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Joshua D. Feder, MD
Editor-in-Chief

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IN THIS ISSUE

Autism in Children and Adolescents

Learning Objectives

After reading these articles, you should be able to:

1. Identify the pros and cons of various pharmacologic treatments for irritability in autism.
2. Assess for and treat suicidality in autism.
3. Differentiate between psychosis and autism and recognize psychosis in autism.
4. Summarize some of the findings in the literature regarding psychiatric treatment for children and adolescents.

Treating Irritability in Autism: Functional and Medication Approaches

Joshua D. Feder, MD. Editor-in-Chief, The Carlat Child Psychiatry Report.

Dr. Feder has no financial relationships with companies related to this material.

Jane is 10. She watches the children's program The Backyardigans *every morning, mimicking "Hey, they fit together. They do? They do!" When her parents take her electronic device, Jane screams and bangs her head. Her mother tells you, "We can't live like this."*

Irritability creates substantial distress for autistic individuals and their families. Risperidone and aripiprazole are FDA approved in the US for irritability in autism. While often effective, their side effects include weight gain (even with aripiprazole), neurotoxicity, tardive dyskinesia, and

Highlights From This Issue

Feature article
Avoid the side effects of using antipsychotics for irritability in autism. There are multiple steps we can take before we get to the point of using the FDA-approved medications.

Feature Q&A
When autistic kids and teens become despondent or suicidal, we need to modify our assessment to communicate effectively and address the problem.

Q&A on page 6
Use a careful history to differentiate between symptoms of psychosis and autistic traits, then address each more specifically as needed.

Research Update on page 8
Autism does not confer a greater risk of car accidents, but it may affect the kind of accidents that occur, and that knowledge can help drivers know where to focus their skill building.

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Q&A With the Expert

Addressing Suicidality in Autistic Children and Teens
Paul Lipkin, MD

Neurodevelopmental and developmental behavioral pediatrician. Director, Medical Outpatient Services, Kennedy Krieger Institute, Baltimore, MD.

Dr. Lipkin has served as an advisor for EarliTec and Sarepta Diagnostics. Relevant financial relationships listed for the author have been mitigated.

CCPR: How do the rates of suicidal thinking and suicide in autistic kids compare with the general population of kids?
Dr. Lipkin: Most of the data on suicide and autism comes from young adults—Kaiser Permanente in the US and public sources in England and Scandinavia. We ran a survey in 2017 with about 600 parents of autistic children where 40% said their child had expressed suicidal thoughts or behaviors. That's an astronomical number and skewed toward families affected by suicide. The general numbers are probably between 10% and 15%, which is still much higher than the general population (Segers M and Rawana J, *Autism Res* 2014;7(4):507–521). It's important to remember that the risk of injury is higher than the risk of death in most cases. We're not just here to prevent death. We also want to prevent injury.
CCPR: How do you think other co-occurring disorders, such as depression, impact suicide risk in autistic kids?

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Expert Interview—Addressing Suicidality in Autistic Children and Teens
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Dr. Lipkin: Depression and anxiety play a role. In 2019, Dell'Osso found a very high rate of anxiety disorders and mood disorders in autistic children, and in 2021, Blanchard found that co-occurring conditions are probably important risk factors for suicidal thinking (Dell'Osso L et al, *Compr Psychiatry* 2019;91:34–38; Blanchard A et al, *JAMA Netw Open* 2021;4(10):e2130272). In that paper, the odds of both self-harm and suicidality in autistic children and adults were three times the odds in those without autism.

CCPR: What is the impact of other factors on suicidality in autism such as social communication problems?

Dr. Lipkin: The social communication piece is a factor, with misuse or misunderstanding of language. Children on the spectrum are frequently bullied, and many experience loneliness with social isolation, which might lead to suicidal thinking. Perseverative and repetitive thinking are probably important too.

CCPR: How do you differentiate self-injurious behavior from suicidality in autistic children and teens?

Dr. Lipkin: Autistic children who have suicidal behavior tend to be in the mild range of intellectual disabilities or learning disabilities. Children with classic self-injurious behavior tend to have more severe disabilities and repetitive behaviors (eg, biting or slapping themselves, or banging their head against the wall). In many cases, this behavior is an expression of anger or sadness, but there's no clear wish to no longer be alive. If a child talks specifically about dying or not wanting to live, then it needs to be taken seriously as a suicidal thought regardless of degree of learning or language challenges.

CCPR: Are there common patterns in how autistic kids communicate and think about suicide that might help us to see it from their point of view?

Dr. Lipkin: Age and language skills are important factors in the way suicide words are used. Language problems can either be receptive or expressive. The child may have a hard time interpreting other people's language and at the same time have difficulty expressing themselves. They might say "I'm going to hang myself" without knowing what that means. Or a child who is in distress may not have the means to tell anybody. Neurotypical children at different levels of verbal expression have different ways of expressing themselves and understanding concepts. It's hard to generalize, and the words that the children choose can steer the listener in confusing directions. An 8-year-old neurotypical child will often say things like "I wish I were dead. I want to kill myself." At age 8, neurotypical children have a limited understanding of the consequences of their actions, of death, and of the words that we all use every day associated with death. These statements indicate distress but usually not a wish to self-harm or die. This is not the same as a 15-year-old who would say the same thing in terms of vocabulary, but with a different understanding of death and understanding of consequences.

CCPR: How do autistic kids and teens express suicidality?

Dr. Lipkin: It varies. Autistic children ages 13–18 may express themselves like younger, neurotypical children. That said, autistic teens with expressive and intellectual skills closer to neurotypical teens may have suicidal thoughts like neurotypical kids their age and talk about them in a similar way. We need to strike a balance between saying "Oh, you don't have to worry about him; he's too young to understand these things" and thinking that every child who says "I wish I were dead" is a suicide risk.

CCPR: Does social contagion occur in autistic youth? We have seen some of this in the general teen population associated with the recent series *13 Reasons Why*.

Dr. Lipkin: We have not seen that kind of social contagion, but older autistic teens and young adults may tend toward social misinterpretation and not considering the consequences of their actions. They may hurt themselves by imitating what's on TV. Conversely, some autistic people have a problem stepping into other people's shoes. They can't absorb another's experience into their own, and maybe that's a protective factor.

