XR) naltrexone (Vivitrol) is an injectable version of naltrexone that lasts for 4 weeks and is FDA approved for opioid use disorder (OUD). Although effective, there is some concern that XR naltrexone may cause or worsen psychiatric symptoms because of its opioid blockade. Prior research has been mixed on this issue, and studies have been limited by not comparing XR naltrexone with an active control medication. This new study is the first to directly compare XR naltrexone with buprenorphine in terms of their effects on anxiety, depression, and insomnia.

The outpatient Norwegian study contained two components: a 12-week randomized controlled trial (RCT) and a 36-week follow-up study. In the RCT, 159 participants diagnosed with OUD were randomly assigned, but not blinded, to treatment with flexibly dosed daily buprenorphine/naloxone or monthly injections of XR naltrexone. At the end of 12 weeks, participants could choose treatment with buprenorphine/naloxone or XR naltrexone, and they were then followed for an additional 36 weeks.

Outcome measures included symptoms of anxiety, depression, and insomnia, as assessed by the Hopkins Symptom Checklist and the Insomnia Severity Index. These scales measure symptoms, but they are not diagnostic, and there was no mention of the prevalence and distribution of mood, anxiety, and sleep disorders between the groups.

RESULTS

The results showed that the two treatments were comparable. During the RCT component of this study, XR naltrexone was not significantly different than buprenorphine in terms of anxiety and depression symptoms, and it was slightly better than buprenorphine regarding insomnia symptoms (effect size −0.32; $p = 0.008$). There were no significant differences between groups in the follow-up component. Encouragingly, throughout all components of the study, anxiety, depression, and insomnia symptoms improved over time.

THE CARLAT TAKE

It appears that XR naltrexone does not worsen symptoms of anxiety, depression, or insomnia in people with OUD and even improved throughout the study. Strengths of the study include long follow-up time and real-world design in the open-label extension period.

PRACTICE IMPLICATIONS

When we are deciding between XR naltrexone and buprenorphine/naloxone for OUD, the primary factors should be efficacy and patient access and preference. Both medications are effective in treating OUD and according to this research would not exacerbate psychiatric symptoms.

Switching From Buprenorphine to Extended-Release Naltrexone: Does It Work?

REVIEW OF: Solli KK, Latif ZEH, Opheim A, et al. Effectiveness, safety and feasibility of extended-release naltrexone for opioid dependence: A 9-month follow-up to a 3-month randomized trial. *Addiction*. 2018 Oct;113(10):1840–1849.

STUDY TYPE: Prospective cohort study

Extended-release (XR) naltrexone (Vivitrol) has had some good data, yet getting patients on it remains a challenge because an opioid-free period is required before starting it. Understandably, practitioners get nervous when patients stabilized on buprenorphine ask to be transitioned to XR naltrexone. But if needed, can this switch be made safely and effectively?

To answer this question, researchers in Norway conducted an open-label continuation of a 3-month controlled trial (see "Does Extended-Release Naltrexone Worsen Psychiatric Symptoms?" on the previous page). In the original study, 159 patients were randomized to up to 24 mg of buprenorphine/naloxone daily or 380 mg of XR naltrexone injection monthly. At the end of 3 months, participants were offered the option of continuing on XR naltrexone, switching from buprenorphine to XR naltrexone, or treatment with buprenorphine at a program outside the study. Of the 122 participants who completed the first phase, 117 chose XR naltrexone, and 5 chose buprenorphine outside of the study. XR naltrexone was not commercially available in Norway, which may account for the large number of people choosing it over buprenorphine.

The switch was carefully made during a detox admission, where XR naltrexone was initiated after a test dose of naloxone and a minimum of 72 hours following any opioid intake (which is a lot shorter than the commonly recommended washout period), and adjunctive medications were available to help relieve withdrawal symptoms. Participants were followed for another 9 months, and the primary outcomes were continuation of treatment and abstinence rates for those who remained on XR naltrexone (n = 54) compared with those who switched to XR naltrexone (n = 63).

Participants were men and women ages 18–60 years with opioid use disorder (DSM-IV opioid dependence) and without alcohol dependence or serious somatic or psychiatric comorbidities. Pregnant and nursing women were excluded. The majority of participants were men (75%), and the mean age was 35.6 years.

RESULTS

Nine months later, there were no significant differences in outcomes between participants who continued XR naltrexone and those who switched to it from buprenorphine. Twenty-eight participants (51.9%) who were originally on XR naltrexone and 30 (47.6%) who newly started on it completed 9

months of follow-up. Complete abstinence from opioids was self-reported by 53.7% of participants continuing XR naltrexone and 44.4% of those newly started. Adverse events were generally related to withdrawal symptoms. Two patients discontinued XR naltrexone due to serious injection site reactions requiring surgery, after which they recovered completely.

THE CARLAT TAKE

The results of the study imply that switching from buprenorphine to XR naltrexone may work as well as starting XR naltrexone from scratch. The study was not perfect—the design was open-label, there was no objective confirmation of abstinence, and the switch was carefully done on an inpatient unit, limiting our confidence that it can be done as safely and effectively in outpatient settings.

PRACTICE IMPLICATIONS

The naturalistic setting of this study makes it similar to clinical practice, and the 50% self-reported abstinence rate is encouraging. Switching from buprenorphine to XR naltrexone can be attempted in select patients, but we recommend approaching switch requests with great caution. We continue to think of XR naltrexone as a second-line option for patients who cannot be on agonist treatment.

More Evidence of Lives Saved by Medications for Opioid Use Disorder

REVIEW OF: **Larochelle MR, Bernson D, Land T, et al. Medication for opioid use disorder after nonfatal opioid overdose and association with mortality: A cohort study. *Ann Intern Med*. 2018 Aug 7;169(3):137–145.**

STUDY TYPE: **Retrospective cohort study**

We are in the middle of an opioid crisis in the US, with many lives lost daily to opioid-related deaths. Pharmacotherapy with methadone, buprenorphine, or naltrexone represents an important tool for clinicians during this crisis. But just how good are these medications in saving lives? A recent retrospective cohort study evaluated the effects of methadone, buprenorphine, and naltrexone on all-cause and opioid-related mortality in the 12 months after an opioid overdose.

This analysis used data from Massachusetts government and hospital records from 2012 to 2014 to identify adults who survived an opioid overdose, then looked at the 12 months after that overdose. If an individual had multiple overdoses during that period, the first overdose was used for the data collection. A total of 17,568 cases were identified. In the 12 months after the index overdose, 11% (2,040) were on methadone for a median of 5 months, 17% (3,022) were on buprenorphine for a median of 4 months, and 6% (1,099) were on naltrexone for a median of 1 month.

RESULTS

All-cause mortality over 12 months was significantly reduced in those receiving methadone (adjusted hazard ratio [AHR] 0.47 [CI 0.32–0.71]) and buprenorphine (AHR 0.63 [CI 0.46–0.87]), but not those on naltrexone (AHR 1.44 [CI 0.84–2.46]). Similarly, opioid-related mortality was significantly decreased for patients on methadone (AHR 0.41 [CI 0.24–0.70]) and buprenorphine (AHR 0.62 [CI 0.41–0.92]), but not those on naltrexone (AHR 1.42 [CI 0.73–2.79]).

THE CARLAT TAKE

This study represents real-world population data linking treatment with methadone or buprenorphine after an opioid overdose to a decrease in all-cause and opioid-related mortality in the following year. Remember, these results were tallied over a 1-year period even though most patients discontinued treatment within 6 months. Naltrexone failed to show a significant difference in mortality, perhaps because most people stopped it after 1 month, or because the researchers could not distinguish between the oral and extended-release injectable formulations (unlike oral naltrexone, extended-release naltrexone has shown treatment efficacy).

PRACTICE IMPLICATIONS

Another takeaway from this article is that only about a third of those who had an opioid overdose were ever prescribed any form of opioid use disorder pharmacotherapy. More lives could

be saved with medication-assisted treatment. Much work remains to be done to provide better access to life-saving treatment for opioid use disorder.

Guidelines for Switching From Methadone to Buprenorphine

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

STUDY TYPE: Prospective cohort study

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

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

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

RESULTS

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

the guidelines. Most patients stabilized their BNX dose by day 3, with 96% using ≥ 12 mg/day. Overall, 79% (26/33) were still on BNX treatment at day 7 and were considered to have successfully transferred.

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

THE CARLAT TAKE

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

PRACTICE IMPLICATIONS

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

Opioids Not Superior to Other Medicines for Some Chronic Pain

REVIEW OF: Krebs EE, Gravely A, Nugent S, et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: The SPACE randomized clinical trial. *JAMA*. 2018 Mar 6;319(9):872–882.

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

Rising rates of opioid overdose deaths have sounded alarm bells over opioid prescribing practices for chronic pain. Unfortunately, and despite the absence of quality data on risks vs benefits, long-term opioid management has remained a common approach to managing chronic musculoskeletal pain.

