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Psychiatry Practice Boosters

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Carlat Psychiatry

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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.

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

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

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).

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.

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

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.

PSYCHIATRY PRACTICE BOOSTERS, THIRD EDITION

Insights from research to enhance your clinical work

As a clinician, you need to keep up on the latest developments in psychiatry. But you can't possibly read every potentially relevant research study published in a given year. At Carlat Publishing, we try to make your life easier by sifting through the contents of the major psychiatric journals for you. The studies that meet our criteria—tackling interesting topics and yielding actionable recommendations for your practice—have made it into our new edition of *Psychiatry Practice Boosters*.

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- Is Ketamine Just Another Opiate?
- Can Buprenorphine Improve PTSD Symptoms?
- Are All Psychotherapies for Anorexia Created Equal?

EDITORIAL TEAM

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