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Joshua D. Feder, MD
Editor-in-Chief

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IN THIS ISSUE

Depression in Children and Adolescents

Learning Objectives

After reading these articles, you should be able to:

1. Identify the role of transcranial magnetic stimulation (TMS) in treating children and adolescents with depression.
2. Describe the strengths and weaknesses of the current medications used to treat depression in children and adolescents.
3. Determine how to conceptualize clinical questions and the differences among kinds of research evidence that can help answer clinical questions.
4. Summarize some of the current findings in the literature regarding psychiatric treatment for children and adolescents.

Transcranial Magnetic Stimulation (TMS) for Depression in Children and Adolescents

Editor's note: This article is about the "usual" TMS that we have been hearing about for many years. We are covering trigeminal nerve stimulation (eTNS) separately in this issue in a News of Note as it is far newer with far less clarity about its utility.

The search for safer treatment

With concerns about both safety and efficacy surrounding antidepressant use in children and adolescents, we are always looking for safer, effective treatments for our patients. TMS has been around since 2008, and its use in youth is expanding. But what is the evidence supporting its use? Is this more a matter of marketing than science? And are there side effects we should worry about?

In Summary

- Although transcranial magnetic stimulation (TMS) is FDA-approved in adults for treatment-resistant depression and OCD, it is not currently FDA-approved for psychiatric use in children and adolescents.
- Preliminary findings in older adolescents suggest TMS for depression treatment doesn't adversely alter cognitive functioning; however, long-term effects on children and young adolescents have not been established.
- TMS may be a helpful option for depression in older adolescents if other modalities have failed or as an adjunctive treatment.

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Q&A With the Expert

Medications for Depression
Martha J. Ignaszewski, MD

Chief Fellow, Clinical Fellow in Psychiatry at Boston Children's Hospital

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

CCPR: You recently published an article reviewing the placebo-controlled trials done over the past 10 years on depression in kids (Ignaszewski MJ and Waslick B, *J Child Adolesc Psychopharmacol* 2018;Epub ahead of print). Can you tell us about your findings?

Dr. Ignaszewski: Historically, there's been a lot of controversy about the effectiveness of antidepressants in children. Some studies have suggested that antidepressants work no better than placebo in depression—but it's important to note that this has not been the case for non-depressive disorders.

CCPR: You mean they do seem to work for such things as anxiety disorders?

Dr. Ignaszewski: Right. There's more robust evidence for the use of SSRIs and other classes of antidepressants for pediatric anxiety disorders and OCD, where the active treatment actually separates from placebo. The efficacy has been demonstrated to be greatest for non-OCD anxiety, intermediate for OCD, and more

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Expert Interview – Medications for Depression

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modest for major depressive disorder, with numbers-needed-to-treat of 3, 6, and 10, respectively. In 2016, a huge network meta-analysis published in *Lancet* assessed antidepressant tolerability and comparative efficacy for depression in children and adolescents. They identified 34 studies looking at 14 antidepressant medications through randomized placebo-controlled, double-blinded trials. The researchers concluded that medications offered no clear advantage over placebo for the treatment of pediatric depression when weighed against the risk-benefit profile (Cipriani A et al, *Lancet* 2016;(10047)388:881–890).

CCPR: Help us understand how your more recent review is different.

Dr. Ignaszewski: We based our review on an earlier meta-analysis (Bridge JA et al, *JAMA* 2007;297(15):1683–1696) and then looked at and compiled the data on randomized controlled trials that were published since then using stringent criteria. We found 7 relevant trials: 4 acute efficacy trials, 2 of which also looked at extension treatment; 1 separate extension trial; and 2 studies that looked at relapse prevention after acute and extended treatment.

CCPR: What were the main findings?

Dr. Ignaszewski: First, and not unexpectedly, all of the treatment arms had high rates of placebo effect that likely masked the effects of active treatment. In doing our more focused review, we found that in the research over the last decade, escitalopram and fluoxetine have the best evidence as first-line treatments for pediatric depression. Second—and this was the more striking finding—we found no evidence of an increased signal of emergent suicidality when using these medications.

"In our more focused review of research over the last decade, escitalopram and fluoxetine have the best evidence as first-line treatments for pediatric depression. The more striking finding was that we found no evidence of an increased signal of emergent suicidality when using these medications."

Martha J. Ignaszewski, MD

CCPR: No treatment-emergent suicidality when antidepressants are used with depressed kids? That's different from what we've been hearing in other studies.

Dr. Ignaszewski: Correct. Research in the last decade assessing the safety and tolerability of antidepressants in pediatric populations has progressed. There are now more systematic efforts to evaluate for treatment-emergent suicidality and compare to baseline suicidality. This is primarily done through the use of the C-SSRS (Columbia Suicide Severity Risk Scale). Past studies identified only spontaneously reported treatment-emergent symptoms that were not necessarily compared with symptoms at the onset of treatment. With the C-SSRS, the statistical signal that was picked up in other studies was not present in these 7 trials.