This study examined long-term outcomes in chronic pain with opioid vs non-opioid treatment. Researchers conducted a 12-month randomized trial evaluating patients who—despite analgesic use—had moderate to severe chronic back pain or hip/knee osteoarthritic pain. Patients were recruited from Veterans Affairs primary care clinics in Minneapolis, Minnesota between 2013 and 2015.

The study compared opioid and non-opioid therapy. Patients in each group were prescribed multiple medications over three steps. In total, 240 patients were randomized, with a mean age of 58.3 years; females made up 13% of the group.

In the opioid group, the first phase was immediate-release morphine, oxycodone, or hydrocodone/acetaminophen. Second- and third-step options included sustained-action morphine and transdermal fentanyl.

For the non-opioid group, the first stage was acetaminophen or an NSAID. Second- and third-phase choices comprised adjuvants, such as gabapentin or nortriptyline; topical analgesics; and drugs such as duloxetine and tramadol.

Outcomes measured included the impact of pain on daily functioning, rated on the Brief Pain Inventory [BPI] interference scale; pain intensity on the BPI severity scale; and adverse medication-related symptoms. The BPI interference scale records the influence of pain on activities like sleep, walking, relationships, work, and life enjoyment. For both BPI scales, the range is 0–10, with higher scores indicating worsened functioning or higher pain intensity.

RESULTS

Over 12 months, the groups did not significantly differ on pain-related function. The mean BPI interference was 3.4 for the opioid group and 3.3 for the non-opioid group. Unexpectedly, the non-opioid group reported significantly less pain intensity at 12 months, with a BPI severity of 4.0 for the opioid group and 3.5 for the non-opioid group. Adverse medication-related symptoms were significantly more common in the opioid group.

THE CARLAT TAKE

The noteworthy result here is that chronic pain patients on opioids may not be any better off than those taking alternative agents. While psychiatrists are not the primary treaters of musculoskeletal pain, the current opioid crisis has had wide-ranging impact, and there are calls for a multipronged approach.

PRACTICE IMPLICATIONS

Many patients with chronic pain develop opioid dependence after long-term opioid treatment, and we should be ready to share this study's results with our patients and medical colleagues. There are a variety of non-opioid medication treatments that may not only treat chronic pain but have less long-term side effects or risks overall.

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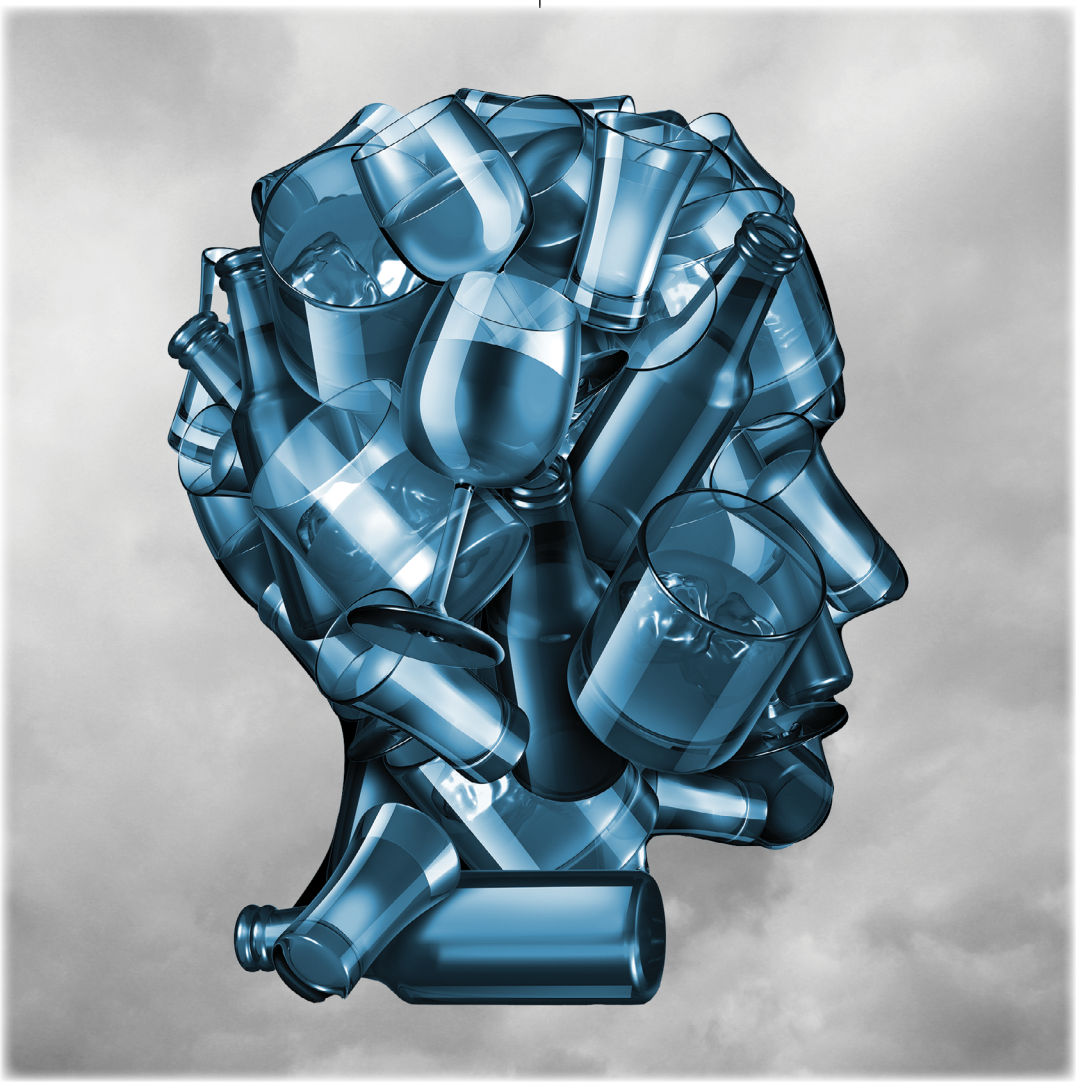
ALCOHOL USE DISORDER



Prazosin for Alcohol Use Disorder

REVIEW OF: Simpson TL, Saxon AJ, Stappenbeck C, et al. Double-blind randomized clinical trial of prazosin for alcohol use disorder. *Am J Psychiatry*. 2018 Dec 1;175(12):1216–1224.

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

Prazosin is often used as a second-line option for a broad array of psychiatric conditions, including anxiety, insomnia, nightmares, and post-traumatic stress disorder (PTSD). It is a high blood pressure medication that also modulates the stress-response system through noradrenergic effects, blocking alpha-1 receptors in the brain. Since stress is a common trigger for excessive drinking, this study set out to test whether prazosin could improve sobriety in alcohol use disorder (AUD).

Eighty subjects with AUD were randomized to receive either prazosin or placebo. Subjects with PTSD were excluded in order to isolate the potential benefits of prazosin for drinking directly. Prazosin was titrated up to a target dosage of 16 mg/day, as tolerated. All subjects were actively drinking at the start of the study, and they reported their daily alcohol consumption and cravings for the previous day through a toll-free interactive voice system during the 12-week study. Assessments were double-blind, and the primary outcomes were number of drinks per week, number of drinking days per week, and number of heavy drinking days per week.

RESULTS

Compared to placebo, those receiving prazosin reported fewer drinks (mean decrease of 8.0 vs 1.5 drinks per week; $p = 0.03$) and fewer heavy drinking days (mean decrease of 0.8 vs 0.3 days per week; $p = 0.01$), though the number of drinking days was no less with prazosin. Drowsiness and edema were the only two side effects associated with prazosin.

THE CARLAT TAKE

This trial gives us some encouraging evidence that prazosin can help people reduce their drinking. We know that for those with AUD, any decrease in the amount someone is drinking can lead to better health outcomes. Other studies have shown limited efficacy of prazosin for AUD, but on post-hoc analysis it may be more helpful for those with higher drinks per week at baseline (Wilcox CE et al, *J Addict Med* 2018;12(5):339–345).

PRACTICE IMPLICATIONS

Given its relatively benign side effect profile and established track record, prazosin can be considered a reasonable second-line option for AUD. For patients with any combination of anxiety, insomnia, nightmares, PTSD, or hypertension, prazosin is an even more appealing option.

The COMBINE Study: A Core Paper in the Treatment of AUD

REVIEW OF: Anton RF, O'Malley SS, Ciraulo DA, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: The COMBINE study: A randomized controlled trial. *JAMA*. 2006 May 3;295(17):2003–2017.

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

Conducted from 2001 to 2004 and published in 2006, the COMBINE study was the largest pharmacotherapy study that assessed the treatment of alcohol use disorder (AUD). Although there were significant data on the use of naltrexone and acamprosate (both had been FDA approved), widespread use had not been adopted for either medication, and extended-release naltrexone was still undergoing its approval process. The prior large NIAAA-funded study of AUD interventions was Project MATCH, which focused exclusively on psychosocial therapies, whereas COMBINE evaluated the effectiveness of naltrexone, acamprosate, and specialty therapy both alone and in combination. By doing so, the authors hoped to shed light on the following questions: 1) Are there synergistic intervention combinations? 2) Is effective treatment of AUD feasible in a primary care setting?

