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Joshua D. Feder, MD
Editor-in-Chief

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IN THIS ISSUE

Anxiety in Children and Adolescents

Learning Objectives

After reading these articles, you should be able to:

1. Describe some of the challenges in assessing and diagnosing anxiety in children and adolescents.
2. Identify some of the benefits and drawbacks of using benzodiazepines to treat anxiety in children and adolescents.
3. Summarize some of the current findings in the literature regarding psychiatric treatment for children and adolescents.

Benzodiazepines in Children and Adolescents

Murat Pakyurek, MD. Director, Child and Adolescent Psychiatry Division, University of California, Davis Medical Center

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

Michael, who's 9, is brought in by his parents for his first psychiatric assessment. His parents report that lately, Michael has been worrying all the time. He asks to sleep in his parents' bed. This past month, he also began having problems separating from his parents in the morning for school. Michael's therapist suggested a medication assessment. His parents are distressed, and his mother recently gave

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In Summary

- Anxiety disorders often drive cognitive and learning problems as well as conduct problems.
- Research shows benzodiazepines to only be effective in children for a narrow set of situations.
- Although there's a trend toward using benzodiazepines for child anxiety, there are many potential problematic outcomes. If you prescribe these drugs, keep their use short term and monitor closely.

Q&A With the Expert

Acting Out: Is It Anxiety?
Ira Glovinsky, PhD

Licensed psychologist and principal at the Glovinsky Center for the Child and the Family in West Bloomfield, MI.

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

CCPR: We see so many kids who are acting out. Can you begin by telling us about how anxiety can be hidden in oppositional or other acting-out behavior?

Dr. Glovinsky: I see that all the time. What you're bringing up are two groups. One group looks like oppositional behavior with comorbid anxiety underneath. The other is a group of kids who are having difficulty with comprehension and learning, and when teachers ask them to perform, they get flooded with anxiety. A teacher will call me in to observe a kid who is acting out, and what I will see is that the teacher is really having difficulty understanding what's going on. The teacher is expecting me to focus on aggressive, sometimes destructive behavior, and I'll bring up the term anxiety, explaining that it is like putting a glass under a faucet, turning it on, and forgetting that you've turned on the water. At some point, it floods over. This child is very uncomfortable in the classroom setting.

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Benzodiazepines in Children and Adolescents

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Michael half of her own 0.5 mg tablet of alprazolam, which "worked beautifully." Michael now declines to go to therapy and asks for the "fear pill." However, his parents tell him this must be prescribed by his own "worry doctor."

Michael may be like a lot of your patients. Because of their quick action, benzodiazepines (BZDs) are frequently prescribed to treat patients with anxiety and other conditions. However, as we already see with Michael and his family, clinicians need to consider the potential for unintended and problematic consequences of benzodiazepine use. The following is a primer that might help you decide how to approach these challenging situations.

First, though, here's a brief history of benzodiazepines. In 1955, while working to replace barbiturates, Polish chemist Leo Sternbach discovered chlordiazepoxide. Further investigations showed the compound to have potent sedative, anticonvulsant, anxiolytic, and muscle-relaxing effects. In the 1970s, BZDs became the world's most commonly prescribed medications. The Rolling Stones' 1966 hit "Mother's Little Helper" was about diazepam. In the 1980s, research uncovered how chronic benzodiazepine use could cause dependence and withdrawal (Lader M, *J Clin Psychiatry* 1987;1(48):12-6).

How do benzodiazepines work? They increase the efficiency of gamma-aminobutyric acid (GABA), which is the major inhibitory neurotransmitter in the brain. GABA's function is to slow or calm neural processes, which may explain why enhancing its efficiency helps to treat anxiety disorders in adults and children.

About child/adolescent anxiety

Anxiety disorders affect 15%–20% of youth (Kessler RC et al, *Int J Methods Psychiatric Res* 2012;21(3):169–184). Clinical research in pediatric anxiety focuses on three main syndromes: generalized anxiety disorder, social phobia, and separation anxiety disorder, which all share a similar neurophysiology, comorbidity, and treatment response.

All three of these conditions respond to benzodiazepines, SSRIs, and cognitive behavioral therapy (CBT), which includes psychoeducation of children and caregivers, relaxation training and breathing techniques, cognitive restructuring, problem solving, and systematic exposure to feared stimuli, among other strategies.

Medication studies for anxiety have focused more on SSRIs than benzodiazepines. As an example of SSRI research, the efficacy of both medication and therapy was demonstrated in the CAMS (Child/Adolescent Anxiety Multimodal Study), which randomly assigned 488 children and adolescents ages 7–17 to CBT, sertraline, sertraline plus CBT, and placebo. All active treatments were superior to placebo. The combination therapy was superior to medication or CBT alone, and over 80% of acute responders maintained positive response at 24- and 36-week follow-ups (Piacentini J et al, *J Am Acad Child Adolesc Psychiatry* 2014;53:297–310).