CCPR: That alone is a tremendously important finding, given the concerns raised since 2004 and the black box warning.

Dr. Ignaszewski: Yes, this was the finding that I found the most compelling, given that one of the major controversies related to the use of antidepressants in this patient population is around safety concerns—specifically treatment-emergent suicidality. Treatment-emergent suicidality has been a major barrier for primary care providers in treating depression, and it also is an understandable concern for anxious parents. These worries have contributed to high rates of undertreatment in many pediatric patients.

CCPR: What about differences in clinical efficacy between different kinds of medications in the treatment of pediatric depression? Tell us about that.

Dr. Ignaszewski: We looked at a number of treatments—some of which are seldom used, but these studies were ones that made the cut. For example, we looked at the selegiline transdermal patch and at fixed and flexible duloxetine dosing at acute phase and extension. Escitalopram, fluoxetine, and sertraline were active treatments, and fluoxetine was used as a comparator in some of the research we looked at, in addition to placebo.

CCPR: What did you find?

Dr. Ignaszewski: Much as others have, we found really high placebo rates, from 41% at the lowest to almost 70% at the highest. That muddies any response that we're going to see from active treatment.

CCPR: Did any of the medications show a level of efficacy or response rate greater than placebo?

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Expert Interview – Medications for Depression

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Dr. Ignaszewski: There were only 2 medications that actually separated from placebo. One was escitalopram, which showed better rates of response in both the acute as well as the extension phase. The other was fluoxetine, when used for relapse prevention.

CCPR: It's interesting that fluoxetine showed separation only in relapse prevention, but not in the acute phase or the extension phase. We usually tout fluoxetine as the medication with the best overall track record.

Dr. Ignaszewski: Right. And yet the relapse prevention rate was huge for fluoxetine. The odds ratio demonstrated a 3.2-fold reduction in the relapse rate for fluoxetine in pediatric depression. This might speak more to the methodology and inclusion criteria in these studies rather than the actual "effect" of the medication; there are a number of factors that can conflate the impact of active treatment. It is also important to think about who is involved in the diagnosis and treatment in a trial: Funding from NIMH may require more fidelity in assessment and diagnosis compared to industry studies that may push to rapidly recruit patients, who may not be representative of the clinical population. For example, the inclusion of pre-pubertal children in study samples has been associated with high placebo rates, which may be due to subthreshold depressive illness. Further, patients with severe depression who are at heightened risk for suicide tend to be excluded from studies. The number of study sites is also correlated with high placebo rates and tends to be lower in publicly funded trials.

CCPR: Any word on bupropion?

Dr. Ignaszewski: We did not include studies on bupropion because none had been published as randomized controlled trials in the last decade. Bupropion has not been extensively studied in kids. There are a handful of open-label trials that are hard to really compare to specific randomized controlled trials. That huge network meta-analysis from 2016 didn't include bupropion because they didn't have any randomized controlled trials to compare it to either.

CCPR: So no help there, and then there are the 2 recent desvenlafaxine trials that were negative studies.

Dr. Ignaszewski: Right. Those came after 2016, so I did not include them, but as negative studies a lot of providers may view these results as helpful in guiding us away from desvenlafaxine. Actually, this is one of the points that I talk about in the article: trying to distinguish between "negative trials" and "failed trials."

CCPR: What do you mean?

Dr. Ignaszewski: Well, there are a number of methodological challenges that may contribute to high placebo rates, and it has been suggested that trials with high placebo rates should be considered "failed" rather than "negative." This notion is supported through differences in outcomes in industry vs publicly funded studies. For example, NIMH studies have a lower placebo response rate at 30%–35%, which is more similar to adult studies; this in turn leads to more substantial between-group differences in placebo vs active treatment. NIMH studies use a number of quality indicators to try to reduce the placebo response rates, such as collection of data about mediating and moderating variables to improve the internal validity of the study sample. Further, efficacy is only one of the major outcomes that is routinely evaluated through experimental research. Trials also provide information about safety and tolerability, which is important for providers to be able to speak about with families.

CCPR: Yes. What about side effect profiles? What did you find to help us differentiate between medications or classes of medications?

Dr. Ignaszewski: Essentially, this study showed that the medications, especially the SSRIs, tend to be pretty well tolerated. They do have the expected nuisance side effects early on, such as headaches and a little bit of GI upset. But interestingly, these side effects did not consistently separate significantly from the same side effect rates with placebo treatment. Venlafaxine, on the other hand, was poorly tolerated. It had a series of side effects that really limited ongoing use, and there were higher rates of discontinuation and treatment-emergent adverse effects in comparison to any of the other medications, which is similar to the Cipriani network meta-analysis.