A total of 1,383 recently abstinent subjects across 11 academic sites were randomly assigned to nine groups, and the trial was conducted over 16 weeks. Outcomes included percentage of days abstinent and return to heavy drinking. Combined behavioral intervention (CBI), an amalgamation of the evidence-based therapies used in Project MATCH (cognitive behavioral therapy, 12-step facilitation, and motivational interviewing), was a specialty therapy developed for this study. One group received only CBI (no pills) and the eight pill-taking groups received varying combinations of CBI, acamprosate, naltrexone, and placebo, including a placebo-only group. Those eight groups also received medical management (MM), a brief evaluative and supportive intervention with a health care professional similar to a primary care encounter.

RESULTS

Compared to placebo, naltrexone reduced the percentage of participants who returned to heavy drinking (68.2% vs 71.4%; $p = 0.02$), but not percentage of days abstinent (78.8% vs 77.2%; $p = 0.25$). In contrast, acamprosate did not separate from placebo in any condition or interaction. A more striking result, however, was how poorly the CBI-only group performed in comparison to the pill-taking + MM groups, including in comparison to the placebo groups. For instance, placebo groups produced significantly greater percentage of days abstinent than CBI alone ($p < 0.001$). Although the authors point out a statistically significant interaction between CBI and naltrexone, this is not very convincing, as the data for this interaction included subjects receiving placebo. For those who received actual naltrexone, the CBI + naltrexone group was no better than naltrexone alone.

THE CARLAT TAKE

This core study of AUD treatment is worth looking at again as it has guided our clinical decision-making. Strengths include a large number of participants and treatment sites, which allowed for many comparison arms. This study emphasized primary care settings and not needing specialty referral to access initial medication management for AUD.

PRACTICE IMPLICATIONS

This study demonstrates that evidence-based AUD treatment can be delivered in non-specialty settings, which would expand access tremendously. Although clearly not a panacea, naltrexone performed well in the MM model. Acamprosate did not fare well, and it may perform better when initiated after a longer period of abstinence. This was also a disappointing study for psychotherapy, but the findings aren't enough reason to write it off, and psychosocial interventions in addiction treatment continue to be a recommended part of the treatment plan.

Gabapentin Enacarbil XR Efficacy Less Than Expected for AUD

REVIEW OF: Falk DE, Ryan ML, Fertig JB, et al. Gabapentin enacarbil extended-release for alcohol use disorder: A randomized, double-blind, placebo-controlled, multisite trial assessing efficacy and safety. *Alcohol Clin Exp Res*. 2019 Jan;43(1):158–169.

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

Gabapentin enacarbil extended-release (GE-XR) (Horizant) is an extended-release version of gabapentin. GE-XR is a prodrug, meaning that once ingested it is metabolized into gabapentin. It is currently approved for treatment of postherpetic neuralgia and restless legs syndrome. It differs from the immediate-release (IR) version in dosing (twice a day for the GE-XR, as opposed to 3 times a day) and has less variable blood levels. Several previous studies showed that IR gabapentin may be helpful for reducing withdrawal symptoms and promoting abstinence in alcohol use disorder (AUD) (Anton RF et al, *Am J Psychiatry* 2011;168(7):709–717; Mason BJ et al, *JAMA Intern Med* 2014;174(1):70–77). Since an extended-release version might be easier to prescribe and increase adherence, researchers tested this XR formulation for AUD.

This trial assigned 346 adults with moderate AUD to two groups: the treatment group (n = 173) received GE-XR tablets titrated to 600 mg twice daily, whereas the control group (also n = 173) received identical placebo tablets. Moderate AUD was defined as ingestion of at least 21 standard drinks per week for women and at least 28 standard drinks per week for men (1 standard drink = 0.6 oz of pure alcohol). Participants were not currently using any other substances and were not diagnosed with a major psychiatric disorder. The trial lasted 26 weeks.

RESULTS

The primary outcome was change in the percentage of subjects with no heavy drinking days, defined as 4 or more drinks for women or 5 or more drinks for men per drinking day. There were several secondary outcomes, such as percentage of heavy drinking days, percentage of days abstinent, and others. For the primary outcome and all secondary outcomes, no statistical advantage was seen between the GE-XR group and placebo. Patients taking GE-XR actually did significantly worse than the placebo group in two of the secondary outcomes: average number of DSM-5 AUD criteria (3.4 vs 2.8; p = 0.046) and depressive symptoms on the Beck Depression Inventory-II (6.5 vs 5.2; p = 0.046).

For the safety assessment, patients in the GE-XR group reported significantly more fatigue (25.9%), somnolence (17.6%), and tremor (5.9%) than the placebo group. There were also more patients reporting suicidal ideation in the GE-XR group (7 vs 1, but just below significance level at p = 0.067).

THE CARLAT TAKE

This study had a strong design, adequate sample size, and a basis for success in the previous positive trials of IR gabapentin (Mason BJ et al, *JAMA Intern Med* 2014;174(1):70–77). However, GE-XR didn't show any positive outcomes and even had worse outcomes for AUD and depressive symptoms.

PRACTICE IMPLICATIONS

These negative findings may have potentially been due to the dosing used in this trial or altered bioavailability of the XR prodrug formulation in an AUD population. Similar trials with IR gabapentin used a higher effective dose. Regardless, GE-XR at the dose studied in this trial can't be recommended for treating AUD at this time.

Prevalence of Fetal Alcohol Spectrum Disorder

REVIEW OF: May PA, Chambers CD, Kalberg WO, et al. Prevalence of fetal alcohol spectrum disorders in 4 US communities. *JAMA*. 2018 Feb 6;319(5):474–482.

STUDY TYPE: Cross-sectional study

New evidence suggests that the prevalence of fetal alcohol spectrum disorder is higher than previously documented. In this study, prevalence estimates were derived from 13,146 first-grade children in four US communities between 2010 and 2016.

The study used active-case ascertainment, which the authors assert is a more reliable approach for identifying this cluster of disorders (eg, fetal alcohol syndrome, partial fetal alcohol syndrome, and alcohol-related neurodevelopment disorder). With active-case ascertainment, surveillance personnel conduct research by reviewing data from all areas of a hospital that come in contact with a neonate, instead of limiting themselves to the neonatal intensive care and labor and delivery units.

Furthermore, standardized consensus criteria were employed to classify cases (https://www.cdc.gov/ncbddd/fasd/facts.html). Assessments included four relevant domains: growth, dysmorphology, neurodevelopment, and prenatal alcohol exposure (the latter assessed during maternal interviews).

RESULTS

During this time period, 222 children were identified as having fetal alcohol spectrum disorder. Notably, only 2 of these children had been previously diagnosed. Using the more conservative approach, the prevalence rates of fetal alcohol spectrum disorders across the four sites ranged from 11.3 (95% CI, 7.8–15.8) to 50.0 (95% CI, 39.9–61.7) per 1,000 children. This corresponds to a range of approximately 1%–5%, the latter of which is higher than previous published estimates (eg, 1%–2%). The less conservative estimates that were reported in this study peaked at 98.5 per 1,000 children (nearly 10%) at one site.

THE CARLAT TAKE

According to this new research, fetal alcohol spectrum disorders are not rare events in the US, which suggests we need to improve our ability to detect these cases.

PRACTICE IMPLICATIONS

Given the negative (and preventable) consequences associated with fetal alcohol spectrum disorders (eg, poor academic achievement, mental health disorders), we recommend proactive education on the adverse consequences of drinking alcohol during pregnancy, in addition to enhanced prevention and intervention efforts. Also, support services should be provided for individuals affected by this condition, with the goal of improving their long-term prognosis and enhancing their quality of life.

Is Varenicline Effective for Alcohol Use Disorder?

REVIEW OF: O'Malley SS, Zweben A, Fucito LM, et al. Effect of varenicline combined with medical management on alcohol use disorder with comorbid cigarette smoking: A randomized clinical trial. *JAMA Psychiatry*. 2018 Feb 1;75(2):129–138.

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

Acting on the nicotinic acetylcholine receptors, varenicline (Chantix) is an FDA-approved treatment for smoking cessation. These receptors are implicated in both nicotine and alcohol reward pathways, so could varenicline also be helpful for treating alcohol use disorder (AUD)? So far, the evidence has been mixed, but some studies have shown a greater benefit of varenicline in those who use both alcohol and cigarettes, compared to those who just use alcohol.

This 16-week study was a phase two, randomized, double-blind, placebo-controlled trial comparing the effects of varenicline and medical management to medical management plus placebo for treatment of AUD. The 131 participants recruited (including 39 women) met DSM-IV-TR criteria for alcohol dependence and smoked at least 2 days a week. The intervention group was given varenicline titrated up to 1 mg twice a day, and both groups were seen for 12 medical management sessions for AUD, which is a behavioral intervention used by medical professionals to support medication adherence (4 sessions) and use strategies for achieving drinking goals (8 sessions).