Reasons to use benzodiazepines in children

Although SSRIs are usually the medication treatment of choice for anxiety in children, benzodiazepines are becoming increasingly popular. A study in the United Kingdom showed a significant increase in anxiolytic prescriptions for youth seen in primary care settings between 2003 and 2011 (John A et al, *Journal of Affective Disorders* (2015);183:134–141). As the authors hypothesize, controversies about the suicide risk of SSRIs may be steering general practitioners away from these meds and toward benzodiazepines, which are seen as less risky.

There is good evidence that benzodiazepines are effective in children for a narrow set of situations, in particular episodic stressors like surgical procedures that may trigger acute anxiety, leading to concentration problems, insomnia, behavioral issues, and functional impairment. In a meta-analysis on the efficacy of BZDs as acute anxiolytics in children undergoing procedures, 21 trials involving 1,416 participants were reviewed, and the conclusion was that BZDs are effective and well-tolerated when used as short-term anxiolytics for pediatric patients (Kuang H et al, *Depress Anxiety* 2017;34:888–896). In particular, there was no difference in the emergence of irritability in the BZD vs control groups.

Another condition where BZDs can be helpful is pediatric catatonia. This likely under-recognized condition

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Anxiolytic Options for Children and Adolescents							
Generic Name (Brand Name) Year FDA Approved [G] denotes generic availability	**Relevant FDA Indication(s)**	**Available Strengths (mg)**	**Onset of Action (oral)**	**Half-Life (hours)**	**Duration of Action (hours)**	**Usual Pediatric Dosage Range (starting–max) (mg)**	**Comments**
Alternatives to SSRIs, TCAs, and Benzodiazepines							
Buspirone (BuSpar) [G] 1986	GAD	Tablets: 5, 7.5, 10, 15, 30	1–2 weeks+	2–3	N/A	5 mg TID–20 mg TID	Very limited data, showing no benefit over placebo in GAD in children
Clonidine (Catapres, Kapvay) [G] 1974	ER approved for ADHD (6–17 years); anxiety, tics (off label)	IR tablets: 0.1, 0.2, 0.3 ER tablets: 0.1, 0.2	30–60 min	1	12–16	0.1–0.6, divided BID to TID (HS to BID for ER)	Used especially when comorbid ADHD or tics
Clonidine Transdermal (Catapres TTS) [G] 1984	ADHD, anxiety, tics (off label)	Patches: 0.1, 0.2, 0.3 per 24 hours	2–3 days	20	5–7 days	8–20 kg: 0.1 weekly > 20 kg: 0.2 weekly	Controlled amount released over 7 days but may seem to lose effect after 5 days; less data in peds population; caution of inadvertent chewing on patch, which may lead to serious cardiovascular toxicity
Guanfacine IR (Tenex) [G] 1986	ADHD (only ER approved)	Tablets: 1, 2	1 hr	13–14	N/A	0.5–4 QD (do not increase faster than 1 mg/wk)	Very limited data suggesting improvement in generalized, separation, or social anxiety disorder; do not stop abruptly (rebound hypertension); not a 1:1 conversion from IR; do not give with high-fat meals; use especially when comorbid ADHD
Guanfacine ER (Intuniv) [G] 2009	ADHD (6–17 years)	ER tablets: 1, 2, 3, 4	30–60 min	13–14	N/A	1–4 QD (do not increase faster than 1 mg/wk) (adolescents 7 mg/day max)	
Prazosin (Minipress) [G] 1976	PTSD (off label)	Capsules: 1, 2, 5	1–2 hrs	2–3	4–6	1 mg/day–10 mg/day QHS or divided BID	Limited data in adults suggest improvement in nightmares associated with PTSD
Propranolol (Inderal) [G] 1973	Performance anxiety (off label)	Tablets: 10, 20, 40, 60, 80	60 min	3–6	4–6	< 35 kg: 10–20 mg TID > 35 kg: 20–40 mg TID	Start at 10 mg and titrate up (*Ed. note:* I also use long-acting preparations of 60 and 80 mg ER)
Benzodiazepines							
Alprazolam (Xanax, Xanax XR, Niravam) [G] 1981	GAD Panic disorder	Tablets: 0.25, 0.5, 1, 2 ER tablets: 0.5, 1, 2, 3 ODT: 0.25, 0.5, 1, 2 Liquid: 1 mg/mL	30 min (IR, ODT) 1–2 hrs (XR)	11–16	3–4 (IR) 10 (XR)	0.375–3.5 mg/day divided TID	Very limited data, showing no benefit over placebo in GAD or school refusal/separation anxiety
Clonazepam (Klonopin, Klonopin Wafers) [G] 1975	Panic disorder; insomnia (off label)	Tablets: 0.5, 1, 2 ODT: 0.125, 0.25, 0.5, 1, 2	1 hr	20–80	4–8	0.25 mg BID–1 mg BID	Very limited data, showing no benefit over placebo in GAD or social phobia
Diazepam (Valium, Diastat) [G] 1963	GAD; alcohol withdrawal; anxiety (short term)	Tablets: 2, 5, 10 Liquid: 5 mg/5 mL, 5 mg/mL Injection: 5 mg/mL Rectal gel: 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20	30 min	> 100	4–6	0.04–0.2 mg/kg Q2–4h PRN (0.5–12) 2–10 mg BID–QID (> 13)	Typically used as one-time dose in emergency, dental, or seizure settings
Lorazepam (Ativan) [G] 1977	GAD; insomnia (off label)	Tablets: 0.5, 1, 2 Liquid: 2 mg/mL Injection: 2 mg/mL, 4 mg/mL	30–60 min	10–20	4–6	0.05 mg/kg Q4–8h PRN; max 2 mg/dose	Limited use in pediatric patients