CCPR: Are there differences in suicidality in autistic kids and teens related to gender, culture, or race?

Dr. Lipkin: Suicidal behavior is much higher in Black communities than in other communities in general as well as for children living in poverty. Also, in the general population, more males tend to die from suicide attempts because they're more likely to use firearms than girls. In the autism community, we don't have data on firearm risks. Perhaps firearm deaths are less of a risk with more limited access to lethal weapons and more safeguards put in place by family and others, as well as frequent problems in learning and motor skills in autistic youth.

CCPR: How do you and your colleagues screen for suicidality in autistic patients?

Dr. Lipkin: At Kennedy Krieger Institute, we now routinely screen all children for suicidality every three to six months in both medical and behavioral health programs (Rybczynski S et al, *J Dev Behav Pediatr* 2022;43(4):181–187; *Continued on page 3*

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Expert Interview—Addressing Suicidality in Autistic Children and Teens

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www.tinyurl.com/34znxsh4). Over the past five years, it has become a normal part of our practice. Most parents now accept it as routine just like checking the child's pulse and blood pressure when they come for a visit and often appreciate it because they see the stories about suicide in the media. The ideal with children is asking them separately from their parents.

CCPR: What screening tool do you use?

Dr. Lipkin: We use the Ask Suicide Screening Questions (ASQ), which the National Institute for Mental Health (NIMH) developed for neurotypical children (*Editor's note: See "Suicide Assessment Tools for Autistic Adolescents and Teens" table*). A lot of people have been afraid to ask these questions because they're afraid of putting ideas in children's heads. There's no evidence to support this conception. The fear of initiating suicidal thought and behavior is unfounded. But on the other hand, we know that children who have never been asked before are reporting these thoughts.

"Take any expression of suicidal thought seriously. Ask about duration of thoughts, thoughts about suicidal actions, any suicide preparation, and presence of firearms in the home. This is the same thing one would do with neurotypical children to make sure they are in a safe place and see if they need any more help and attention."
Paul Lipkin, MD

CCPR: Do you modify the ASQ for autistic kids and teens?

Dr. Lipkin: In our research, we are validating a modification of the assessment for youth with autism or developmental disorders. We are testing a version using simpler vocabulary along with questions to learn about their understanding of death. We are also comparing the ASQ and our modifications for the autism community to the NIMH Brief Suicide Safety Assessment (BSSA) (www.tinyurl.com/bdfeddk5). We hope to have enough data to share these in about a year. Many child psychiatrists know the Columbia-Suicide Severity Rating Scale (C-SSRS), which has become a national standard; however, it's longer and has more complex language, so it may be less useful for autistic children. We are also comparing the ASQ to the Suicidal Ideation Questionnaire (SIQ) for children in our sample of children with autism and other developmental disabilities.

CCPR: What comes next after screening?

Dr. Lipkin: For children who screen positive, we follow up with a more detailed suicide assessment and suicide safety planning by psychiatrists and behavioral health clinicians. This does require more in-depth questioning and more clinician experience than the ASQ. For clinicians, I would take any expression of suicidal thought or suicidal verbalization seriously and then do a more in-depth interview and ask about duration of thoughts, thoughts about suicidal actions, any suicide preparation that the child or teen may have, and presence of firearms in the home since this is the most common cause for death by suicide. This is the same thing one would do with neurotypical children who express suicidal thoughts to make sure that they are in a safe place and see if they need any more help and attention.

CCPR: Can you talk about the different levels of care to treat suicidality in autistic children and teens?

Dr. Lipkin: Yes. I had an 18-year-old autistic woman hospitalized on an adult psychiatry unit, and they had no idea how to work with her perseverative ideation. That was striking because in Baltimore we have excellent hospitals and professionals. And I worry even more about children in the heartland where there aren't such specialized resources available. In any treatment setting, we need to look beyond the person's language and consider their disabilities and their complexities. In outpatient settings, we are delivering traditional care related to impulsivity or mood or anxiety and trying to figure out what the right approach is. We know how to create a safety plan for a neurotypical 14-year-old. We make sure that harmful things aren't available and help them express their thoughts. But autistic children may need an alternative means such as visual picture stories or discussions through play for expressing their thoughts, and we may need similar ways of responding back to them.

CCPR: How do you decide what level of care is needed for a suicidal autistic patient?

Dr. Lipkin: For any child with active ideation, if we think that they may do something that day if given the opportunity, we send them for further evaluation at a hospital where they can be seen by a psychiatrist or behavioral health clinician. For children who have general thoughts, but not active thoughts of harming themselves, we try to verify that they have mental health providers already, and we contact those providers so that they are aware. If they do not, we connect them as soon as possible with psychiatrists and therapists. And we emphasize discussion with the child and the parents on a regular basis about these thoughts (Jager-Hyman S et al, *J Autism Dev Disord* 2020;50(10):3450–3461).

Suicide Assessment Tools for Autistic Adolescents and Teens

Name	Description and URL
Ask Suicide Screening Questions (ASQ)	A four-question screener for use with pediatric and adult patients (free): www.tinyurl.com/4h9t8zfu
Brief Suicide Safety Assessment (BSSA)	An assessment guide for health care providers for use after a patient screens positive for suicide risk on the ASQ (free): www.tinyurl.com/bdfeddk5
Columbia-Suicide Severity Rating Scale (C-SSRS) Pediatric-Since Last Contact	A tool for clinicians to help assess pediatric patients for suicidal ideation or behavior since last contact (free): www.tinyurl.com/37dkedv7
Suicidal Ideation Questionnaire (SIQ)	A screener for frequency of suicidal ideation in adolescents (must be purchased): www.parinc.com/Products/Pkey/413

CCPR: Do you have guidance when schools want you to "clear" an autistic child to return to school after talking about suicide?

Dr. Lipkin: I'd rather schools err on the side of over-concern rather than under-concern, making that judgment to prompt further clinical evaluation. When the child seems safe, it can put the school at ease and inform the school as to how to interpret the child's comments. This includes recommending good supervision to prevent bullying that might trigger the suicidality.

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

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exacerbation of catatonia (Breaux R et al, *J Am Acad Child Adolesc Psychiatry* 2023;62(3):318–334). This article describes our approach for irritability in autism that minimizes the use of antipsychotic medications.