CCPR: How did people tolerate the selegiline patch?

Dr. Ignaszewski: Pretty well. The selegiline patch also didn't have statistically significant side effects. I'm sure that would have been different with the oral form, but I think the transdermal system mitigates a lot of the side effects that you see with oral dosing.

CCPR: Any other thoughts about how this study applies to day-to-day clinical practice?

Dr. Ignaszewski: I think the part that I was most excited about, and sort of unexpectedly discovered, was the safety profile of antidepressants in kids, with the use of the C-SSRS to assess for treatment-emergent suicidality. I think it's really important that the comparison to baseline behaviors didn't show a statistically significant change in the signal for emergence of suicidality. We all think about the black box warning, and we absolutely need to provide that information in the process of giving informed consent to our families. But when the black box warning came out, there was a dramatic drop in antidepressant prescriptions, followed by a dramatic increase in suicidality.

CCPR: This underlines the importance of continuing research vs calling the risk of emergent suicidality "settled science."

Dr. Ignaszewski: Exactly. I think that as newer studies are pursued, we are developing more refined tools that better equip us to look carefully at issues that we are concerned about. With continued research, we may not find that same increased risk, and that's going to actually tip the balance more in favor of treating with those medications that are also proving efficacious. As providers, this new finding really shifts the balance of safety and our efforts to weigh the balance of risks to benefits. I think this is so important because as psychiatrists, we know that the biggest risk for suicidal ideation, attempts, and completion is untreated depression—so we want to see kids receiving appropriate treatment and recovering from it.

CCPR: Thank you for your time, Dr. Ignaszewski.

Transcranial Magnetic Stimulation (TMS) for Depression in Children and Adolescents
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What is TMS?
TMS is a noninvasive neuromodulation therapy in which a magnet, similar in strength to a magnetic resonance imaging (MRI) machine, is applied to the scalp. Nerve cells in areas of the brain controlling mood are then activated by magnetic pulses. The claim is that these pulses can affect the brain's neurotransmitter levels and correct dysfunctional brain pathways. Patients remain awake during the procedure, and unlike ECT, TMS does not induce a seizure. Because a strong magnet is used, TMS is contraindicated in patients who have metallic objects or implanted stimulator devices in or near their head.

Does it work?
Studies on the use of TMS in adults with depression have been promising, though not spectacular. The FDA has approved its use for treatment-resistant depression, migraines, and obsessive-compulsive disorder.

Research in children and adolescents, meanwhile, is unfortunately lacking and consists almost entirely of case reports and open-label studies. The only randomized controlled trial involved just 2 patients! The available reports include a total of 112 patients, mean ages 11–21 years. Most of the youths had treatment-resistant depression, and more than half responded to TMS (Croarkin PE et al, *Child Adolesc Psychiatric Clin N Am* 2019;28(1):33–43). Since the majority of studies involved older adolescents and young adults, it is unknown if TMS is as effective for depression in children and younger adolescents.

The largest, and most recent, trial by MacMaster and colleagues included 32 outpatients with moderate to severe treatment-resistant depression, ages 13–21 years. Patients underwent a 3-week, open-label trial of TMS. The primary outcome measure was change in Hamilton Depression Rating Scale scores. There were 18 (56%) responders, with 14 (44%) achieving remission. No serious adverse events were noted. The most common side effects were mild to moderate headaches (19%) and mild neck pain (16%). The compliance rate with treatment was 99% (MacMaster FP et al, *Front Psychiatry* 2019;10(article 170);1–6). A larger randomized controlled trial of TMS is in progress and will conclude in December 2019 (https://clinicaltrials.gov/ct2/show/NCT01804270).

Treatment protocols
Since TMS is not FDA-approved for depression in children and adolescents, a standardized protocol has not been established. In the MacMaster study, TMS was applied at 10 Hz with each run consisting of 40 pulses at 120% the resting motor threshold over 4 seconds. Treatment sessions lasted 37.5 minutes with 75 runs/3,000 pulses. Patients received TMS every weekday for 3 weeks, 15 days in total (MacMaster FP et al, *Front Psychiatry* 2019;10(article 170);1–6). In other studies, the average duration of treatment has been 6 weeks/30 sessions.

Is it safe?
While the research is limited, TMS is apparently safe for use in children and adolescents. Krishnan et al conducted a meta-analysis that included data from 48 studies involving more than 513 youths, ages 2.5–17.8 years. Side effects were mild and transient. The most common were headache (11.5%), scalp discomfort (2.5%), and twitching (1.2%) (Krishnan et al, *Brain Stimulation* 2015;8(1):76–87). There are a few case reports of TMS inducing seizures, syncope, or hypomania.