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presents with motor, vocal, and behavioral features. Its specific symptoms may include rigidity, posturing, stupor, negativism, and echopraxia/echolalia, among many others. A BZD challenge with lorazepam may help with both the diagnosis and treatment of pediatric catatonia (Benarous X et al, *Schizophr Res* 2017;30(17):430–439).

Checklists are also helpful for diagnostic clarification. These include SCARED (the Screen for Child Anxiety Related Emotional Disorders), SCAS (the Spence Children's Anxiety Scale), PARS (Pediatric Anxiety Rating Scale), and others.

The psychiatrist meets with Michael and his parents (both separately and together) and obtains relevant checklists (SCARED, PARS). He decides Michael meets criteria for generalized anxiety disorder as well as separation anxiety disorder. He prescribes lorazepam 0.5 mg daily, because lorazepam has a longer half-life and therefore may be less likely than alprazolam to cause dependence.

If you decide that a specific situation warrants use of benzodiazepines, which are the best ones to prescribe for children? In our experience, it is usually better to favor mid-range half-life medications, such as lorazepam, over either the shorter-range alprazolam or the longer-range diazepam. Drugs with shorter half-lives may bring rebound anxiety and craving, and those with longer half-lives can lead to accumulation of the drug and oversedation. Although some clinicians use PRN dosing for specific events, many will use a fixed dosing schedule when treating an ongoing symptom—this helps avoid withdrawal and craving that might lead to psychological and physiological dependence.

At follow-up a few weeks later, the parents note that Michael becomes irritable more often now, particularly before taking the lorazepam. The lorazepam also doesn't seem to be working as well for Michael's core anxiety symptoms as it had initially. The parents ask if Michael can take 2 pills to see if that will work better.

Problems with benzodiazepine usage

Common BZD withdrawal symptoms, such as anxiety and insomnia, occur in both children and adults. But since younger children can't always effectively articulate what they are feeling, it may be more difficult to differentiate their withdrawal symptoms from symptoms of the underlying anxiety issue. Long-term use of BZDs typically leads to tolerance, dependence, and withdrawal. In controlled BZD studies in children, irritability, fatigue/drowsiness, and dry mouth appear to be common problems. Additionally, these medications have a high abuse and diversion potential, so they must be carefully controlled.

Before prescribing BZDs, you should get informed consent from parents, making sure they understand the risks of dependency (mostly an issue with teenagers) and withdrawal. Children who are treated with BZDs chronically may have BZD withdrawal if the dosage is abruptly reduced, or if the medication is stopped—make sure parents understand this danger.

Tolerance, dependence, and withdrawal are potential issues in all patients using BZDs, including children. As with adults, tolerance and dose escalation may be a higher risk for individuals with past use of psychotropics and with a longer duration of use (Tvete I et al, *BMJ Open* 2013;3(10):e003296). Risk factors for benzodiazepine dependence also include alcohol dependence, sleep issues, and use of antidepressants.

The psychiatrist explains to the family that, despite the initially positive effect, the lorazepam is not working well for Michael's anxiety and is causing withdrawal side effects between doses. He prescribes a modest 25 mg daily dose of sertraline, plans for gradual reduction and discontinuation of the lorazepam, and encourages the family to return to the referring therapist for CBT. Michael's providers work together well, and within a few months his separation issues and fears gradually improve. His parents are instructed to avoid benzodiazepines in treating Michael's symptoms.

Care must be taken in the reduction and discontinuation of benzodiazepines to reduce the risk of withdrawal and craving. Benzodiazepines are thought to interfere with therapy, specifically CBT, partly due to memory impairment. Because BZDs reduce anxiety, they can leave patients less motivated to participate in therapy that is important to their long-term recovery.

Conclusions

Anxiety disorders, such as generalized anxiety disorder, social phobia, and separation anxiety disorder, are very common in children and adolescents. Current research supports use of psychological interventions (e.g., CBT) and, in moderate to severe cases, the addition of SSRIs. When faced with dental or surgical procedures, BZDs may have a limited but helpful role in children with acute anxiety. Keep their use very short term and monitor closely.

CCPR VERDICT: While benzodiazepines can be helpful for children, their most established uses are for acute anxiety management prior to dental and surgical procedures, and for catatonia. Try to avoid them when treating anxiety disorders—here, SSRIs and CBT are the treatments of choice.

Differentiating ADHD From Anxiety: Tips for Clinicians

Paula Jurczak, BSW. Child and family therapist. Joshua Feder, MD. Editor-in-chief, The Carlat Child Psychiatry Report.