Set functional goals

Jane's parents implement a system that links screen time to the behavioral goal "no screaming." This helps for two days, then the screaming resumes. At your next appointment, Jane says "I get mad and yell." You suggest a functional goal: "helping Jane feel calm."

Behavioral goals (used in applied behavioral analysis) aim to change behavior, while functional goals support meaningful interaction. Behavioral goals may bypass underlying factors such as sensory differences, communication problems, and comorbid conditions (eg, anxiety and ADHD). "No screaming" doesn't address the reasons behind Jane's screaming. Is she overwhelmed by a busy household or unable to process her parents' requests? Functional goal setting inspires brainstorming to address underlying factors, which can reduce the use of medications. Other functional goals might include sustaining meaningful interactions, managing sensory differences, or responding adaptively to social problems such as teasing.

Treat co-occurring conditions

Treat co-occurring conditions first as these may drive irritability. Start with non-pharmacologic approaches for conditions such as sleep problems, ADHD, depression, and anxiety. This might include exercise and cognitive behavioral therapy for insomnia (CBTi) modified for autistic patients (eg, using visualization); breaking down tasks for ADHD; and parent-implemented developmental relationship-based intervention (DRBI—see "Related Carlat Resources" table on page 5) or CBT for anxiety, depression, or everyday problem solving. Work with colleagues, such as occupational therapists and speech and language pathologists, to address sensory processing, motor planning, and communication challenges, and collaborate with special educators to address challenges related to learning that create frustration and irritability.

You coach Jane's parents in DRBI, building on Jane's interests to help her feel calm. They add brisk morning Backyardigans*-styled "treasure hunts," and Jane is calmer after this meaningful and physical activity. The school reframes Jane's curriculum around* The Backyardigans, *making the material more engaging. Jane is better but still anxious.*

Off-label medications for irritability

Once you have the non-pharmacologic treatments in place, medications might help, whether for co-occurring conditions or to try to directly address the irritability. Try non-prescription alternatives such as valerian, omega-3 fatty acids, melatonin (daytime), and lavender. They have limited data but might help. If these are ineffective, there is a range of prescription options to consider. Most reports on medication treatments for autism are open label without control groups or effect sizes (see table for more on interpreting research). With that caveat, here are some off-label options ranked within groups from more to less evidence of efficacy.

Neurotransmitter related

Stimulants (dopamine)

Despite negative clinical lore, a recent study suggests stimulants work as well in autistic individuals as anyone else. They have no additional side effects, and at similar dosages for ADHD they may help with irritability and aggression (Lilja MM et al, *J Neurodevelop Disord* 2022;14(1):17).

SSRIs (serotonin)

SSRIs may help irritability by treating co-occurring depression or anxiety. They generally work better for anxiety than depression for neurotypical kids and teens, but research on SSRIs in autistic children is limited. A recent controlled trial of sertraline for language outcomes in young autistic children ages 24–72 months showed no effect but no significant side effects either (Potter LA et al, *Front Psychiatry* 2019;10:810). Consider using SSRIs for anxiety, depression, OCD, and repetitive behaviors (after naturalistic approaches). Titrate carefully to avoid behavioral activation.

Memantine (N-methyl-d-aspartate [NMDA] glutamate receptors)

Will decreased glutamate activity reduce irritability? Three controlled trials show memantine is well tolerated and helps receptive language in autistic children (Soorya LV et al, *J Child Adolesc Psychopharmacol* 2021;31(7):475–484). Maximum dosing is 3 mg daily for kids under 20 kg, 6 mg daily for 20–39 kg, 9 mg daily for 40–59 kg, and up to 15 mg daily for 60 kg and over (Aman MG et al, *J Child Adolesc Psychopharmacol* 2017;27(5):403–412).

Bumetanide (GABA)

Animal autism models have increased GABAergic activity. What about decreasing GABA tone with bumetanide? In the only controlled human trial, bumetanide showed no effect on irritability or other autism symptoms (Sprengers JJ et al, *J Am Acad Child Adolesc Psychiatry* 2021;60(7):865–876). Recommendation? Skip it.

Autonomic approaches

Guanfacine

This central alpha-agonist reduces sympathetic tone, fostering calm, with occasional dizziness or paradoxical irritability. A 2015 study demonstrated that, for ADHD symptoms, about half of autistic children improved with few side effects (Scahill L et al, *Am J Psychiatry* 2015;172(2):1197–1206). Start at 1 mg daily and titrate to 4 mg daily, or 2 mg for kids less than 90 lbs.

Propranolol

This beta-blocker reduces racing heart rate to lower anxiety but may also lower exercise tolerance or exacerbate asthma. A 2016 controlled pilot study using a single dose of propranolol showed improved conversational reciprocity in autistic kids, and if effective

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would presumably help problem solving and therefore irritability (Zamzow RM et al, *Psychopharmacology (Berl)* 2016;233(7):1171–1178). Dose at 5–10 mg daily, increasing by 5 mg weekly, usually to a maximum of 20 mg daily.

Hormonal

Balovaptan

This medication blocks central vasopressin activity. A preliminary double-blind placebo-controlled study in autistic children ages 6–12 years showed improved social function and reduced anxiety (Parker KJ et al, *Sci Transl Med* 2019;11(491):eaau7356). We want more research before recommending it.

Oxytocin

This "bonding hormone" is a non-starter since multiple adult autism trials have failed (Sikich L et al, *N Engl J Med* 2021;385(16):1462–1473).

Opioid system

Low-dose naltrexone (LDN). Small older studies show that LDN may help irritability in autism. If you try it, titrate to 3–5 mg daily and watch LFTs (Salazar de Pablo G et al, *J Am Acad Child Adolesc Psychiatry* 2022;62(2):151–168).

Trials of guanfacine and low-dose fluoxetine have no impact on Jane's irritability, so you try low-dose (0.5 mg) naltrexone. The medication requires compounding, insurance does not cover it, and the cost is beyond what the family can afford.

Social determinants

Culture and other social determinants can impact off-label prescribing in autism: Some medications are too expensive, and approval of prior authorizations may be difficult without definitive research. Families may mistrust the medical system and view off-label "experiments" in a context of historical injustices (www.tinyurl.com/4mj8zyvr). Listen and offer neutral information and perhaps these concerns will abate. Offer options based on your clinical judgment and existing research and let families choose based on their culture, values, and circumstances.