In terms of cognitive effects, preliminary findings in older adolescents suggest TMS doesn't adversely alter cognitive functioning and may provide modest improvement of verbal memory (Wall CA et al, *Front Psychiatry* 2013;4(article 165):1–8). An unanswered yet critical question is the long-term effect of TMS as a neuromodulatory treatment on the developing brains of children and young adolescents.

Logistics
Typical costs for TMS are $300–$500 per session. Multiplied by 5 sessions a week for the first 4–6 weeks, the price tag can be anywhere from $6,000 to $15,000 (https://www.medpagetoday.com/psychiatry/depression/56168). By comparison, ECT costs about twice as much per session, while medications and therapy typically cost much less over similar time periods. Still, it is not uncommon to hear recommendations for extended TMS treatment, which may, like extended medication and therapy, result in fairly similar raw costs. However, with FDA approval only for adults 18 and older, insurance coverage for TMS in children and adolescents is nonexistent.

In this age of poor reimbursement and high overhead, many providers consider providing TMS. Costs of machines range from $50,000 to more than $100,000. However, machines can be leased for as low as $900/month (https://mycloudtms.com/tms-machine). Some factors to consider in setting up a TMS practice include staffing and space: A standard-sized room, 12 x 15 feet, is needed. No special shielding is necessary, but the machine must be operated by a trained medical professional. Ethical issues include how one markets and how one provides truly informed consent in an off-label TMS clinic—particularly in light of the scant research and unclear potential risks in children.

CCPR VERDICT: While the long-term impact of TMS on people, especially children, is unknown, in short-term use TMS is probably safe for teens, although headaches may pose a limiting factor for some patients. However, efficacy is unclear, and the cost and time required for treatment are important considerations. Specific medications such as fluoxetine and therapies such as CBT have better research to support their use in depression in children and teens, but TMS may be a helpful option in cases where those modalities have failed or are less palatable to families, as well as an adjunctive treatment.

Q&A With the Expert

Practical Approaches to Vetting Clinical Research

Darren B. Courtney, MD, FRCPC

Staff Psychiatrist for the Youth Addictions and Concurrent Disorders Service at the Centre for Addiction and Mental Health (CAMH), Toronto, Ontario, Canada

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

CCPR: Tell us a bit about your current work. What is your population? Whom do you treat?

Dr. Courtney: My clinical population are patients with concurrent addictions and mental health issues. These patients present complex clinical challenges, and so I have made efforts to use a method to think about and sort through those problems.

CCPR: Please share with us the method that you prefer to use to efficiently frame clinical questions.

Dr. Courtney: Sure. It's called the PICOT method. The idea here is that you need to narrow your literature search down to your specific clinical case. The "P" stands for population—specifically, the age groups, the overall condition of the population (diagnostic, socioeconomic, etc), and the inclusion and exclusion criteria. The "I" stands for intervention: the intervention of interest that you're looking for in the clinical literature. Often, it's related to medication or specific psychosocial intervention (Riva JJ et al, *J Can Chiropr Assoc* 2012;56(3):167–171).

CCPR: I've heard some people spell it PECOT instead of PICOT.

Dr. Courtney: Right. If it's an observational study, you might spell it PECOT, with the "E" standing for exposure. For example, if you're interested in knowing if trauma increases the risk of depression or substance use, then the study involves an exposure instead of an intervention. The "C" stands for comparison: You might be interested in comparing the intervention to a wait list, to treatment as usual, or to another active intervention. The "O" stands for outcomes: What's the primary outcome that you're interested in? It could be symptom reduction, or better functioning, or many other things. And lastly, the "T" stands for timing: the time course over which you're expecting to see the outcomes for your clinical question.

CCPR: How can this method help in everyday clinical life to clarify our thinking about a patient?

Dr. Courtney: The idea is to apply the evidence we have to our clinical presentations and then see how research studies apply. By framing your clinical question in this PICOT format, it's easier to see which studies might apply to your question, or to what extent they might apply. PICOT helps frame the clinical question in a way that makes it easier to search through literature, to know what's relevant or not relevant for your question.

CCPR: Do you have a specific example of how you would use the PICOT method?

Dr. Courtney: Sure. Say a child shows up with symptoms of ADHD. It's common for parents to ask whether there are any effective non-pharmacological interventions or even nutraceuticals like omega-3s. Using the PICOT method, you would start by asking about the population. So what age range is this child: prepubescent, pubescent, or adolescent? There are likely to be different papers on each of those age groups, and also on various presentations, such as ADHD combined type or inattentive symptoms only.

CCPR: That already narrows down our literature search considerably.

Dr. Courtney: Right. And then what is the intervention of interest—say, psychosocial interventions or specific psychotherapies, like cognitive behavioral therapy (CBT) or parent training? Which of those might you want to look at more specifically? Now, what do you want as the comparison group? Another treatment, perhaps treatment as usual for this kind of problem in this population in this community? Or perhaps comparing it with no treatment? Then there's the outcome: What specifically? Are you looking for decreases in aggression? Are you looking for improvement in school functioning? Are you looking for decreases in ADHD symptoms as your primary outcome? Lastly, are you hoping for an outcome within a certain amount of time?