Ms. Jurczak and Dr. Feder have disclosed that they have no relevant financial or other interests in any commercial companies pertaining to this educational activity.

When parents bring in their kids for concentration, attention, and learning issues, it's common to assume a provisional diagnosis of ADHD. In many children, however, anxiety can be the real cause of these problems.

Studies have long shown that about two-thirds of children and adolescents who present for ADHD evaluation have comorbid conditions, including learning disorders, mood disorders, anxiety disorders, sleep problems, and disruptive behavior disorders (Biederman J et al, *J Affect Disord* 1998;51(2):101–112). These underlying problems can all drive anxiety, and we must address each one to optimize treatment.

In this article, we will talk about how anxiety can profoundly affect cognitive ability in children, and give you tips on how to identify and treat this problem. But let's start by looking at the mechanisms of anxiety and how anxiety interferes with cognitive processes.

Mechanisms of anxiety in children

Most of us have experienced the muddled thoughts anxiety can cause. Public speaking is a classic and common example: You are an expert on a topic and normally an articulate person—but on the podium, panic suddenly strikes, and you forget your carefully practiced train of thought.

Bruce Perry, MD, PhD, whose career has focused on how stress and trauma affect child development, explains how the arousal states of anxiety interfere with the thinking of children and adolescents. According to Perry, there are five levels or states of general arousal: calm, alert, alarm, fear, and terror (See "Clinical Applications of the Neurosequential Model of Therapeutics," at http://bit.ly/2BMtGHI).

In the *calm state*, we can think and reflect, alone or with others. Our highest, most fully developed cognitive abilities are intact and active.

The *alert state* is the workhorse of everyday life; it provides us with the level of arousal necessary to ensure that we pay attention to the world around us. As an example, children are in the alert state when they raise their hand in class, the teacher calls on them, and they easily recall studied information.

In the *alarm state*, our ability to use learned skills and cognitive abilities is impeded, and ideas and judgments are cast in emotional terms. Children with anxiety-related concentration problems spend much of their time in this state. This is also the state where we might see tantrums, avoidance of tasks, comfort eating, or—in teens—substance cravings.

In the *fear state,* children tend to run off and escape from a classroom, from a house, or from your office. Alternatively, children might hide under the bedcovers at home or in the school nurse's office, or even cover their heads and faces with their sweatshirts during your appointments.

Finally, in the *terror state,* arousal is so high that it either renders children unable to respond or causes them to wildly strike out. While these episodes may pass, they can be of such severity that they often result in a referral for mental health evaluation or even an assessment for inpatient care.

How to identify anxiety as the cause of inattention

Knowing that anxiety may impair cognition is the easy part. What's tougher is distinguishing anxiety—as opposed to ADHD—as the cause of poor attention.

In your assessment, try to talk with the child, parents, teachers, and other caregivers. Ask them about the difficulties they observe, including which kinds of academic and social activities go well for the child, and which ones don't.

For the activities that go well, get a sense of whether the child is in a calm or an alert state, and how the child is thinking, relating, and concentrating during those times.

For the activities that are not going well, ask about how the child is different when in an alarm state. Often, as children enter this state, their thinking becomes black and white, more concrete, and less abstract. They lose the ability to see the big picture. As an example, children might not understand that if they pay attention now in math class, afterward there will still be time to play.

Ask about changes in the child's scope of time. When anxious, children will have less ability to think about yesterday, today, and tomorrow, and are more fixated on the frustration of the moment.

Find out what the child wants from the people who can help. Children in a calm or alert state are more able to ask for and accept help from adults. In an alarm state, they might want to take a break or have a snack. In a fear (or terror) state, they are not able to ask for help.

After the fact, children often have trouble recalling what an episode was like—this is an indication that arousal was overwhelming, that at the very least it was an alarm state, and that it interfered with creating sustained memories.

Helping children lower anxiety

There are some useful tips that can help you specifically treat the type of anxiety that leads to inattention. Consider the following:

Planning ahead: Catalog. By asking the right questions, you can make a list of the specific arousal states the child is experiencing during different activities. In particular, identify activities that are difficult for the child, and if the overall level of arousal is too high during a particular activity. Share this catalog with parents and teachers so that they can recognize when the child is over-aroused and anxious, and can find new ways to help the child based on this understanding.

During tough moments: Assess-Help-Recover. When a child is over-aroused, it is common for adults to become upset themselves and respond in a rigid, commanding, or angry manner. This generally creates more anxiety in the child, resulting in worsening of symptoms. Whether in your office, at home, or in school, you or the caregiving adult can try this simple plan,

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Differentiating ADHD From Anxiety: Tips for Clinicians

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developed by Dr. Diane Cullinane, to help things go better:

- *Assess:* Identify the state that the child is in.
- *Help:* See if the child can tell you what might help, and try to offer some of what the child wants. If the child cannot tell you, try staying calm and present, using fewer words, or giving the child some space while ensuring safety.
- *Recover:* Allow the child time to recover.