The primary outcomes were reduction in drinking by percentage of heavy drinking days (PHDD) and no heavy drinking days (NHDD), defined as ≥ 5 standard drinks a day for men or ≥ 4 for women. One standard drink equaled a 12-ounce beer with an alcohol content of 5%, 5 ounces of wine (12% alcohol), or 1.5 ounces of distilled spirits (40% alcohol). Secondary outcomes were prolonged abstinence (28 days) from smoking, confirmed by plasma cotinine levels < 6 ng/mL.

RESULTS

The results of the primary outcome, PHDD, showed no significant difference in the overall sample between those on varenicline or placebo. However, there was a significant difference between the response of men and women in the study. PHDD in men showed a greater (but still non-significant) reduction than women, and the NHDD in men was nearly significant—29% on varenicline had NHDD vs 6% for placebo (95% CI, 0.22–1.03). Smoking outcomes showed a significant difference in prolonged abstinence from smoking for those on varenicline—13% vs 0% ($p = 0.003$). The only significantly different side effect was more abnormal dreaming in the varenicline group (43.8% vs 22.4%), which was experienced more often by women than men—women taking varenicline were 35% more likely than men to report this complaint.

Three adverse events happened in the varenicline group: an admission to alcohol rehabilitation, a hospitalization for suicidal ideation, and another hospitalization for blood pressure monitoring. Two

adverse events happened with placebo: psychiatric hospitalization in one, and hospitalization for an infection in another. Women on varenicline were more likely to report abnormal dreams and to reduce or discontinue the medication than either men or women on placebo.

THE CARLAT TAKE

While the results are not robust, they point to a greater benefit in men with AUD than in women. However, the small number of women in the study limits this conclusion, and it could be that women don't tolerate treatment doses of varenicline as well.

PRACTICE IMPLICATIONS

More research is needed to investigate these gender differences in varenicline efficacy and tolerance. There isn't enough evidence to support varenicline's use as a treatment of AUD. Another take-home point is that, even without any other smoking cessation interventions, varenicline helped some people achieve prolonged abstinence from smoking.

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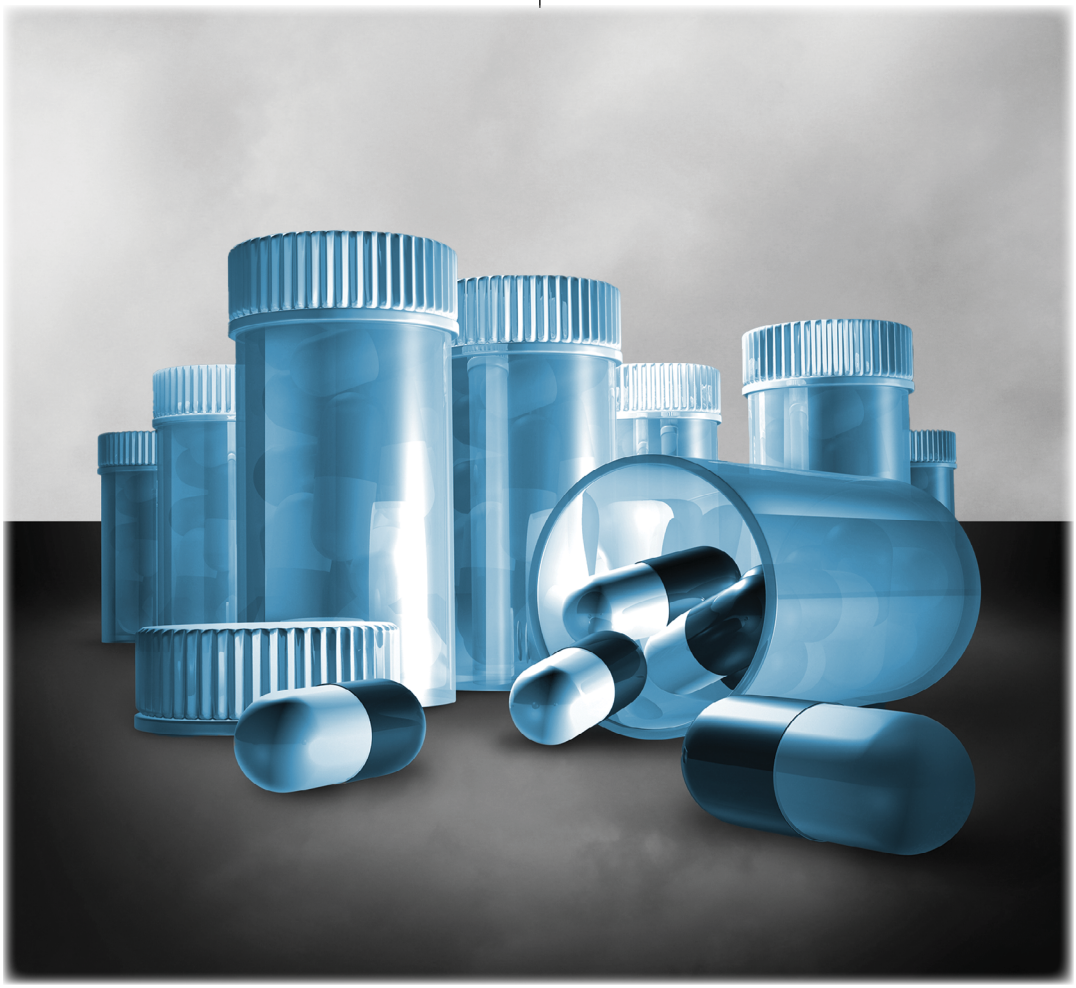
PHARMACOTHERAPY DEVELOPMENTS



Olanzapine for Anorexia Nervosa

REVIEW OF: Attia E, Steinglass JE, Walsh BT, et al. Olanzapine versus placebo in adult outpatients with anorexia nervosa: A randomized clinical trial. *Am J Psychiatry*. 2019 Jun 1;176(6):449–456.

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

Antipsychotics have been tried in anorexia since 1960, but their success has been mixed and often outweighed by their risks. Seven controlled trials have tested atypical antipsychotics in anorexia, and although most were positive, their pooled benefits were too small to be detected in a meta-analysis (Dodd M et al, *Psychother Psychosom* 2015;84(2):110–116). That leaves us with an uncertainty that is best answered by a larger controlled trial, which is where this new research comes in.

In this randomized placebo-controlled trial, researchers studied the effects of olanzapine on change in body weight and obsessionality in adult outpatients (n = 152) with anorexia nervosa for 16 weeks. Nearly all patients were female (96%) and most were taking psychotropics (41%, mainly antidepressants). Average BMI was 17 and Yale-Brown Obsessive Compulsive Scale (YBOCS) score was 16.5 (moderate severity). Olanzapine was started at 2.5 mg/day × 2 weeks, titrated to 5 mg/day × 2 weeks, and then increased to 10 mg/day as tolerated (average final dose 7.8 mg/day). Primary outcome measures were rate of change in body weight and rate of change in obsessionality measured by the YBOCS.

RESULTS

Relative to placebo, the olanzapine group experienced a significant increase of 0.165 BMI points, which is approximately 1 pound per month over the 16 weeks. Relative to placebo, the olanzapine group did not see a benefit in obsessionality or cognitive symptoms of anorexia and had significantly more concerns about body weight. Lab abnormalities and hospitalization rates did not differ between the groups.

THE CARLAT TAKE

This study's strengths include the large sample size and enrollment of diverse patients with various comorbidities that are more reflective of outpatient practice. The sample size is almost as large as all the past atypical antipsychotic studies of anorexia combined. The study's main weaknesses include the large dropout rate (45%) and a duration that was probably not long enough to detect lab abnormality differences. On the other hand, the dropout rate was similar for olanzapine and placebo, and the data were analyzed on an intent-to-treat basis.

PRACTICE IMPLICATIONS

Despite a positive result, these modest gains in weight do not inspire a ringing endorsement of olanzapine for anorexia. At least seven other controlled trials of olanzapine in anorexia have been published, and a meta-analysis of them did not find a hair of difference with olanzapine or with other antipsychotics (Cassioli E et al, *J Psychopharmacol* 2020;34(8):864–873). Reserve olanzapine for severe, treatment-resistant patients where weight restoration is essential, or for patients with anorexia who have comorbidities—like mood disorders—where olanzapine is indicated.

Another Black Eye for Prazosin in PTSD?

REVIEW OF: McCall WV, Pillai A, Case D, et al. A pilot, randomized clinical trial of bedtime doses of prazosin versus placebo in suicidal posttraumatic stress disorder patients with nightmares. *J Clin Psychopharmacol*. 2018 Dec;38(6):618–621.

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

Prazosin has become a mainstay in the pharmacologic treatment of PTSD. A selective antagonist of the noradrenergic alpha-1 receptor, it has modest benefits in sleep and nightmares that are supported by around half a dozen clinical trials. That mainstay of practice was recently rocked by a large trial of twice-daily prazosin in (mainly male) military veterans that found no benefit for distressing dreams or sleep quality (Raskind M et al, *NEJM* 2018;378(6):507–517). But the study had flaws, particularly in the way that patients were selected to participate. Now we have a second report questioning prazosin's utility in PTSD.