CCPR: Right, I wondered about that.

Dr. Courtney: Yes. Typically, with stimulants you might see a pretty rapid improvement; but with psychosocial interventions, you might expect something to take more like 3 months or 6 months. So, the PICOT format makes it easier to do your search; when various studies come up, or even meta-analyses or systematic reviews or clinical practice guidelines (CPGs), you can apply the specific question and look for your answer in a more focused way. This is far better than doing a general search on psychosocial interventions for ADHD, which is too broad of a topic.

CCPR: You've mentioned several types of resources: studies, meta-analyses, systematic reviews, CPGs. What are the best kinds of studies for busy clinicians to look at? Is there a hierarchy that you suggest?

Dr. Courtney: We recommend relying on good CPGs first and foremost. That said, there's a large variety of CPGs out there, and they're of varying quality. Our group has done a systematic review of CPGs for

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Expert Interview – Practical Approaches to Vetting Clinical Research

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depression and anxiety, and we are currently working on one for ADHD and disruptive behavior disorders. We have found only a select few that meet a high standard, so it's important to understand what makes a quality guideline.

CCPR: What if there are gaps in the literature?

Dr. Courtney: That's pretty common. When that happens, a good CPG uses methods to arrive at consensus among experts. High-quality CPGs also incorporate feedback from family members, from caregivers, and from people who've struggled with the disorder in question.

CCPR: What if there isn't a high-quality CPG to turn to?

Dr. Courtney: Then we move on to meta-analyses, which synthesize multiple studies and pool the information and data in such a way that we can estimate the effects a specific treatment has relative to the comparison group. And if that's not available, you can go with the primary randomized controlled trials (RCTs); in many cases, that's all we have for various PICOT questions. But we have to be careful with that, because often one randomized trial is done and shows one result, but then another randomized trial is done and shows a very different result. So we have to be wary about just counting on results from one study.

CCPR: And systematic reviews are not quite as valuable as meta-analyses, but more valuable than one or two RCTs, right?

Dr. Courtney: Yes. Systematic reviews would come in between meta-analyses and individual RCTs. The downside is that they don't pool the data. Sometimes studies are so different that pooling data makes no sense and it is better to do a systematic review, which describes what data are out there.

CCPR: In child and adolescent psychiatry, we often don't have the studies that we want, which is why confirmation studies are critical. Would you concur that if you don't have much else, a second RCT adds a lot more certainty versus just having one?

Dr. Courtney: Yes, I would agree with that. Having at least two RCTs is required to be considered Level 1 evidence or Level A evidence, depending on which system you're using (https://tinyurl.com/yxzabd3z). We can feel more confident with the results if they're replicated in two RCTs (see the "Categories of Evidence for Clinical Practice" table below).

CCPR: If two RCTs is an A, what would constitute a B?

Dr. Courtney: Level B (or Level 2) is if there's one RCT. There is a mood and anxiety disorders guideline system in Canada, the Canadian Network for Mood and Anxiety Treatments (CANMAT), that has different criteria than the UK's National Institute of Clinical and Health Excellence (NICE) guidelines or the APA guidelines. Each of them uses slightly different methods to assess their evidence. But a top level of evidence requires at least two RCTs.

CCPR: Right, and with the advent of required registration and reporting of clinical trials, we are seeing publication of negative trials, like the two negative RCT trials on desvenlafaxine for depression in children.

Dr. Courtney: I think it's a great effort to try and make sure that we're publishing negative as well as positive trials.

CCPR: Do you have go-to sources for CPGs and other good data to assess clinical questions?

Dr. Courtney: NICE in the UK is consistently high quality and is a good place to start (https://www.nice.org.uk). They do systematic reviews on the relevant PICOT questions, as well as focus groups with people who have struggled with a disorder or with their caregivers. They do a good job of linking the evidence to the clinical questions. Next, I often look at Cochrane Reviews because I know their methods are sound (https://www.cochranelibrary.com/cdsr/about-cdsr). However, Cochrane Reviews often say

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"The PICOT format makes it easier to do your search; when various studies or meta-analyses or systematic reviews come up, you can apply a specific question and look for your answer in a more focused way. This is far better than doing a general search on something like psychosocial interventions for ADHD, which is too broad a topic."

Darren B. Courtney, MD

Categories of Evidence for Clinical Practice

For use in addressing clinical questions, arranged from most to least weight of evidence.