Replace questions with statements. In trying to help an anxious child talk through difficulties, avoid the question form of inquiry. Questions create a new demand of the child and can increase anxiety. Statements are usually less anxiety-provoking and allow the child an opportunity to correct you. For example, instead of saying, "Why are you so angry?" you might say, "I can see that you are really angry. Help me understand why." The child might tell you why, or correct you and say, "I'm not angry, I'm scared because ..."

Use "we" language. Using phrases such as "we can figure this out" is different from telling the child, "You need to ..." or "I'm going to ...," which often raises anxiety levels. Stating that you (rather than we) are solving the problem can keep the child from building a sense of competence.

Adjust your adult intensity. In most instances, it's important to stay calm and empathic, and not use a lot of words. This approach may allow the child to calm down. If it doesn't work, it is often because the child feels you don't care enough. Consider turning up your empathic intensity so you come off as concerned without being upset. For example, say to the child, "That sounds awful." The child might then feel better understood and can step down a notch from high arousal to a more workable level of concern.

Take a deep dive. Once the difficult moment has passed, the team needs to sort through and address the various reasons for the child's sensitivity to a situation. Although ADHD might be a factor, the entire differential should be considered. Look at sensory, motor, and specific learning challenges; biological rhythms, such as sleeping; toileting and eating; and other psychological, psychiatric, and social factors.

Choose the right therapy. There are many types of therapies designed to help children with anxiety. These include cognitive behavioral approaches, psychodynamic psychotherapies, play therapies, and supportive office care. Most therapies require a calm, clear, and patient approach. Harsh limits or edicts typically result in worsening symptoms, or if the child doesn't comply, a poor ability to generalize and adapt to new challenges.

Choose the right medication. Many medications can be helpful for anxiety. (See the medication table on page 3 for a look at the range of possible drugs to try.) While medication alone is not likely to address the child's problems, it can often make therapy and daily management more successful. Think about arousal levels and consider use of central alpha agonists, such as guanfacine, before resorting to SSRIs, which may have more side effects. As benzodiazepines may create even more unintended problems, we recommend avoiding them. (See lead article on page 1.) Other medications to consider include beta blockers, such as propranolol, and—when used with care—occasionally the older tricyclic antidepressants. The most severe forms of anxiety sometimes require consideration of anticonvulsant-class medications or antipsychotics; however, look again at the overall plan of therapy and support to the child before getting into complex psychopharmacology.

For more information on resources for child anxiety, see the table above. It can be used as a handout for parents and children as well as educators.

Child Anxiety Resources

Resource	Website	Description
Anxiety and Depression Association of America	www.adaa.org	FAQs and access to a community of experts on child anxiety
American Academy of Child & Adolescent Psychiatry	www.aacap.org	Resources for parents and children through AACAP's Anxiety Disorders Resource Center
Child Anxiety Network	www.childanxiety.net	Independent and easy-to-use site providing information for parents, teachers, and children
KidsHealth	www.kidshealth.org	Nonprofit designed to provide info that speaks to kids and parents in straightforward terms they can understand
Child Mind Institute	www.childmind.org/audience/for-families	Education for families on all common childhood disorders, including anxiety
Temple University's Child and Adolescent Anxiety Disorders Clinic	www.childanxiety.org	Includes tips for parents and suggested readings
WorryWiseKids	www.WorryWiseKids.org	A free resource center of information and tools to help parents and educators understand anxiety disorder and pick up on warning signs

CCPR VERDICT: Consider anxiety as a central factor when a child has poor academic function or poor attention. You should do a thorough assessment and model good, responsive caregiving practices in your office, including parents and/or teachers in the assessment and treatment plans. With these steps, the child will often do much better.

Expert Interview
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CCPR: So, how do you help the teacher better understand what's happening?

Dr. Glovinsky: Teachers often say to me: "The child's behavior evokes a feeling in me of wanting to punish the child for this behavior." And that usually ends up with the child being emotionally aroused and behaviorally active, the teacher being reactive to the child's actions, and the child then escalating further. Many times, that then leads to an emotional explosion by the child. But when I suggest to the teacher that this child is anxious, I want to get into a discussion with the teacher about how—rather than reacting—the teacher can think first about what is troubling this child. I then show the teacher how to respond by providing the support, structure, and scaffolding to decrease the child's uncomfortable feelings. When we do this, I've seen pretty dramatic behavioral changes.

CCPR: That's really helpful when it comes to having teachers help as part of treatment. But can you also talk about assessing a child in a clinical setting?

Dr. Glovinsky: Assessment requires us to pay attention at multiple levels. The first level is harder to measure. It's where we pay attention to our own reactions, emotional and physiological, and to the child and the family. We are all busy clinicians, but if we pause and take note of our natural responses and learn how we typically respond to various kinds of kids, we gain a valuable tool that supports our ability to effectively and efficiently assess a child. It may seem less scientific to cultivate intuition, but there is a growing body of research that supports this aspect of assessment (Marsh JK et al, *Psychol Assess* 2016;28(2):181–193). When a child has anxiety, I have a different reaction than with other behaviors, such as more pure conduct problems. My physiological response to anxiety is different than my response to a child's aggression or anger. Different emotions in the child trigger different emotions in me. Being aware of my own emotions enables me to respond to the child's emotional expression in a way that will help support the child. Our challenge is to be attuned to the child's emotions and to respond supportively and empathically rather than reactively.