You ask the pharmacy to discount the naltrexone price and they agree. Jane is calmer and engaging better with others. Six months later, her parents report that she is learning and building friendships.

Escalating to antipsychotics

If your patient remains significantly irritable, consider moving to antiepileptic drugs (eg, gabapentin, oxcarbazepine, valproate, or topiramate). If irritability is persistent or severe, consider antipsychotics that are less metabolically problematic, such as ziprasidone or lurasidone. Note that if the patient's symptoms meet criteria for bipolar depression, it may be easier to get insurance funding for lurasidone if they are age 10 years or older. Reserve risperidone and aripiprazole for severe or intractable situations, and think about using metformin early to help forestall metabolic effects. Track metabolic parameters and abnormal movements. Finally, think about discontinuing the medication when possible (see table for more information).

Related Carlat Resources

Title	Link
Approaches to Autism Intervention (Apr/May/June 2021)	www.thecarlatreport.com/articles/3441-approaches-to-autism-intervention
Assessing and Treating Catatonia in Children and Adolescents (Oct/Nov/Dec 2022)	www.thecarlatreport.com/articles/4231-assessing-and-treating-catatonia-in-children-and-adolescents
Child Medication Fact Book for Psychiatric Practice, Second Edition (2023)	www.thecarlatreport.com/products/category/107-books/product/353-regular-bound-copy-with-pdf-access-and-10-cme-post-test
Exploring the Potential Neurotoxicity of Antipsychotics in Younger Populations (Nov/Dec 2019)	www.thecarlatreport.com/articles/3043-exploring-the-potential-neurotoxicity-of-antipsychotics-in-younger-populations
Guanfacine and Autism (July/Aug 2016)	www.thecarlatreport.com/articles/2471-extended-release-guanfacine-improves-adhd-symptoms-in-autism
Medication Management of Antipsychotic-Induced Weight Gain in Children and Teens (July/Aug/Sept 2022)	www.thecarlatreport.com/blogs/2-the-carlat-psychiatry-podcast/post/4185-medication-management-of-antipsychotic-induced-weight-gain-in-children-and-teens
Medication Strategies for Helping People With Autism Spectrum Disorders (July/Aug 2015)	www.thecarlatreport.com/articles/2374-medication-strategies-for-helping-people-with-autism-spectrum-disorders
Unpacking Aggression Associated With ADHD (Oct/Nov/Dec 2021)	www.thecarlatreport.com/articles/3553-unpacking-aggression-associated-with-adhd

CARLAT VERDICT

There are many potential underlying reasons for irritability in autism, and your approach should try to address those issues and avoid escalation to antipsychotics if possible. Start by trading behavioral goals for meaningful functional goals and implementing non-pharmacologic supports. Consider milder off-label medications and ones with low metabolic impact before turning to the FDA-approved antipsychotics. For a diagrammatic algorithm, see the new edition of our *Child Medication Fact Book* (Feder J et al. *Child Medication Fact Book for Psychiatric Practice.* 2nd ed. Newburyport, MA: Carlat Publishing; 2023).

Q&A With the Expert

Recognizing and Treating Psychosis in Autism

Kristin Cadenhead, MD

Professor of psychiatry. Director, Cognitive Assessment and Risk Evaluation (CARE) Early Psychosis Treatment and Research Program, University of California, San Diego.

Dr. Cadenhead has no financial relationships with companies related to this material.

CCPR: How often does psychosis co-occur with autism?

Dr. Cadenhead: It's more often than the 1% in the general population. A 2022 meta-analysis looked at 53 studies on children and teens and found the co-occurrence of psychosis in autism was about 9% and, separately, bipolar disorder (BD) was 7.5% (Varcin KJ et al, *Neurosci Biobehav Rev* 2022;134:104543). With BD you can also get psychotic symptoms. Interestingly, in this meta-analysis, autistic males were more likely to develop schizophrenia, and autistic females were more likely to be diagnosed with BD. Adults with autism with normal IQs have lower rates than those with low IQs. In one systematic review of psychosis patients, only seven studies met inclusion criteria, and the range was huge, with 9%–61% of psychotic patients showing autistic traits (Kincaid DL et al, *Psychiatry Res* 2017;250:99–105). More large-scale studies would be helpful to better understand the rate of co-occurrence.

CCPR: How severe are psychotic symptoms in autistic vs non-autistic kids?

Dr. Cadenhead: One study found the severity of psychotic symptoms was about equal in people with schizophrenia spectrum and patients who are autistic and have psychotic symptoms (Sunwoo M et al, *Schizophr Res* 2020;216:310–315).

CCPR: Are there shared risk factors for psychosis and autism?

Dr. Cadenhead: Yes, including obstetrical complications and urbanicity. Being a first-generation immigrant, the child of an immigrant, or in a minority within an immigrant population can put people at risk for both (Morinaga M et al, *Eur J Public Health* 2021;31(2):304–312; Brandt L et al, *JAMA Psychiatry* 2019;76(11):1133–1140). While I haven't seen puberty as a risk factor for psychosis in autism in the literature, I have seen autistic teens who misinterpret the intent of others, thinking the other person likes them when they don't. It can look like an erotomanic delusion, possibly driven by hormonal changes.

CCPR: Are autistic kids who use cannabis more prone to psychosis?

Dr. Cadenhead: Yes. Autism increases their vulnerability to psychosis caused by cannabis, but it may also reduce substance use behavior in some individuals (Bortoletto R and Colizzi M, *Healthcare (Basel)* 2022;10(8):1553). One study in the Varcin meta-analysis showed co-occurring psychosis and autism predicted less substance use and higher employment than neurotypical kids (Varcin et al, 2022).

CCPR: Symptoms like unusual affect, social isolation, misperceiving social interactions, and even suspicious thinking happen in both autism and psychosis. Are there specific questions that we can ask to sort out whether a patient has autism, psychosis, or both?

Dr. Cadenhead: I get a careful developmental history to look for psychotic symptoms in earlier childhood. I look for changes in behavior compared to baseline symptoms. They may have always had idiosyncratic interests or trouble reading other people. But when it changes into something that is not characteristic of that individual, like a belief that the government is monitoring them, that may be a psychotic symptom.