The authors hypothesized that prazosin might reduce suicidality in patients with PTSD, based on prior research suggesting a link between insomnia and suicide. They randomized 20 civilians (17 women, 3 men) with PTSD to prazosin or placebo for 8 weeks. Prazosin was given at night in escalating doses as tolerated (the mean final dose was 5.5±3.5 mg qhs). Prior to randomization, the subjects were stabilized for at least 4 weeks on an SSRI or, if suffering from bipolar depression, at least 4 weeks on an FDA-approved bipolar medication. The primary outcome was suicidality, as measured by the Scale for Suicide Ideation (SSI) and the Columbia-Suicide Severity Rating Scale (C-SSRS). Secondary measures included the Disturbing Dreams and Nightmare Severity Index (DDNSI), the Insomnia Severity Index (ISI), and PTSD as measured by the PTSD-checklist-specific version.

RESULTS

The results were surprising. Contrary to expectations, the placebo group showed greater improvement on all measures, including nightmares and insomnia, but also on measures of depression and PTSD overall. However, the study had significant weaknesses that make it difficult to conclude much from these results. The sample size was small, and only 6 of the 20 subjects completed the full 8 weeks. The placebo response was also very high. Suicidality remitted *completely* on placebo, as measured by the SSI, but on prazosin it only declined 70%.

THE CARLAT TAKE

The placebo response has risen in the last 20 years, and that means we're seeing more studies like this where an otherwise effective treatment fails to separate from placebo. Transcranial magnetic stimulation, behavioral interventions for PTSD, and now prazosin have all shared this fate.

PRACTICE IMPLICATIONS

The lesson is to beware of media headlines that proclaim a common therapy ineffective. Sometimes the treatment is flawed; sometimes it's the study. In this case, we're not convinced that it's time to give up on prazosin in PTSD. After this study was released, a meta-analysis of six randomized controlled trials of prazosin in PTSD concluded that it treated PTSD with a small effect size for core PTSD symptoms, a medium effect on sleep, and a large effect on nightmares (Reist C et al, *CNS Spectr* 2020;25(1):1–7).

Is Ketamine Just Another Opiate?

REVIEW OF: Williams NR, Heifets BD, Blasey C, et al. Attenuation of antidepressant effects of ketamine by opioid receptor antagonism. *Am J Psychiatry*. 2018 Dec 1;175(12):1205–1215.

STUDY TYPE: Randomized, double-blind, placebo-controlled, crossover study

Ketamine's rapid antidepressant effects have now been demonstrated in over two dozen double-blind, placebo-controlled trials, but how it works is less clear. For many years, NMDA receptor antagonism was thought responsible, but other NMDA antagonists have not worked well in depression. Another possibility is the endogenous opioid system, which is responsible for ketamine's analgesic effects. If that system is also involved in ketamine's antidepressant effects, then the opioid antagonist naltrexone ought to interfere with those benefits. This study sought to determine whether naltrexone would in fact dampen ketamine's benefits in depression.

Thirty subjects with chronic, highly refractory depression were enrolled (with a mean of 9.8 unsuccessful antidepressant trials). Each participant received, in random order, two separate IV infusions of ketamine 0.5 mg/kg—one preceded by naltrexone 50 mg and the other preceded by placebo. The primary outcome was reduction in depressive symptoms at post-infusion day 1. The dissociative effects of ketamine were examined as well.

RESULTS

When ketamine was given with a placebo, the response (58%) and remission (42%) rates for depression were high, but coadministration with naltrexone brought those rates to zero. In contrast, naltrexone did not have any discernible impact on ketamine's dissociative effects. Data collected on blinding suggested that participants were unable to discern when they were receiving naltrexone vs placebo.

The results were dramatic enough that the study was halted midway through for ethical reasons, so only 12 of the 30 subjects completed both arms.

THE CARLAT TAKE

Could ketamine be nothing more than an opiate masquerading as an NMDA receptor antagonist? While the opioid system appears critical to ketamine's antidepressant effects, that doesn't mean ketamine directly affects opioid receptors in the way that morphine or codeine does. Endogenous opioids have well-known mood elevating properties, and exercise and even placebo stimulate endogenous opioids.

However, the possibility of an opioid-like effect raises uncomfortable questions about potential withdrawal symptoms after stopping ketamine, or its branded cousin esketamine (Spravato). Furthering that concern is the fact that there were 3 suicides in the treatment arm after long-term esketamine was stopped in the registration trials. The suicides were not statistically

significant, so they did not stop Spravato from getting FDA approval for treatment-resistant depression, but they raise red flags that have yet to be answered in light of this opioid finding.

PRACTICE IMPLICATIONS

While ketamine and its branded cousin esketamine (Spravato) treat depression, they do nothing to prevent it, so patients are increasingly placed on these medications long term. The data above suggest that some of these patients may be vulnerable to withdrawal problems, including worsening depression and suicidality, if ketamine or esketamine are ever stopped. Until that possibility is refuted, watch those patients closely.

Serotonin Syndrome Risks With Co-Prescription of Triptan Drugs and SSRIs or SNRIs

REVIEW OF: Orlova Y, Rizzoli P, Loder E. Association of coprescription of triptan antimigraine drugs and selective serotonin reuptake inhibitor or selective norepinephrine reuptake inhibitor antidepressants with serotonin syndrome. *JAMA Neurol.* 2018 May 1;75(5):566–572.

STUDY TYPE: Retrospective cohort study

In 2006, the FDA issued a warning that patients using either selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors (SSRIs or SNRIs) together with triptan antimigraine drugs might be at a heightened risk for serotonin syndrome. Their advisory was based on 27 case reports of suspected serotonin syndrome in people who were prescribed a triptan along with one of these serotonergic antidepressants.

Because migraines are a common comorbidity in depressive and anxiety disorders, many of our patients are co-prescribed these medications. But what is the true risk for serotonin syndrome for these patients?

Orlova at the University of Florida and colleagues from Boston's Brigham and Women's Hospital completed a population-based study to evaluate this risk. They used electronic health records from over 6 million members in the Partners Research Data Registry to identify a cohort of 19,017 patients, who were prescribed both triptans and an SSRI or SNRI between 2001 and 2017, a total of 30,928 person-years of exposure.

RESULTS

Serotonin syndrome was suspected in 17 patients, and concurrent use of triptans and an SSRI/SNRI was confirmed in 7 of these. Serotonin syndrome was considered definite in 2 of those cases and possible in the other 5, yielding an incidence rate of 0.6–2.3 cases per 10,000 person-years of exposure.

The rate of co-prescription did not change after the 2006 FDA warning. Between 2001 and 2014, 21%–29% of triptan users were also prescribed an SSRI or SNRI.

THE CARLAT TAKE

Serotonin syndrome is hypothesized to involve activation of only serotonin 2A and 1A receptors. Triptans are primarily agonists for serotonin 1B and 1D receptors and do not activate serotonin 2A or 1A receptors. Thus, we doubt that triptans would increase the risk of serotonin syndrome.

PRACTICE IMPLICATIONS

The risk of serotonin syndrome with concomitant use of triptans and SSRIs or SNRIs appears to be very low. These results cast serious doubt on the validity of the 2006 FDA advisory and suggest that it should be reconsidered.

QTc Prolongation Risk Management in Hospital Patients

REVIEW OF: Vandael E, Vandenberk B, Willems R, et al. Risk management of hospitalized psychiatric patients taking multiple QTc-prolonging drugs. *J Clin Psychopharmacol.* 2017 Oct;37(5):540–545.

STUDY TYPE: Prospective cohort study

Many of the medications we prescribe, most notably antipsychotics and antidepressants, have some risk of QTc prolongation. Since it's rare to have complications of a prolonged QTc interval—such as torsades de pointes and sudden cardiac death—clinics and hospitals typically don't screen for QTc prolongation using electrocardiograms (ECG).

This study evaluated the impact of combining two medications that are known to cause QTc prolongation, and attempted to stratify patients based on a baseline risk score calculation. The study population consisted of 152 patients in six psychiatric hospitals who were already taking 1 or more QTc-prolonging medications. All patients received a baseline ECG to see whether their existing medication was causing QTc prolongation. When a second torsadogenic medication was added, patients were given another ECG within 14 days. The most common medications prescribed in the study were mirtazapine, quetiapine, escitalopram, and trazodone.

RESULTS

How did adding these medications affect ECGs? Across all patients, there was a statistically significant increase ($p = 0.032$) in mean QTc interval from a norm of 409.1 ms to 411.8 ms with a single QTc-prolonging medication. At follow-up ECG, after the addition of a second QTc-prolonging medication, only 3 participants (2%) developed a prolonged QTc (≥ 450 ms for men and ≥ 470 ms for women). Only 8 patients (6.6%) had an increase in their QTc ≥ 30 ms, and no one had an increase in QTc ≥ 60 ms. No study participants experienced torsades de pointes or sudden cardiac death.