"Assessment requires us to pay attention at multiple levels. Being aware of my own emotions enables me to respond to the child's emotional expression in a way that will help support the child. Our challenge is to be attuned to the child's emotions and to respond supportively and empathically rather than reactively."

Ira Glovinsky, PhD

CCPR: Many of us learned about countertransference in training. This is a great reminder of a powerful tool. What about other levels of assessment?

Dr. Glovinsky: The second level is interviewing the parents and listening to their story about the frequency of their child's negative behaviors, and the duration and the intensity of those episodes. It's important to know, on a scale of 1 to 10, what parents feel are the types of episodes that cause their child the most distress, and where and when these things are happening. Are we talking about pervasive or specific situations? The frequency, duration, and intensity of a child's episodes provides information that can be translated into an intervention plan. Also, the parent needs to know the triggers that cause the child's distress—for example, where, when, and why these things are happening. Are we talking about specific situations or a chronic pattern?

CCPR: Then, where do we go with interviewing the child?

Dr. Glovinsky: In interviewing the child, there should be questions about the uncomfortable feelings. Some anxiety, for example, is related to phobias. The child will often lay it right out there: "I'm afraid of this. This is what makes me feel anxious." You begin to see a pattern. Maybe it happens in math class each day and it doesn't happen with spelling or reading. This gives you a sense of the triggers. These symptoms are nonspecific. You see them in lots of disorders, and kids can very easily get misdiagnosed.

CCPR: So, what do you do next?

Dr. Glovinsky: I like to do longitudinal evaluations (repeated observations of the same variables) and mood charting, which I then teach the parents how to do over a month. It helps you to learn about the child's functioning in different settings. I take my time with the parents and tell them that that we are going to figure this out together. So, I'll do a parent interview, a parent-and-child interview, and a child interview, and have the parents fill out questionnaires to try and pull it all together. It sounds tedious, but it's hard to know what you're seeing unless you have the data. Often professionals make recommendations or start treatments without having all the data to know what they are seeing.

CCPR: How about transference experiences? Are these something that people can be aware of early on that might give clues to a diagnosis?

Dr. Glovinsky: We know that our responses to situations are colored by early experiences, particularly with our parents. Selma Fraiberg refers to this as "ghosts in the nursery," where parents are reacting to their children based on their own experiences with their own parents (Fraiberg S et al, *Psychiatr Enfant* 1983;26(1):57–98). All parents do this to a degree, even if they are not aware of it. We may react to the child based on our past relationships. So, when I talk to parents, I want to talk to them about all those past parenting influences. This almost invariably leads parents to talk about how their upbringing is

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Expert Interview
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affecting how they treat their child—for instance, "My dad yelled at me, and now I coddle my kid too much to make up for it." It is also a reminder to myself to be aware of how I am reacting to the child and to the parents. Our experiences affect our work with people, and being reflective and self-aware is very necessary in our work.

CCPR: How does a busy clinician do this while working with the child or family?

Dr. Glovinsky: In the moment, I will often remark, "Let me take a second to think about that," modeling that kind of reflective stance. When somebody is telling me a story, I might ask a gentle open-ended question, such as, "What's that like?" Then, as I listen, I try to put myself in the shoes of the other person. It is very powerful and enlightening. It's what Atticus Finch told Scout to do in *To Kill a Mockingbird*. But we often forget the importance of doing this and instead become judgmental about the child's behavior or the parents' style of parenting, which obscures our ability to really understand and help them.

CCPR: Can you talk a little about the constitutional factors that might be contributing to anxiety in children—things that we as child psychiatrists should be mindful of?

Dr. Glovinsky: A lot of the work that I do with parents ends up being psychoeducational. I have a whiteboard in my office where I'll draw things first to talk about differences in reactivity. I relate to parents that there's a stimulus, and it can be external or internal, and we all react to stimuli. So, that's a physiological experience, and I'll talk to them about differences in reactivity, and then I'll talk to them about differences in what I call "rise time."

CCPR: Rise time? Please tell us more.

Dr. Glovinsky: Rise time is the rate at which a person reacts and how intense that reaction is. For some of us, we go from 0 to 60—full throttle! But others are very slow to respond to situations. Some of this is physiological: the speed and intensity of sensory processing. Chess and Thomas talk of 9 variables of temperament that describe a person's general reactivity: mood quality, biological rhythmicity of sleeping and eating, and other bodily functions, including approach/withdrawal, persistence, adaptability, activity level, attention, emotional reactivity, and sensory reactivity (Thomas CS. *Temperament in Clinical Practice.* New York, NY: The Guilford Press; 1986). Just think about mood. If we are already anxious, we may be quicker to react and may do so more intensely. When we are depressed, we may be sluggish in our responses. I find it very helpful to talk with parents about their child's individual profile. So, instead of concluding that a child is being oppositional, we understand that this is an active child, who is quite reactive to emotions in others. This gives us a more rational, less judgmental map for parenting and for treatment.