CCPR: Are there tests or other tools to differentiate psychotic symptoms from autistic ones?

Dr. Cadenhead: There's no specific test. Neurocognitive tests can look at theory of mind and the ability to interpret the intent of others. People with schizophrenia have intact theory of mind and can read social cues prior to the onset of their illness. With autism, those difficulties would have been there from early on. Genetic tests are nonspecific; for example, schizophrenia and autism are both associated with 22q deletion syndrome (a multiorgan genetic condition also known as DiGeorge or velocardiofacial syndrome).

CCPR: Is there a general timing to the onset of psychotic symptoms for schizophrenia, BD, and schizoaffective disorder in autism that can help us to sort out the nature of the psychotic symptoms?

Dr. Cadenhead: In my clinical experience, the age of onset of psychotic disorders in autism is in line with what you see in non-autistic cases. Affective disorders can occur at younger ages than schizophrenia. It is rare for schizophrenia to begin before age 15, so if I see psychosis in a young adolescent, I am highly suspicious that it is an affective psychosis. There are also other clues: Sometimes young patients become psychotic after an antidepressant is initiated. This suggests that they have a predisposition to BD or schizoaffective disorder rather than schizophrenia.

CCPR: Does prodromal schizophrenia look like autism?

Dr. Cadenhead: It can look like autism and can last from a few weeks to a few years, with symptoms including neuromotor deficits and learning disabilities. Since it's a retrospective diagnosis, you can't say it's prodromal until the patient becomes psychotic. To identify individuals at clinical high risk (CHR) for psychosis, we look for subsyndromal positive symptoms like

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perceptual changes where they think they hear things or see things, but they still have insight and realize "I know this sounds weird, but I think I hear a voice talking to me." They have some insight and haven't lost touch with reality. Same thing with delusions. They may be a bit paranoid, but if you push them, they're able to say "Yeah, I realize I'm just insecure sometimes and self-conscious, so I think people are talking about me." Negative symptoms like social isolation can also be present in CHR youth.

CCPR: Are there other risk factors that can predict which prodromal kids will become psychotic?

Dr. Cadenhead: We can predict about 25% who will become psychotic using clinical criteria alone. We developed a "psychosis risk calculator" that incorporates other variables, such as neurocognition, that can predict with greater certainty who will become psychotic. Use of the calculator requires the results of the Structured Interview for Prodromal Syndromes (SIPS), neurocognitive tests, and other specialized functional assessment scales (Cannon TD et al, *Am J Psychiatry* 2016;73(10):980–988).

CCPR: Is there an advantage to looking for a diagnosis other than psychosis to explain the symptoms?

Dr. Cadenhead: Yes, you may find other conditions that are more responsive to treatment. Many non-autistic kids have ADHD, anxiety, or depression, which are important to treat and might be present before somebody notices new odd thinking. With young autistic people, I look for bipolarity if psychotic symptoms are emerging because there may be a better prognosis for affective psychoses. Those tend to be episodic and don't persist the way schizophreniform psychoses do.

CCPR: How do you talk with families about psychosis and autism?

Dr. Cadenhead: I talk to them about the psychotic symptoms, and we collaborate with clinicians with expertise in autism. These are complicated cases. But when the voices calm down and stop interfering, many patients care about relationships, independence, work, or school. A lot of young adults are annoyed about living with their parents. It's about setting goals. I'll ask "What kind of functionality do you want to get to? What steps do you need to take to get there?"

CCPR: Are there specific cultural impacts that might make it harder to clarify psychosis vs autism in certain populations?

Dr. Cadenhead: It varies by family and culture. Some children, depending on access to health care, are not diagnosed early with neurodevelopmental disorders. Certain communities avoid mental health care because of stigma. Some families have high expectations of kids and have trouble accepting their mental health issues. Some families don't tell me that their child is autistic. This history is important in making a diagnosis of a psychotic spectrum disorder vs autism.

"Autistic kids may have more psychotic symptoms related to stress. Reducing stress with individual therapy or through social skills training could relieve these symptoms. Look for bipolarity or severe depression with psychotic features that might respond to mood stabilizers without an antipsychotic. If it's a persistent and fixed delusional belief or hallucinations, then you'll likely need antipsychotics."

Kristin Cadenhead, MD

CCPR: How does treatment differ in the use of antipsychotics with kids who have a single diagnosis of autism vs psychosis?

Dr. Cadenhead: One study found that people with co-occurring autism may not be as responsive to antipsychotics (Downs JM et al, *J Clin Psychiatry* 2017;78(9):e1233–e1241). Autistic kids have increased stress related to sensory, motor, and communication challenges. They may have more psychotic symptoms related to stress, so reducing stress with individual therapy or helping them to reinterpret things through social skills training could relieve these symptoms. I also look for bipolarity or severe depression with psychotic features that might respond to mood stabilizers without an antipsychotic. But if it's a persistent and fixed delusional belief or hallucinations, then you'll likely need antipsychotics.

CCPR: What antipsychotic medications do you start with?

Dr. Cadenhead: I start with a second-generation antipsychotic that's more weight-neutral (eg, lurasidone or aripiprazole) or has a long-acting depot form (risperidone, paliperidone, or aripiprazole). If the first antipsychotic doesn't work, I switch to one that has different pharmacologic properties because some are dopamine D2 receptor-focused and some target multiple receptors like serotonin. Side effect profiles also help. For example, olanzapine can help sleep disturbances. Not all insurance plans approve newer antipsychotics, so I start with psychotropics that are typically covered.

CCPR: What can you say about the risk of seizures in autistic kids taking antipsychotics?

Dr. Cadenhead: I have not seen many autistic people with seizures, although I know this occurs. I saw one patient who had a lesion in his brain causing seizures. The neurology service put him on lamotrigine, and I continued him on antipsychotics but took him off bupropion because it can lower the seizure threshold. Work with a neurologist if the patient also has a seizure disorder.

CCPR: What do you do if people aren't responding to antipsychotics? Do you use pharmacogenetic testing?