Type	Description
Clinical practice guidelines (CPGs)	Combines data from multiple RCTs with expert opinion and patient experiences
Meta-analysis	Combines data from multiple RCTs, giving more power to find results and more precision
Systematic review	Looks at multiple RCTs that might be too different to combine their data in a meta-analysis
Randomized controlled trials (RCTs)	One RCT alone is limited, but two RCTs with similar results makes a far more impressive argument
Open-label studies	Prone to placebo effects of around 50% "improvement" as well as other biases
Studies from related fields	Other conditions, animal models, bench research, etc
Expert opinion alone	Borrowing treatment for another condition for a similar-looking situation

News of Note

FDA Approves Adhansia XR

We are always in need of a new formulation of stimulant medication that might capture a few more of our patients who just do not quite tolerate or respond well enough to the many existing formulations. So whenever a new one is released, we try to set aside our natural skepticism and take a look at the stated facts before judging its merit.

Adhansia XR is a new formulation of extended-release methylphenidate approved by the FDA for the treatment of ADHD in patients 6 years and older. Adhansia XR capsules contain both immediate-release (IR) and extended-release (ER) beads of methylphenidate, in an IR/ER ratio of 20/80. By comparison, IR/ER ratios of other long-acting methylphenidate products are: Aptensio XR 40%/60%, Concerta 22%/78%, Cotempla XR-ODT 25%/75%, and Focalin XR 50%/50% (dexmethylphenidate). Adhansia's composition implies it will have a long duration of effect, and initial studies showed efficacy up to 16 hours.

Approval was based on 4 clinical studies, 1–4 weeks in duration, which showed efficacy for ADHD symptoms in both children and adults. The most common side effects of Adhansia XR were decreased appetite, insomnia, and weight loss in children, and insomnia, dry mouth, and decreased appetite in adults.

Adhansia XR will be available in 6 strengths (25, 35, 45, 55, 70, and 85 mg capsules, which may all be opened and sprinkled), and recommended dosing is to start 25 mg QAM (ages 6 and up) and increase in increments of 10–15 mg in intervals of 5 days or more. Dosages as high as 85 mg/day in pediatric patients and 100 mg/day in adult patients have been studied, but doses greater than 70 mg/day in children and 85 mg/day in adults were associated with greater adverse effects.

CCPR'S TAKE

It is possible that if the 16-hour duration holds, Adhansia may prove useful for families who never seem to remember the afternoon booster that many patients need to get through homework at the end of a long day. However, the news of note here is that Adhansia is likely another "me too" formulation, and it is important to stand clear of the hype and wait for more research, if it is forthcoming.

—Talia Puzantian, PharmD, BCPP, and Joshua Feder, MD. Drs. Puzantian and Feder have disclosed that they have no relevant financial or other interests in any commercial companies pertaining to this educational activity.

First Non-Drug Treatment Approved by FDA for Treating Children With ADHD

NeuroSigma made a splash by announcing that the FDA has granted medical device approval for its external Monarch Trigeminal Nerve Stimulation (eTNS) System for treating kids with ADHD ages 7–12 who are not currently taking medications.

What does medical device approval mean?

The FDA reviewed the Monarch eTNS System through the de novo pre-market review pathway, a less rigorous process than the usual pre-marketing approval process. This is a regulatory pathway for low- to moderate-risk devices of a new type, which asserts that the device is safe to use. The process does not affirm effectiveness of the device for the intended use. This level of approval means that subsequent devices of the same type with the same intended use may go through a process that allows the manufacturer to market its device just by demonstrating equivalence to this first (de novo) device.

How does it work?

The cellphone-sized device is meant to be used at home, under a caregiver's supervision, for 8 hours while the child sleeps. The device has a thin wire that connects to a small adhesive electrode patch, which is placed on the child's forehead just above the eyebrows. It provides a low-level electrical pulse (120 Hz frequency and cycles of 30 seconds on/off with 2–4 milli-amperes of current), causing mild stimulation to branches of the trigeminal nerve.

Is it effective?

A small 4-week study of kids with moderate to severe ADHD compared treatment with eTNS (n = 32) to a sham placebo device (n = 30). The primary outcome measured was the clinician-administered ADHD Rating Scale (ADHD-RS) total score. Although only slightly more than half of eTNS kids had clinically meaningful improvement, a statistically significant reduction was seen compared to placebo (eTNS score 34.1 at baseline to 23.4 at 4 weeks vs placebo device score 33.7 at baseline to 27.5 at 4 weeks), though improvement was seen in both groups. The estimated effect size of 0.5 is similar to the effect sizes seen with non-stimulant medications used to treat ADHD (a medium effect). The number-needed-to-treat (NNT) based on Clinical Global Impression—Improvement (CGI-I) scores at week 4 was 3. This means 3 people would need to be treated to find one who responds (in other words, for every patient who does better than placebo, 2 would have done just as well on placebo).

Is it safe?