CCPR: That's very helpful. Are there other pearls you might share along these lines?

Dr. Glovinsky: Sure. I also like to use the metaphor of a staircase, for which the first step is physiological. If that step is unsteady, then it is hard for the child to get to the next step, which is paying attention. And if she can't pay attention, then she can't manage the third step, which is emotional regulation. Without emotional regulation, she can't reach the next step and make rational cognitive decisions. We tend to focus on the top step, judging her poor behavioral decisions rather than looking at the steps below, particularly those first-step biological aspects.

CCPR: That's a helpful metaphor. Got any more?

Dr. Glovinsky: Yes. Different people respond to different analogies, and one of my favorites to talk with parents about are the autonomic nervous systems of animals. I note that herbivores developed alarm systems way back in time to sense danger, and even as omnivores we carry similar systems with us to this day. Just to be careful, sometimes that system goes off in a child when it doesn't need to, and how we respond to that can make a difference in whether the child becomes even more sensitive or learns to adjust his alarm system.

CCPR: Interesting. Can you give us an example?

Dr. Glovinsky: Sure. Often, when a child says that there are monsters under the bed, the parent checks and says to the child, "See? There are no monsters." But the very fact that the parent is checking is giving the child a message that monsters *could* be there. That then makes the child's "alarm system" more sensitive. I then tell the parents, "We're going to explain to you how to do something different. We're going to teach your child a word for anxiety." I have one little girl who uses a "lion" feeling for anger and a "bunny rabbit" feeling for anxiety. When I talk to her about being anxious, she doesn't have a clue what I'm talking about. But if I talk about that bunny feeling, she's got it. So I'll talk to the parents about finding a word to tap into. That way, if the child says, "There's a monster in my closet," the parent can respond with, "Oh boy, there goes that bunny rabbit feeling. We have to get that bunny rabbit calm."

CCPR: There's one final question that I have, and it always comes up for psychiatrists: What do you see as the role of medication in the treatment plan for children suffering from anxiety? What are your thoughts?

Dr. Glovinsky: I see medication to be extraordinarily helpful. In that, I think we should also look at frequency, duration, and intensity. Anxiety is a little different than mood disorders. Lots of times, because the child is doing chaotic things that could be life-threatening, mood disorders are extreme cases that need to be dealt with as an emergency. I don't see that with anxiety, so my tendency is to try and work with it, and to use different techniques, such as meditation and mindfulness. And then, if those don't seem to be working, we certainly use medication. In my clinical experiences, medication has been very helpful. But at other times, I think people jump in too quickly and don't give themselves the chance to observe, to ask the question about how anxiety has been dealt with by other clinicians.

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

Research Updates IN PSYCHIATRY

OCD

Azithromycin for Acute-Onset Obsessive-Compulsive Disorder in Children

REVIEW OF: Murphy et al, *J Child Adolesc Psychopharmacol* 2017; 27(7):640–651

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 was a randomized, double-blind, placebo-controlled trial comparing 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 four weeks over the study period.

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.

CCPR'S 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. The authors also recognize the limitations of the small study size, and view this as a pilot study that may lead to larger trials in the future. If you do embark on using azithromycin, consider baseline and follow-up electrocardiograms to watch for QTc changes.

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

BIPOLAR

Celecoxib as Adjunctive Treatment in Acute Mania

REVIEW OF: Mousavi et al, *J Child Adolesc Psychopharmacol* 2017; 27(6):494–500

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

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

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

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

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Research Updates IN PSYCHIATRY

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reported adverse events. Cardiovascular health was also monitored by physical exam and electrocardiogram, which remained normal throughout the study.

CCPR'S TAKE

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

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

DEPRESSION

Negative Efficacy of Desvenlafaxine and Fluoxetine for Children and Adolescents With MDD

REVIEW OF: Weihs et al, *J Child Adolesc Psychopharmacol* 2018;28(1):36–46

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

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

Patients were randomly assigned (1:1:1) to placebo, desvenlafaxine, or fluoxetine. Desvenlafaxine dose was chosen by body weight: 20 to < 35 kg: 25 mg/day; 35 to < 70 kg: 35 mg/day; and ≥ 70 kg: 50 mg/day. The patients were assessed weekly for the first month and again at weeks 6 and 8. The primary endpoint, change in the CDRS-R score from baseline to week 8, did not differ statistically from placebo (-23.1) for either desvenlafaxine (-22.6) or fluoxetine (-24.8). Adverse events (AE) attributed to medications were present in all study groups (desvenlafaxine, 28.7%; fluoxetine, 32.1%; and placebo, 34.8%). The most common treatment-emergent AEs were headache, upper abdominal pain, and nausea. There were no deaths in the study, but 5 patients receiving either desvenlafaxine or fluoxetine experienced serious AEs—suicidal ideation, a suicide attempt, disinhibition, and postpartum hemorrhage.

CCPR'S TAKE

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

But more importantly, this landmark publication of a negative study, where neither desvenlafaxine nor fluoxetine were efficacious for treating MDD in children and adolescents, was conducted with financial and medical writing support from Pfizer Inc. As we go to press, another negative study for depression in children is being published on desvenlafaxine by the same journal. There appears to be a sea change happening on the heels of the final rule from the FDA, which severely penalizes (through fines) the suppression of negative studies.