Dr. Cadenhead: Check blood levels and consider long-acting injectable antipsychotics to improve compliance. We move to clozapine early if somebody fails at least two atypical antipsychotics. If there are illicit drugs involved, that might explain why they haven't responded. Pharmacogenetic tests don't tell you about efficacy of an antipsychotic for a particular person, more about how they metabolize the drug, and that doesn't necessarily correlate with clinical response, but there are rare ultra-fast metabolizers.

CCPR: If you think there is bipolarity, what mood stabilizers do you use?

Dr. Cadenhead: I favor lithium because it has both antimanic and antidepressant qualities.

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Expert Interview—Recognizing and Treating Psychosis in Autism
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Some people use lamotrigine, but there is not much evidence for its use in mania. Lamotrigine is typically used more in BD II where depression is prominent. You can also use atypical antipsychotics like lurasidone or aripiprazole for mood instability. For a depressive component, I pick agents approved for bipolar depression (aripiprazole, quetiapine, lurasidone).

CCPR: How difficult might it be to treat schizoaffective disorder with autism?

Dr. Cadenhead: The treatment of schizoaffective disorder is similar to treatment of affective disorders and schizophrenia. In my experience, I use the same pharmacologic strategies as I do in non-autistic kids, but I often find a therapist experienced with social skills training, family therapy, and other therapies that are more specific for autism.

CCPR: What about the use of stimulants when we are concerned about psychosis?

Dr. Cadenhead: I'm cautious with stimulants in anybody who's been psychotic. Clinicians who often treat BD may feel comfortable with patients on mood stabilizers using stimulants without inducing a psychotic episode. I would proceed with caution and treat the BD first before even considering targeting ADHD.

CCPR: Do you use alternative or complementary approaches?

Dr. Cadenhead: Some people hope to avoid medications or use unstudied herbal treatments. We recommend evidence-based psychotherapies like cognitive behavioral therapy for psychosis and social skills training. We are interested in omega-3, cannabidiol (CBD), anti-inflammatory interventions related to diet, and mindfulness meditation, but we need more studies. We have ongoing clinical trials with CBD, anti-inflammatory diet, and family-focused therapy.

CCPR: What are your thoughts about prognosis for these patients?

Dr. Cadenhead: Co-occurring autism and psychosis are more difficult to treat, and the patients I see tend to need more resources. I think there's more negative stigma with purely psychotic patients because people worry that they're dangerous. Autistic patients with psychosis may be less frightening, and that might explain why they may find jobs more easily, even though they too are underemployed.

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

Research Updates IN PSYCHIATRY

AUTISM

Autistic Drivers Perform Well

Jason Emejuru, MD. Dr. Emejuru has no financial relationships with companies related to this material.

REVIEW OF: Curry AE et al, *J Am Acad Child Adolesc Psychiatry* 2021;60(7):913–923

STUDY TYPE: Retrospective cohort study

Driving is an important skill for autistic patients; however, clinicians and families worry about the risk of accidents. To address this concern, researchers completed the first longitudinal comparison of autistic and non-autistic drivers. The study linked statewide driver licensing and hospital-reported crash databases in New Jersey. It compared the driving records of autistic and non-autistic drivers, looking at how many crashes were caused by the driver in their first four years on the road.

In all, 163 of 486 autistic drivers (33.5%) and 27,018 of 70,990 non-autistic drivers (38.1%) were involved in police-reported crashes. While there were similar or lower rates of crashes among autistic drivers compared to non-autistic drivers, autistic drivers had far fewer moving violations and were half as likely to crash due to unsafe speeds. Autistic drivers also had more accidents from not yielding to the right of way and while making left turns and U-turns.

The authors suggest that these differences reflect challenges with executive skills, visual processing speed, and visual-motor integration. Autistic drivers might be prone to focus ahead and drive where they are looking rather than seeing the whole context, and they may miss road hazards that involve motorists and pedestrians.

The study had some limitations. Autistic drivers were identified by hospital records, not with formal assessments. The authors did not assess the abilities of these drivers (eg, the combination of nonverbal communication and visual-motor function needed to anticipate and execute safe left turns). The authors also did not discuss the ages at which the drivers obtained their licenses or their hours of driving experience. This is important since there is a rapid decline in crash rates after the first few years of driving. Moreover, New Jersey's geography skews toward urban driving, and its driving age requirement (17) is higher than most states. This may limit the ability to generalize the study results to younger drivers and those living in rural parts of the country.

CARLAT TAKE

This study suggests that autistic drivers are at least as safe on the road as everyone else. Just as you counsel neurotypical teen drivers about speeding, talk with autistic drivers about how to stay aware of everything happening around them. When appropriate, recommend programs such as Autism Behind the Wheel (www.sellmax.com/driving-with-autism/) that provide specialized support to autistic drivers (Myers RK et al, *Am J Occup Ther* 2021;75(3):7503180110p1–p11).

ADHD

Testing Neurofeedback for ADHD

Alicia Watson, MD. Dr. Watson has no financial relationships with companies related to this material.

REVIEW OF: Neurofeedback Collaborative Group, *J Am Acad Child Adolesc Psychiatry* 2021;60(7):841–855

STUDY TYPE: Randomized controlled trial

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Research Updates

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Does neurofeedback (NF) reduce symptoms of ADHD? A meta-analysis of small studies demonstrated gains for inattention and hyperactivity-impulsivity that persisted at six-month follow-up (Van Doren J et al, *Eur Child Adolesc Psychiatry* 2019;28(3):293–305). A randomized controlled trial found that NF was more effective than computerized attention skills training; however, it did not use a standard protocol (Gevensleben H et al, *J Child Psychol Psychiatry* 2009;50(7):780–789). The authors of the present study wanted to give NF a more thorough test.

In this randomized, double-blind, placebo-controlled trial, researchers assigned 84 children with ADHD to the active NF group and 58 to the control group. Subjects were 7–10 years old, and 111 were male. They were allowed to be on stimulants but no other psychiatric medication.

The treatment group received the theta/beta ratio protocol, one of several NF protocols for ADHD. Control group participants received sham NF. Both groups had a target of 38 treatments and received counseling on sleep and nutrition.

The primary outcome was parent and teacher Conners scores. Both groups had significant improvement from baseline, but there were no statistically significant differences between the active and sham groups at the end of the protocol or at 13-month follow-up.

The authors speculate that both groups may have benefitted from consistent attention to diet and sleep, the EMG biofeedback component that both received, or the reinforcement for an activity requiring attention. They plan to follow up again at 25 months.