Most kids will feel a tingling sensation on the skin. Drowsiness, increased appetite, trouble sleeping, teeth clenching, headache, and fatigue were the side effects most commonly reported in the study. A statistically significant increase in heart rate was seen, but pulse rates were still in the normal range and kids were not symptomatic. Weight gain was also statistically significantly greater in the eTNS group. Skin whitening or discoloration under the patch was seen in both groups, particularly in darker-skinned kids. This was attributed to loss of superficial skin layers when the patch was removed, and the discoloration resolved over time and with sun exposure.

How much will it cost?

The prescription-only device will be available from NeuroSigma "in the coming months," and pricing information is not yet available, although some accounts have priced starter kits at $900.

CCPR'S TAKE

This is an interesting "gee whiz" device that will no doubt capture the

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Research Updates IN PSYCHIATRY

ANXIETY

Prescribing Patterns for Children With Anxiety Disorders

REVIEW OF: Bushnell GA et al, *J Clin Psychiatry* 2018;79(1):pii:16m11415

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 anti-anxiety 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.

Unsurprisingly, most children were started on an SSRI (70%), while some received benzodiazepines (11%), hydroxyzine, guanfacine/clonidine, an atypical antipsychotic, or an antidepressant/anti-anxiety 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.

CCPR'S 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.

Lastly, 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.

—Pavan Madan, MD. Dr. Madan has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

AUTISM

Melatonin for Insomnia in Patients With Autism

REVIEW OF: Maras A et al, *J Child Adolesc Psychopharmacol* 2018;28(10):699–710

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 = .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.

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.

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Research Updates IN PSYCHIATRY

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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.

CCPR'S 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 less reliable pill-to-pill variability.

Still, PedPRM may be a viable treatment option for children with autism and insomnia who have failed a comprehensive sleep hygiene approach including attention to sensory issues, daily exercise, and psychotherapy, all of which might be effective in this population.

—Jess Levy, MD. Dr. Levy has disclosed that she has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

PSYCHOSIS

Steroid-Induced Psychosis in the Pediatric Population

REVIEW OF: Hodgins GE et al, *J Child Adolesc Psychopharmacol* 2018;28(5):354–359

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 8 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.

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/day), the more chances of psychiatric manifestations. Discontinuation of steroids is the gold standard and typically completely diminishes the symptoms within a few days to 1 month. For instances where steroid taper is not possible, a trial of benzodiazepines and antipsychotics was helpful.

CCPR'S TAKE

This case highlights the need to search for specific causes of psychotic symptoms that can usually be resolved, avoiding unnecessary long-term treatments.

—Abhan Nazeer, MD. Dr. Nazeer has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

ADHD

Risk of Psychosis With Stimulants in ADHD Patients

REVIEW OF: Moran LV et al, *N Engl J Med* 2019;380(12):1128–1138

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

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.

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.

CCPR'S TAKE

Amphetamines, such as Adderall, are more likely to lead to psychosis than methylphenidate, though the actual prevalence is quite low. 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.

—Pavan Madan, MD.

Expert Interview – Practical Approaches to Vetting Clinical Research

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that the results are inconclusive, and then we're left without guidance. Still, if they do find a conclusive result, then we can be sure that that's been well-studied. The US Agency for Healthcare Research and Quality (AHRQ) also does good meta-analyses or systematic reviews (https://www.ahrq.gov). I'm constantly scanning literature, including interesting RCTs, but if I'm looking for the broad consensus on a specific topic, I'll look at those three sources.

CCPR: Hopefully, after this, our readers will be able to ask clearer questions and know where to go for decent information. But, of course, sometimes we just don't have the answers. What do you tell families or patients when we don't have the information we'd like?

Dr. Courtney: I work in a tertiary care center where patients have tried all of the evidence-based options that we have—often patients with treatment-resistant depression who've tried fluoxetine, sertraline, and then CBT. That's what we have in terms of robust information. The next-line attempt will depend on my formulation, and it comes with a disclosure that although it may be helpful, we're working with limited information. I reassure them that we're going to continue to monitor to see if it helps, and if not, we're going to switch things around and see where things go.

CCPR: This has been really helpful. Any other thoughts?

Dr. Courtney: We're currently looking at integrated care pathways, where you take the guideline recommendations and put them into a treatment algorithm. Our depression clinic for adolescents is implementing this as a default protocol. Of course, clinicians are still always allowed to make their own clinical decisions. We're examining that now in research and seeing where that goes.

CCPR: Thank you for your time, Dr. Courtney.

News of Note

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imagination of families looking for a simple approach who don't want their kids treated with medications, cognitive behavioral therapy (CBT), or parent training, even though these have a proven track record of safety and efficacy. We're going to need more data than 62 kids in a 4-week manufacturer-run study to understand eTNS' place in therapy for kids with ADHD. Moreover, the weight gain seen in this study begs for more investigation, perhaps having to do with changes in sleep and cortisol.