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

CME Post-Test

To earn CME or CE credit, you must read the articles and log on to www.TheCarlatChildReport.com to take the post-test. You must answer 75% of the questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be completed within a year of each issue's publication date. As a subscriber to *CCPR,* you already have a username and password to log onto www.TheCarlatChildReport.com. To obtain your username and password, please email info@thecarlatreport.com or call 978-499-0583.

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Below are the questions for this month's CME/CE post-test. This page is intended as a study guide. Please complete the test online at www.TheCarlatChildReport.com. Note: Learning Objectives are listed on page 1.

1. According to studies, what percentage of youth are affected by anxiety disorders? (LO #1)
   - [ ] a. 5%–10%
   - [ ] b. 15%–20%
   - [ ] c. 25%–30%
   - [ ] d. 35%–40%

2. A recent study concluded that benzodiazepines are effective and well-tolerated when used as short-term anxiolytics in procedural settings for pediatric patients. (LO #2)
   - [ ] a. True
   - [ ] b. False

3. After attempting non-medication approaches, you are considering using a benzodiazepine to treat your 13-year-old patient's school phobia. According to Dr. Pakyurek, which medication would be the optimal choice to minimize the potential side effects of rebound anxiety or over-sedation? (LO #2)
   - [ ] a. A shorter-range half-life medication, such as alprazolam
   - [ ] b. A dose-dependent half-life medication, such as clonazepam
   - [ ] c. A longer-range half-life medication, such as diazepam
   - [ ] d. A mid-range half-life medication, such as lorazepam

4. The term "ghosts in the nursery" refers to which of the following parent/child scenarios? (LO #1)
   - [ ] a. When children mimic the same reactions to anxiety-provoking scenarios as their parents
   - [ ] b. When parents react to their children based on their experiences with their own parents
   - [ ] c. When children inherit a predisposition to developing an anxiety disorder from their parents
   - [ ] d. When parents lack emotional attachment to their children because they were abandoned by one or both of their own parents

5. What was the outcome of a recent study on azithromycin for acute-onset OCD in children, based on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) and the Clinical Global Impression—Severity (CGI-S) scale? (LO #3)
   - [ ] a. A greater reduction in OCD severity according to both CY-BOCS and CGI-S scores
   - [ ] b. A greater reduction in OCD severity according to CY-BOCS scores, but no significant difference in the CGI-S scores
   - [ ] c. No significant difference in OCD severity according to CY-BOCS scores, but greater reduction in the CGI-S scores
   - [ ] d. No reduction in OCD severity according to both CY-BOCS and CGI-S scores

6. While risks may outweigh benefits, according to clinical research, benzodiazepines may be helpful when treating a pediatric patient with which condition? (LO #2)
   - [ ] a. Adjustment disorder
   - [ ] b. Obsessive-compulsive disorder
   - [ ] c. Sleep disorder
   - [ ] d. Separation disorder

7. According to Jurczak and Feder, approximately ____ of children and adolescents who present for ADHD evaluation also have comorbid conditions such as learning disorders, anxiety disorders, mood disorders, and disruptive behavior disorders. (LO #1)
   - [ ] a. 10%
   - [ ] b. 33%
   - [ ] c. 50%
   - [ ] d. 66%

8. In a recent study on the safety and efficacy of celecoxib for acute mania in adolescents, there were no significant differences in any of the reported adverse events between the celecoxib and control groups. (LO #3)
   - [ ] a. True
   - [ ] b. False

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This Issue's Focus:
Anxiety in Children and Adolescents

Next Time in *The Carlat Child Psychiatry Report:*
Psychotropic Risks in Children and Adolescents

Note From the Editor-in-Chief

Anxiety is a broad concept that permeates pretty much all of our work. In particular, anxiety often compromises cognitive ability and drives acting-out behavior. So, for our 2018 run at the topic, we speak with Dr. Ira Glovinsky about how anxiety manifests as behavioral dysregulation and is often misconstrued as misbehavior. How do we learn to pick up the cues that this may be going on? How do we help parents to step back from mere punishment and understand this process?

We also hear from Paula Jurczak, BSW, who helps us to parse the usual kinds of internal arousal, ranging from calm reflective states to productive alert states, then to the less adaptive states of alarm, fear, and terror. She reviews aspects of these states to help us recognize the level of arousal and its impact on thinking, then how to manage it and help other caregivers to do the same.

Also in this issue, we take on the benzodiazepine controversy. Perhaps no other subject in pediatric psychopharmacology raises such strong feelings. What are the rational indications? What are the risks? How does one approach the psychopharmacology of anxiety in a safe and measured manner? We provide a handy table to help you consider the often off-label but milder approaches if you have concerns about going right to SSRIs, much less benzodiazepines.

We know that this issue will give you a lot to think about, and we hope that it also gives you practical information and ideas to help you in day-to-day practice.

Regards, Josh Feder, MD
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