CARLAT TAKE

This is the first large-scale randomized clinical trial of NF for ADHD, and the results were disappointing. Some families may try it, but we don't recommend referring your ADHD patients to this expensive treatment until studies show clearer benefit.

Is It Worth Adding Coenzyme Q10 to Atomoxetine for ADHD?

Dorothy Chyung, MD. Dr. Chyung has no financial relationships with companies related to this material.

REVIEW OF: Gamal F et al, *CNS Neurol Disord Drug Targets* 2022;21(8):717–723

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

Many supplements have been touted to help ADHD. The pathophysiology of this disorder may be associated with oxidative stress, so it is reasonable to consider an antioxidant intervention (Joseph N et al, *J Atten Disord* 2013;19(11):915–924). In this study, researchers tested whether augmentation of atomoxetine with the antioxidant coenzyme Q10 would further improve ADHD symptoms.

Researchers recruited 60 children ages 6–16 years who continued to have ADHD symptoms despite taking atomoxetine for six months. Half received placebo and the other half received coenzyme Q10 (1–3 mg/kg/day). Serum levels were not checked in this study; however, the dosage range came from a pediatric migraine study that showed increased coenzyme Q10 serum levels from a mean of 0.6 µg/mL to 1.2 µg/mL (Hershey AD et al, *Headache* 2007;47(1):73–80). ADHD symptoms were measured with the Conners Parent Rating Scale-48 before and after one, three, and six months of treatment. There was no industry funding for this study.

The addition of coenzyme Q10 yielded a 16% greater improvement than placebo in ADHD hyperactivity, impulsivity, and learning problems after six months of treatment. Adverse effects included nausea; however, there was no statistically significant difference in adverse effects between the groups.

Since this study was conducted in Egypt, where stimulants are not widely available, the patient population may be different than in the US, where many people are prescribed atomoxetine if they are unable to tolerate stimulants.

CARLAT TAKE

There is not yet enough evidence to recommend coenzyme Q10 as a standard treatment for ADHD. However, many patients with ADHD do not tolerate stimulant medication or get only partial benefit from atomoxetine or alpha-agonists. For children who continue to struggle with hyperactivity, impulsivity, and learning despite optimizing existing treatments, we can add coenzyme Q10 to our list of understudied, probably harmless, and possibly helpful adjunctive supplements to try.

Does Treatment of ADHD Help Caregiver Stress?

Muruga Loganathan, MD. Dr. Loganathan has no financial relationships with companies related to this material.

REVIEW OF: López FA et al, *J Child Adolesc Psychopharmacol* 2021;31(3):179–186

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

We know that when caregivers are doing better, kids tend to do better developmentally. But when kids improve in treatment, do caregivers find relief?

In this three-week, randomized, double-blinded, multicenter drug trial, 81 children with ADHD ages 6–12 years were treated with delayed-release/extended-release methylphenidate (DR/ER-MPH; Jornay PM), while 80 others received placebo. Outcome scales included several measures of caregiver strain and ADHD symptoms.

Higher caregiver strain scores predicted high severity on most ADHD rating scales. Lower caregiver stress tracked with improved ADHD and global function. Over the course of treatment, a drop in caregiver stress tracked with the child doing better. For instance, when there was a 30% improvement in the ADHD-Rating Scale IV and the Clinical Global Impressions scale, there was a nine-point drop in the caregiver strain scale. Put another way, for every four children treated, one caregiver experienced less stress.

The study had notable limitations. Three weeks is a brief run for chronic and complex problems like caregiver stress, and the study did not look at other stressors in the lives of the caregivers. Also, half of the children did a washout of prior medication before starting DR/ER-MPH, which might have affected stress measures in the caregivers. The study also excluded kids with comorbid conditions, so these kids might not represent the usual complex diagnostic picture we see in day-to-day practice.

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Research Updates

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CARLAT TAKE

Perception may be reality—caregivers do experience stress with their children's ADHD behaviors. We want to see more studies on this, but in the meantime, treating the child may help some caregivers as a welcome bonus.

Stimulant Treatment Effect on Anxiety in ADHD

Gaurav Mishra, MD. Dr. Mishra has no financial relationships with companies related to this material.

REVIEW OF: Soul O et al, *J Child Adolesc Psychopharmacol* 2021;31(9):639–644

STUDY TYPE: Prospective, open label

Anxiety is one of the many side effects commonly listed for stimulant medications. Although a 2015 meta-analysis showed that stimulants did not worsen anxiety symptoms in children with ADHD compared to placebo, none of the studies included in that paper used prospective methodology (Coughlin CG et al, *J Child Adolesc Psychopharmacol* 2015;25(8):611–617). Now Soul and colleagues have published the first prospective study looking at whether stimulants exacerbate anxiety.

This 12-week study recruited 104 children ages 6–15 years at the beginning of their stimulant treatment for ADHD. Parents filled out the ADHD-RS and SCARED anxiety scales. Of the 57 participants who finished the study, 18 had a diagnosis of an anxiety disorder: Eight had separation anxiety disorder, two had generalized anxiety disorder, four had social anxiety disorder, one had panic disorder, and three had a specific anxiety disorder. The prescribed stimulants included long-acting methylphenidate for 51.8% of participants, with other prescriptions split among osmotic-release oral system methylphenidate, lisdexamfetamine, mixed amphetamine salts, dexmethylphenidate, and immediate-release methylphenidate.

ADHD symptoms improved as expected with stimulants, and the SCARED scale showed that 19% of patients reported reductions in anxiety. There were significant decreases on subdomains of generalized anxiety disorder, separation anxiety disorder, and a school-avoidant behavior subscale, but the effect sizes were small—none beyond 0.14. The presence or absence of anxiety disorders did not impact the improvement of ADHD symptoms based on ADHD-RS. About 14% of the patients reported side effects of irritability, tension, and anxiety symptoms, and 12% reported depressive symptoms.

This study was limited by its open-label design, lack of a control group, small sample size, and loss of patients. Still, its prospective naturalistic design and the use of validated scales along with inclusion of children with anxiety disorder strengthens the results.