The study also explored potential predictors of QTc prolongation by assigning a risk score at baseline. This score, called the "RISQ-PATH score," was computed using the patient's age, sex, cardiac risk factors, and number of QTc-prolonging medications currently prescribed.

According to the RISQ-PATH score, 58 patients (38.2%) were considered high risk at baseline, and these patients had a significantly higher QTc interval in the follow-up ECG compared to low-risk patients (420.7 ms vs 406.2 ms, $p < 0.001$).

THE CARLAT TAKE

There is a direct correlation between the number of QTc-prolonging medications and a longer QTc interval. However, for most patients in this study, the absolute increase in QTc interval was

very small, with only 2% of patients developing a prolonged QTc. And, regardless of the QTc prolongations, none of these patients developed any clinical symptoms attributable to the ECG changes. A risk score, such as the RISQ-PATH score, would be helpful in choosing which patients need ECG monitoring, but this test needs further validation before being used in the general psychiatric population. Also, since the problem may be greater among the elderly, these data may not be reassuring for a geropsychiatrist.

PRACTICE IMPLICATIONS

Combining QTc-prolonging medications can have an additive effect on the QTc interval, but the magnitude of this effect is small, with a very low probability of clinical consequences in most patients. While prudence would dictate avoiding such combinations, if the patient's symptoms require these medications, go ahead and prescribe them while monitoring the ECG. Exercise caution in patients with additional risks for QT interval prolongation, including those with congenital long QT syndrome, electrolyte abnormalities, or the elderly.

Varenicline and Bupropion: Soaring Again With EAGLES?

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 Jun 18;387(10037):2507–2520.

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

Varenicline (Chantix) and bupropion (Zyban and others) are effective treatments for tobacco use disorder, but their use (and sales) took a big hit in 2009 when the FDA slapped both with black box warnings linking them to psychiatric complications, including suicidal ideation. Although these concerns did not appear in clinical trials, the FDA responded primarily to numerous post-marketing case reports. Clinicians began to steer clear of these agents, especially after a cottage industry cropped up suing for psychiatric damages purportedly caused by them. To allow removal of the warning, the FDA required the manufacturers of Chantix and Zyban (Pfizer and GlaxoSmithKline, respectively) to perform a sufficiently large randomized trial that adequately assessed these safety issues. The result is the massive and complicated Pfizer- and GSK-sponsored "EAGLES" trial—a somewhat tortured acronym of "Evaluating Adverse Events in a Global Smoking Cessation Study."

This randomized, double-blind clinical trial recruited 8,144 smokers ages 18–75 from 140 centers in 16 countries. Subjects were split into two cohorts, one with and the other without psychiatric disorders. Each cohort was then divided into four treatment groups in a 1:1:1:1 ratio: varenicline (target dose 1 mg BID), bupropion SR (150 mg BID), transdermal nicotine patch (21 mg/day with taper), or placebo. The treatment phase lasted 12 weeks, followed by a 12-week non-treatment follow-up phase. Subjects were assessed for both tobacco abstinence and for 16 categories of neuropsychiatric symptoms. The main goal was to determine whether the treatments differed in terms of serious psychiatric side effects.

RESULTS

Not surprisingly, there were more reported neuropsychiatric adverse events in the psychiatric cohort (5.8%) than in the non-psychiatric cohort (2.1%). However, the overall incidence of these events was the same in each of the four treatment groups. In fact, anxiety and depression symptoms improved about equivalently in all groups. The most common adverse events by treatment group were nausea (varenicline 25%), insomnia (bupropion 12%), abnormal dreams (nicotine patch 12%), and headache (placebo 10%). Rates of suicidal ideation and behavior overall were quite low, but in the psychiatric cohort they were non-significantly higher in the placebo and varenicline groups. The lone completed suicide was in the non-psychiatric placebo group.

All three of the active treatments were more effective for tobacco abstinence than placebo, but varenicline was superior to both bupropion and nicotine patch.

THE CARLAT TAKE

The EAGLES study described here has been criticized for its use of an unvalidated scale for adverse events. Further, the FDA raised concerns over inconsistencies in EAGLES' data collection, but ultimately found that, even when unreliable data were excluded, the results seemed consistent with the study's conclusions. As a result, the FDA removed the black box warning for varenicline, and it modified the warning for Zyban by removing language about serious psychiatric effects in patients quitting smoking.

PRACTICE IMPLICATIONS

These agents, particularly varenicline, can help patients stop smoking, and serious psychiatric adverse effects seem relatively rare. So, we can all breathe somewhat easier in prescribing varenicline and bupropion for smoking cessation. But as with all psychotropic agents, it would be prudent to employ reasonable screening, discussion of risks, and monitoring effects of these agents, particularly in patients who have preexisting psychiatric symptoms.

Does Augmenting Varenicline With Bupropion Work Better Than Varenicline Alone?

REVIEW OF: **Cinciripini PM, Minnix JA, Green CE, et al. An RCT with the combination of varenicline and bupropion for smoking cessation: Clinical implications for front line use. *Addiction* 2018 Sep;113(9):1673–1682.**

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

We have a good array of smoking cessation treatments to choose from, including nicotine replacement therapy (NRT), bupropion, and varenicline. Varenicline is the most effective monotherapy agent, somewhat better than bupropion and single-product NRT, and comparable to combination NRT. Theoretically, adding bupropion to varenicline would be even more effective. A couple of studies have tested this strategy with mixed results. This latest study attempted to further clarify the efficacy of this combination.

Researchers randomly assigned smokers (at least 1 pack per day) to three treatment arms: varenicline alone (n = 166), varenicline plus bupropion (n = 163), and placebo (n = 56). All participants were also given behavioral therapy (13 in-person individual 15-minute visits for smoking cessation counseling and 2 brief supportive telephone sessions) for 12 weeks of active treatment. They were then followed for 12 months. The primary outcome measure was abstinence at 1 year, which was verified by measuring expired carbon monoxide. The majority of participants were male (58%), and the average age was 49.

RESULTS

After 12 months, the quit rates were similar in the two active treatment groups. Beginning with the last 4 weeks of treatment, participants on varenicline alone had a continuous abstinence rate of 22.29% vs 20.25% for the varenicline + bupropion group. Both of these were superior to placebo, which had a continuous abstinence rate of 5.36%.

As expected, the rate of adverse events was higher in the varenicline + bupropion (98.1%) and varenicline-only (95.78%) groups compared with placebo (89.29%; $p < 0.021$). Specifically, varenicline + bupropion participants experienced decreased appetite, altered taste, and increased dry mouth, insomnia, creatinine, and edema compared with placebo. Varenicline-only participants had increased rates of abnormal dreams, diarrhea, and nausea compared with placebo.

THE CARLAT TAKE

While it's tempting to combine two effective treatments, it appears that adding bupropion to varenicline is no better than varenicline alone. Varenicline comes with a host of side effects, but if tolerated can help many people quit smoking.

PRACTICE IMPLICATIONS

While all smoking cessation agents can be used as first-line treatment, in Carlat's *Medication Fact Book for Psychiatric Practice*, we lay out an approach that starts with nicotine replacement therapy, and then moves on to either varenicline or bupropion. These results are in line with that approach.

Can Buprenorphine Improve PTSD Symptoms?

REVIEW OF: Lake EP, Mitchell BG, Shorter DI, et al. Buprenorphine for the treatment of posttraumatic stress disorder. *Am J Addict*. 2019 Feb;28(2):86–91.

STUDY TYPE: Retrospective case series

For many years, the mainstay of treatment for PTSD has been the SSRI class of medications, but many of our patients still suffer crippling symptoms despite optimal antidepressant medication dosing. PTSD is often accompanied by opioid misuse, sometimes in an effort to self-treat the hyperarousal and hypervigilance related to PTSD. So, can treatments like buprenorphine/naloxone that target opioid receptors also have an effect on PTSD symptoms?

This retrospective study looked at three groups of patients with PTSD treated at VA medical centers over a 6-year period—those receiving SSRIs, buprenorphine/naloxone, and full-agonist opioids. Patients could only have been receiving 1 of these medications during the study period. A total of 2,015 patients were identified, out of which 55 patients were selected for each group after applying the inclusion criteria and then using a random number generator. The subjects were mostly white (76.4%) and male (88.5%), with an average age of 43. PTSD symptoms were assessed using either the PTSD Checklist for Clinicians (PCL-C) or the VA Primary Care PTSD Screen (PC-PTSD)—the PCL-C scores were converted to the PC-PTSD scale for the analysis. This new standardized score was a 4-point scale, with 1 being minimal and 4 being maximal symptoms. A score of 3 or 4 is considered a "positive" screening for PTSD. The primary outcome was the most recent standardized PTSD rating scale score, with a secondary outcome of change in score from initial to most recent assessment.