—Talia Puzantian, PharmD, BCPP, and Josh Feder, MD.

Carlat Publishing News

Updates on additional clinical resources we're working on

The Carlat Psychiatry Report: The May issue features a lead article on the sexual side effects of medications and an Expert Q&A discussing evidence-based dietary plans for managing depression. The June/July double issue will feature lead articles on esketamine as well as auditory hallucinations, while the Expert Q&A will cover the practical management of psychotropic side effects such as nausea, sweating, and dry mouth. The August issue will feature lead articles on l-methylfolate for depression as well as sexual dysfunction in women. August's Expert Q&A will continue the coverage on the practical management of psychotropic side effects, discussing hair loss, weight gain, akathisia, and orthostasis.

The Carlat Addiction Treatment Report: The May/June double issue features lead articles on managing substance-related agitation as well as cognitive behavioral therapy for substance use disorders. The two Expert Q&As cover the treatment of co-occurring psychiatric disorders and co-occurring addiction and PTSD. The July/August issue will feature a primer on confidentiality in addiction treatment, while the Expert Q&A will cover treating addiction in patients transitioning to or from incarceration.

Current book titles:

- *The Medication Fact Book for Psychiatric Practice* (Fourth Edition), available with 12 CME credits
- *The Child Medication Fact Book for Psychiatric Practice*, available with 8 CME credits
- *Psychiatry Practice Boosters* (Second Edition), available with 8 CME credits
- *Addiction Treatment—A Carlat Guide*, available with 8 CME credits

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1. Which of the following is the most common side effect of noninvasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS), in children and adolescents younger than 18? (LO #1)

   [ ] a. Seizure
   [ ] b. Nausea
   [ ] c. Headache
   [ ] d. Scalp discomfort

2. According to a recent study, SSRIs and other classes of antidepressants have been shown to have the greatest efficacy for treating which pediatric disorder? (LO #2)

   [ ] a. Panic disorder
   [ ] b. Non-OCD anxiety
   [ ] c. Major depressive disorder
   [ ] d. Specific phobia

3. The letter "O" in the PICOT format for framing research questions stands for _____. (LO #3)

   [ ] a. Outcomes
   [ ] b. Other
   [ ] c. Observation
   [ ] d. Organizational

4. In a 2018 study examining the prescribing patterns for the initial treatment of pediatric anxiety, what percentage of the patients received both a diagnosis and a prescription on the same day? (LO #4)

   [ ] a. Under 10%
   [ ] b. Approximately 25%
   [ ] c. Approximately 45%
   [ ] d. Over 50%

5. According to Dr. Ignaszewski, which medications are the best first-line treatment choices for children and adolescents with depression? (LO #2)

   [ ] a. Sertraline and escitalopram
   [ ] b. Duloxetine and fluoxetine
   [ ] c. Sertraline and fluoxetine
   [ ] d. Fluoxetine and escitalopram

6. Although TMS can average $300–$500 per session, insurance reimbursement rates for TMS in children and adolescents are usually high, with at least 50% of the cost covered by most plans. (LO #1)

   [ ] a. True
   [ ] b. False

7. Children with autism taking pediatric prolonged-release melatonin (PedPRM) medication for sleep problems had which of the following outcomes? (LO #4)

   [ ] a. Improved sleep outcomes in the short term; no sustained improvements after 37 weeks
   [ ] b. 25% of patients discontinued use after 16 weeks due to daytime fatigue
   [ ] c. Over half of patients discontinued use after 37 weeks due to daytime fatigue
   [ ] d. Improved sleep outcomes in the short term; sustained improvements after 37 weeks

8. According to the levels of evidence for clinical studies, having one randomized controlled trial (RCT) qualifies the evidence to be considered as Level A (or Level 1). (LO #3)

   [ ] a. True
   [ ] b. False

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Note From the Editor-in-Chief

In this double issue, we tackle a range of questions. First, does TMS help kids and teens with depression? Is it safe? Since many clinics are advertising TMS, we thought it was worth a close look. This leads us to a broader question: How should we develop and then try to answer the questions that come up in daily clinical practice? Our interview with Dr. Courtney helps us understand this process, and we've included a table on different kinds of evidence to help you vet the research you find. Then, in a newer and more sophisticated approach to analyzing studies on the treatment of depression in children and teens, our interview with Dr. Ignaszewski reveals eye-opening and reassuring insights.

Ever interested in the headlines we are all seeing, we look at two notable new releases in the field related to ADHD: Adhansia and eTNS. Are they useful? Should we be considering them? And finally, this issue looks at research on practice patterns in treating anxiety in kids by different kinds of clinicians over time, as well as a study on the utility of melatonin for supporting sleep in children with autism. It is a fully packed and practical double issue. As always, please let us know what you think!

Regards,
Josh Feder, MD
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