CARLAT TAKE

While it will be helpful to have better-controlled studies, for now we have some reassurance that you are unlikely to cause or worsen anxiety when you use stimulants to treat anxious kids with ADHD.

RESEARCH

Why Do So Many Pediatric Antidepressant Research Trials "Fail"?

Pavan Madan, MD. Dr. Madan has no financial relationships with companies related to this material.

REVIEW OF: Mossman S et al, *J Child Adolesc Psychopharmacol* 2021;31(4):259–267

STUDY TYPE: Meta-analysis

Many research studies report a 30%–60% placebo response rate in pediatric selective serotonin reuptake inhibitor (SSRI) research, rendering the trial "negative" despite a 55%–60% response from the SSRI. We know that different SSRIs are equally effective in adults with major depressive disorder (MDD), so why does fluoxetine fare better than other SSRIs in pediatric MDD meta-analyses? Is it a true difference or research error? This study explored some of the complex factors that influence research outcomes in children and adolescents with anxiety and depression, and the results can help our patients.

After careful screening, the authors analyzed 49 randomized, double-blinded, placebo-controlled trials of the effectiveness of antidepressants for the treatment of depression or anxiety in youth. They examined demographics, funding sources, disorders targeted, and dosing schedules. More studies received industry funding than federal funding (57% vs 33%), more targeted depression than anxiety (74% vs 27%), and more used flexible dosing than fixed dosing (57% vs 33%). The trials covered 19 antidepressants from five classes, most commonly fluoxetine (κ=7). The mean enrollment was 176 patients per study, and the median treatment duration was eight weeks.

Surprisingly, federally funded antidepressant research trials had a 25% greater chance of showing efficacy as compared to industry-funded trials. While medication response was similar irrespective of funding, industry-funded trials had higher placebo response rates ($p<0.001$), leading to more frequent trial "failures" despite their incentive to report positive findings (recall the infamous Study 329, where industry researchers misrepresented data to create a treatment effect for paroxetine).

Greater placebo response in industry-funded trials was associated with fewer patients per site and larger numbers of sites. The authors argue that the 1997 FDA Modernization Act and the 2003 Pediatric Research Equity Act prefer research completion over outcomes, thus incentivizing low-quality, underpowered, hastily implemented research studies over higher-quality ones.

Fluoxetine was the only SSRI to have a federally funded study, and the better-quality research design may account for its relative superiority to other SSRIs in children and adolescents. Fluoxetine's long half-life may be another factor, making it more forgiving with fewer withdrawal problems when there are lapses in compliance.

CARLAT TAKE

Higher placebo rate in pediatric antidepressant trials may be related to poorly designed industry-funded studies, which might be excluded from future meta-analyses to improve accuracy. Step back and deploy a range of lifestyle interventions and therapies, and keep an open mind for trying other medications if fluoxetine fails.

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1. Co-occurring conditions should be addressed prior to treating irritability in autism with antipsychotic drugs (LO #1).
   [ ] a. True [ ] b. False

2. Which of the following individuals would be expected to pose the most significant suicide risk (LO #2)?
   [ ] a. An autistic 17-year-old who watches a TV show depicting suicide
   [ ] b. An autistic child with severe disabilities and history of self-injurious behavior
   [ ] c. A neurotypical 8-year-old who repeatedly expresses that he wishes he were dead
   [ ] d. An autistic teenager with co-occurring anxiety and depression

3. According to Dr. Cadenhead, psychosis occurs at a rate of 1% in the general population. What is the co-occurrence rate of psychosis in autistic individuals (LO #3)?
   [ ] a. 4% [ ] b. 9% [ ] c. 18% [ ] d. 61%

4. According to a 2021 retrospective cohort study, when compared to non-autistic drivers, autistic drivers had a higher rate of which of the following types of accidents (LO #4)?
   [ ] a. Not yielding to the right of way, left turns, and U-turns
   [ ] b. Reckless driving and running red lights
   [ ] c. Distracted driving such as texting and talking on the phone
   [ ] d. Moving violations such as speeding and improper overtaking

5. Which of the following off-label medications shows the strongest evidence for treating irritability in autistic individuals (LO #1)?
   [ ] a. Bumetanide [ ] b. Guanfacine [ ] c. Low-dose naltrexone [ ] d. Balovaptan

6. According to Dr. Lipkin, why might the Ask Suicide Screening Questions (ASQ) questionnaire be preferable to other assessment tools when screening autistic children and adolescents (LO #2)?
   [ ] a. The evidence for the ASQ is definitive for predicting suicide in autistic children
   [ ] b. The ASQ is the only measure that can be used with modified language for autistic children
   [ ] c. The ASQ is specifically designed for use with autistic children
   [ ] d. The Columbia-Suicide Severity Rating Scale is widely used but may be too complex for autistic children

7. Autistic individuals who use which of the following drugs are more vulnerable to psychosis (LO #3)?
   [ ] a. Cannabis [ ] b. Tobacco [ ] c. Alcohol [ ] d. Opioids

8. According to a 2021 randomized controlled trial on neurofeedback (NF) for ADHD, what was the effect of NF on ADHD symptoms in the test group as compared to the control group (LO #4)?
   [ ] a. The NF group showed no significant improvement from baseline; the control group showed moderate improvement
   [ ] b. Both the NF group and the control group showed no statistically significant improvement
   [ ] c. The NF group showed moderate improvement from baseline; the control group showed no significant improvement
   [ ] d. Both the NF group and the control group showed similar significant improvement, but there were no clear statistical differences between the groups

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Note From the Editor-in-Chief

CCPR is adopting neurodiverse nomenclature: *supporting autistic children* rather than *treating children with autism spectrum disorder*. Perhaps ADHD and other "disorders" will follow. For your families, follow their lead as some aren't ready for this approach, and insurance companies still only fund treatment of a disorder. In this issue, we sort through suicide and autism with Dr. Paul Lipkin, psychosis in autism with Dr. Kristin Cadenhead, and irritability in autism following the algorithm in our new *Child Medication Fact Book,* Second Edition. This issue also includes a mini-conference of research updates focused largely on ADHD. One more thing: Fentanyl is killing more and more people, and bystanders aren't acting to intervene. Promote bystander training for opioid overdose. It's free from the American Red Cross at www.redcross.org/take-a-class/opioidoverdose. As always, we welcome your feedback and comments.

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