RESULTS

The buprenorphine group had the best final standardized PTSD score, significantly better than the SSRI group (2.473 vs 3.164; $p = 0.048$). There was no significant difference between the final scores of the SSRI vs full-agonist opioid groups or between the buprenorphine vs full-agonist opioid groups. For the change from initial to final standardized PTSD score, the buprenorphine group also did the best, with significantly greater change in scores compared to the SSRI group ($p = 0.026$), and again no differences were found in the other two group comparisons.

THE CARLAT TAKE

The results are interesting but should be taken with a grain of salt. This study was set up as a retrospective chart review, not a prospective efficacy study. The time intervals for rating scale assessments weren't standardized, there was no standard length of treatment, and the study did not control for confounding factors such as age, comorbid conditions, or concurrent psychotherapy.

PRACTICE IMPLICATIONS

At most, this study gives us more confidence in using buprenorphine/naloxone when treating comorbid PTSD and opioid use disorder, but randomized controlled trials are needed to establish efficacy in PTSD treatment.

PSYCHOTHERAPY INTERVENTIONS

Are All Psychotherapies for Anorexia Created Equal?

REVIEW OF: Zeeck A, Herpertz-Dahlmann B, Friederich HC, et al. Psychotherapeutic treatment for anorexia nervosa: A systematic review and network meta-analysis. *Front Psychiatry*. 2018 May 1;9:158.

STUDY TYPE: Meta-analysis of randomized controlled trials

Psychotherapy is the main treatment for anorexia nervosa, but which type works best? Several therapies have good evidence in this population, but they differ in their models and methods, and head-to-head comparisons among them are rare. To overcome that limitation, this study used a technique called "network meta-analysis," which evaluates different treatments based on how they measured up against a common comparison group. For example, suppose that cognitive behavioral therapy (CBT) and family therapy have never been directly compared to each other but both have been compared to supportive therapy. A network meta-analysis would compare CBT to family therapy based on how each fared relative to supportive therapy.

Only a handful of therapies have good evidence to work in anorexia, and most of them were included in this study. Effective therapies had two common ingredients: a focus on weight restoration and work on psychosocial factors. It was in the psychosocial focus that the therapies differed, which ranged from skill building (CBT), relationship dynamics (focal psychodynamic therapy, interpersonal psychotherapy), family work, and supportive psychotherapy (specialist supportive clinical management). The family therapies empowered parents to re-feed their child, and then progressed to work on family dynamics (systemic family therapy) or adolescent development (family-based treatment and the Maudsley model) as normal weight was restored.

RESULTS

No single therapy was more effective than the others in this analysis of 18 randomized controlled trials. The authors followed that up with another new-fangled technique, called "standardized mean change analysis," which compared the degree of weight gain among all of the therapies after 1 year of treatment. This analysis allowed naturalistic studies to be included, bringing the total number of trials to 38. Again, no single therapy stood out, but weight gain was more rapid with inpatient vs outpatient treatment, and overall weight gain was greater in adolescent studies than it was for adults (inpatient: 1.4 pounds/week for adolescents, 1.2 pounds/week for adults; outpatient: 0.42 pounds/week for adolescents, 0.23 pounds/week for adults).

THE CARLAT TAKE

The authors suggested that some therapies may be superior for certain subgroups of anorexia. Most successful therapies for adolescents involved the family, while individual

therapy was the mainstay for adults with anorexia. Adolescents with significant obsessive-compulsive symptoms had greater benefit with systemic family therapy than family-based treatment. For severe anorexia, the Maudsley model was more effective than specialist supportive clinical management.

PRACTICE IMPLICATIONS

While the outcomes for these therapies were similar, this does not mean that any psychotherapy will work for anorexia. These are highly structured therapies with specific behavioral and psychological techniques. When making referrals, psychiatrists should look for therapists that use evidence-based methods, and adolescents may do better with a family approach. Once in therapy, weight gain of 0.23–1.4 pounds/week can be considered a successful outcome.

Mindfulness Therapy for Adult ADHD

REVIEW OF: Janssen L, Kan CC, Carpentier PJ, et al. Mindfulness-based cognitive therapy v. treatment as usual in adults with ADHD: A multicentre, single-blind, randomised controlled trial. *Psychol Med*. 2019 Jan;49(1):55–65.

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

Medications are the first-line treatment for adult ADHD, and the efficacy of psychosocial therapies is less well defined. Mindfulness-based therapy showed promise for adult ADHD in a recent meta-analysis, but there were flaws and significant differences between the included studies (Janssen L et al, *BMC Psychiatry* 2015;15:216).

The current study was a single-blind, randomized controlled trial of mindfulness-based cognitive behavioral therapy (MBCT) as an adjunct to treatment as usual (TAU) in 120 patients with adult ADHD. Both groups received TAU, which consisted of various combinations of medication, psychoeducation, and skills training. The intervention group received 8 weekly sessions of MBCT and a 6-hour silent day of mindfulness. Each MBCT session was 2.5 hours long and consisted of meditation exercises, cognitive behavioral techniques, psychoeducation, and group discussions. For the silent day, study subjects spent 6 hours completing various meditation activities, eating lunch, and having a tea break. Mindfulness practice was encouraged outside of the sessions for 30 minutes a day.

RESULTS

Patients in the MBCT group had significant reductions in clinician-rated and self-reported ADHD symptoms that persisted for 6 months. Significantly more patients in the MBCT group (27%) experienced a ≥ 30% reduction in symptoms compared with the TAU group (5%) ($p = 0.001$). The two groups were similar in their utilization of TAU, although those in the mindfulness group were less likely to make changes to their medications.

THE CARLAT TAKE

Although the results are encouraging, the study had several limitations. Participants were not blinded to the treatment, so placebo effects cannot be completely ruled out. No data were collected on patients who were excluded or declined to participate in the study, raising the possibility that the sample was enriched and limiting the generalizability of the results.

PRACTICE IMPLICATIONS

This study raises the quality of evidence in support of mindfulness therapy in adult ADHD. Mindfulness is reasonable to recommend as an adjunct to medication, and as a solo treatment for patients who cannot tolerate or do not respond to medication.

A CBT App for Refractory Depression

REVIEW OF: Mantani A, Kato T, Furukawa TA, et al. Smartphone cognitive behavioral therapy as an adjunct to pharmacotherapy for refractory depression: Randomized controlled trial. *J Med Internet Res*. 2017 Nov 3;19(11):e373.

STUDY TYPE: Randomized, single-blind, parallel-group trial

Mobile phones have allowed the introduction of guided, self-help cognitive behavioral therapy (CBT) for depression with enhanced accessibility, efficiency, and affordability. Several meta-analyses suggest that computers can augment face-to-face psychotherapy and even work on their own through self-guided programs. Most of those studies involved patients with mild to moderate depression, which leaves open the question of how well this approach would work in more severe cases.

This study tested a self-guided mobile app in patients with moderate to severe depression who had not responded to at least 1 antidepressant trial. The Japanese app, called Kokoro, used cartoon characters to present concepts from CBT, including self-monitoring, behavioral activation, and cognitive restructuring.

The authors randomized 164 patients to an intervention group (medication switch plus Kokoro app) and control group (medication switch only). Although the treatments were not blinded, the outcomes were assessed with blinded raters.

RESULTS

After 9 weeks, the intervention group showed greater improvement in the Patient Health Questionnaire-9, the primary outcome measure ($p < 0.001$). Rates of remission (18% vs 10%) and response (32% vs 18%) were also greater, and the magnitude of the benefit compared favorably with the effect sizes seen in antidepressant trials.

In the second phase of the study, both groups were given access to the app for an additional 2 months. After that time, both groups had similar depression scores. The intervention group maintained their gains, and the control group caught up.

Most patients stayed engaged with the 8-session app, but that engagement was not entirely self-driven. Each week, participants received a brief, personalized email congratulating them on their progress.

THE CARLAT TAKE

This study demonstrates significant benefits for this CBT app in difficult-to-treat depression. Its strengths include a randomized controlled design, blinded ratings, and high levels of engagement and completion. The main limitation is the lack of blinding in the treatment arm, which makes it difficult to rule out a placebo effect. By making changes to medications in both groups at the start of the trial, the authors attempted to minimize expectancy effects.

PRACTICE IMPLICATIONS

For clinicians, the main limitation may be the inaccessibility of the Japanese-language app, a common problem in this type of research. Most of the available mental health apps are untested, and most of the tested apps are not available. A reasonable substitute is IntelliCare, a suite of CBT-based apps made free through NIMH funding (https://intellicare.cbits.northwestern.edu). In a recent randomized controlled trial, IntelliCare was compared to a waitlist control for treatment of anxiety and depression in primary care settings with significant positive results (Graham AK et al, *JAMA Psychiatry* 2020;e201011).

CBT vs Pharmacotherapy for Childhood Anxiety

REVIEW OF: Wang Z, Whiteside SPH, Sim L, et al. Comparative effectiveness and safety of cognitive behavioral therapy and pharmacotherapy for childhood anxiety disorders: A systematic review and meta-analysis. *JAMA Pediatr*. 2017 Nov 1;171(11):1049–1056.

STUDY TYPE: Systematic review and meta-analysis

Managing childhood anxiety can sometimes leave clinicians in a quandary. There is a paucity of evidence comparing treatment approaches, and current guidelines on the subject are old and make inconsistent recommendations. To address this dilemma, researchers at the Mayo Clinic performed a systematic review and meta-analysis comparing pharmacotherapy with cognitive behavioral therapy (CBT) in children with anxiety disorders.

Investigators identified 115 studies with a total of 7,719 participants. All studies evaluated CBT, pharmacotherapy, or the combination of both for treatment of a diagnosed childhood anxiety disorder. The average participant age was 9.2 years (range 5.4 to 16.1), and slightly over half (55.6%) were female. Data were pooled using a random-effects meta-analysis.

RESULTS

Selective serotonin reuptake inhibitors (SSRIs) had significantly better outcomes than placebo for reduction in primary anxiety symptoms reported by parents or clinicians, as well as increased remission (relative risk [RR] 2.04) and response (RR 1.96). Likewise, when compared with placebo, serotonin-norepinephrine reuptake inhibitors (SNRIs) also had a significantly greater reduction in clinician-reported primary anxiety symptoms. The use of tricyclic antidepressants or benzodiazepines was not associated with a significant improvement in anxiety symptoms.

Treatment with CBT compared with no therapy significantly improved primary anxiety symptoms reported by clinicians, parents, and children, as well as remission (RR 4.08) and response (RR 4.72). Moreover, combining CBT with an SSRI resulted in significantly better response rates than treatment with an SSRI alone.

Mild or moderate adverse effects were reported with medication use but not with CBT. However, none of the trials were large enough or long enough to evaluate suicide risk with SSRIs or SNRIs.

THE CARLAT TAKE

This study provides insight into optimal treatment strategies for children with anxiety disorders. SSRIs or CBT are both effective therapies; SNRIs may also be useful alternatives to SSRIs, although the evidence supporting their efficacy is less robust. This study also supports the premise that there is an added benefit in combining CBT with pharmacotherapy. However,

the authors caution that more research is needed to evaluate the comparative effectiveness of therapies—specifically, head-to-head evaluations of medication and CBT.

PRACTICE IMPLICATIONS

Importantly, these results allow clinicians to offer patients and their families several options for effective treatment of childhood anxiety. For most patients, we would suggest that offering a choice between pharmacotherapy or CBT is the best approach, explaining the risks and benefits of both. This allows patient and family preferences to guide the development of a treatment plan.

Exposure Therapy Efficacious for PTSD Co-Occurring With Alcohol Use Disorder

REVIEW OF: Norman SB, Trim R, Haller M, et al. Efficacy of integrated exposure therapy vs integrated coping skills therapy for comorbid posttraumatic stress disorder and alcohol use disorder: A randomized clinical trial. *JAMA Psychiatry*. 2019 Apr 24;76(8):791–799.

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

Patients with co-occurring post-traumatic stress disorder (PTSD) and alcohol use disorder (AUD) have worse outcomes compared to patients with either diagnosis alone. Integrated approaches, in which both diagnoses are simultaneously addressed, are viewed as best practice. Providers, however, are often hesitant to offer prolonged exposure, an evidence-based therapy for PTSD, to dually diagnosed patients for fear that directly addressing patients' trauma might worsen their drinking. This study is the first randomized trial to compare two therapies targeting both disorders: integrated prolonged exposure (I-PE) vs integrated coping skills without exposure (I-CS).

In the study, 119 veterans were randomly assigned to 12–16 sessions of either I-PE or I-CS. Subjects were primarily male (n = 107), and the majority had experienced several trauma events—both related and not related to combat. Primary outcomes were assessed for both PTSD symptom severity and percentage of heavy drinking days (PHDD), which were measured via the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) and Timeline Followback questionnaires, respectively. Data were collected prior to treatment, post-treatment, and at 3 and 6 months following treatment.

RESULTS

Congruent with prior studies, PTSD severity decreased in both arms over time, and there was a significantly greater reduction in the I-PE group ($p = 0.002$). Regarding drinking outcomes, however, both arms were almost identical ($p = 0.91$). Encouragingly, regardless of whether the therapy involved exposure, PHDD dropped from approximately 50% to 20% by the end of the study, and there was a corresponding increase in days abstinent as well.

THE CARLAT TAKE

Prolonged exposure is one of the best treatments we have for PTSD, and this study helps show that it should not be withheld from patients with co-occurring AUD, especially when delivered in an integrated format that can also address alcohol use.

PRACTICE IMPLICATIONS

Our dual-diagnosis patients are often the most difficult to treat. Prolonged exposure therapy is an effective treatment for PTSD but can be very difficult for anyone to go through. This study confirms that prolonged exposure can be helpful for all patients, even those with active AUD.

New Hope: CBT for Internet and Computer Game Addiction

REVIEW OF: Wölfling K, Müller KW, Dreier M, et al. Efficacy of short-term treatment of internet and computer game addiction: A randomized clinical trial. *JAMA Psychiatry*. 2019 Jul 10;76(10):1018–1025.

STUDY TYPE: Randomized, single-blind effectiveness trial

While many of us likely spend far too much time on our various devices—whether for fun or for work—between 0.3% and 1% of the general population might qualify for an internet gaming disorder (Przybylski AK et al, *Am J Psychiatry* 2017;174(3):230–236). Defined as excessive preoccupation with online gaming despite negative life consequences, internet gaming disorder was identified in the 2013 publication of the DSM-5 as a condition warranting more clinical research and experience before it might be considered for inclusion as a formal disorder. In a recent multicenter randomized clinical trial, researchers evaluated the effectiveness of short-term cognitive behavioral therapy (CBT) for internet addiction.

The study randomly assigned 143 patients with DSM-5-proposed research criteria for internet and computer game disorder to short-term CBT (n = 72) or waitlist control (n = 71) and followed them for 6 months. The mean age was 26.2 years, and most participants were single, high school educated, and unemployed. All were male, which was intentionally reflective of the preponderance of treatment seekers.

The treatment group underwent 15 weekly groups of manualized CBT and up to 8 individual sessions that conceptualized their disorder as resulting from an interaction of individual factors, features of online activity, dysfunctional coping strategies, and disorder-specific cognitive biases. The primary outcome was remission based on a self-report measure, the Assessment of Internet and Computer Game Addiction (AICA-S). Secondary outcomes included time spent gaming or online, psychosocial functioning, and depressive symptoms.

RESULTS

The researchers found 69.4% of patients in short-term CBT achieved remission compared with 23.9% of those waitlisted ($p < 0.001$). There was a greater likelihood of remission in short-term CBT vs waitlist after controlling for age, baseline severity, and comorbidity (adjusted odds ratio 10.10; 95% CI 3.69–27.65). Both groups had improved depression ratings, which may have reflected repeat assessments and the prospect of future treatment for those waitlisted. At 6-month follow-up of half the patients in the short-term CBT group, 80.6% were in remission, but the authors claim this result is difficult to interpret owing to high rates of study dropout and the fact that follow-up data were not sought for the control group.

THE CARLAT TAKE

The results of this study offer hope for effective treatment of internet and computer game addiction. Still, more research is needed to better define these conditions, examine treatments among women, and compare short-term CBT with other treatments.

PRACTICE IMPLICATIONS

When managing a patient struggling with problematic gaming and/or internet use, consider CBT as a treatment option. This adds to the data that CBT is an effective treatment for a wide range of addictive disorders.

About Carlat Publishing

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

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Psychiatry Practice Boosters, Third Edition is edited by Thomas Jordan, MD, MPH, and continues in the tradition of the first edition by adapting the research updates published in the Carlat family of newsletters (*The Carlat Psychiatry Report*, *The Carlat Child Psychiatry Report*, and *The Carlat Addiction Treatment Report*). This edition's research update authors include: Chris Aiken, MD, Bachaar Arnaout, MD, Rehan Aziz, MD, Stephanie Fenwick, PharmD, Brian Frankel, MD, Kristen Gardner, PharmD, Jessica Goren, PharmD, BCPP, Adrienne Grzenda, MD, PhD, Edmund S. Higgins, MD, Karen Hoffman, PhD, Thomas Jordan, MD, Jess Levy, MD, Xiaofan Li, MD, Donna Lisi, PharmD, Pavan Madan, MD, Jason Mallo, DO, Randall Moore, MD, Ahsan Nazeer, MD, Michael Posternak, MD, Xavier Preud'homme, MD, Nicholas Rosenlicht, MD, Adam Strassberg, MD, and Christian J. Teter, PharmD, BCPP. Special thanks to the editors reviewing the manuscript: Talia Puzantian, PharmD, BCPP, Chris Aiken, MD, Joshua Feder, MD, Benjamin Oldfield, MD, Osman Ali, MD, James Megna, MD, PhD, DFAPA, Brian McCarthy, MSN, PMHNP-BC, Peter Parry, MBBS, Jonathan Gamze, MD, Travis Lajoie, DO, and Janice Jutras.

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ISBN 978-1-7329522-4-9
90000
9 781732 952249