Current PSYCHIATRY

Caring for patients with autism spectrum disorder

Pharmacotherapy for psychiatric symptoms can maximize the benefits of behavioral therapies

Autism spectrum disorder (ASD) is an umbrella term used to describe lifelong neurodevelopmental disorders characterized by impairment in social interactions and communication coupled with restricted, repetitive patterns of behaviors or interests that appear to share a common developmental course.[1] In this article, we examine psychiatric care of patients with ASD and the most common symptom clusters treated with pharmacotherapy: irritability, anxiety, and hyperactivity/inattention.

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First step: Keep the diagnosis in mind

Prior to 2013, ASD was comprised of 3 separate disorders distinguished by language delay and overall severity: autistic disorder, Asperger's disorder, and pervasive developmental disorder, not otherwise specified.[2] With the release of DSM-5 in 2013, these disorders were essentially collapsed into a single ASD.[3] ASD prevalence is estimated to be 1 in 59 children,[4] which represents a 20- to 30-fold increase since the 1960s.

In order to provide adequate psychiatric care for individuals with ASD, the first step is to remember the diagnosis; keep it in mind. This may be particularly important for clinicians who primarily care for adults, because such clinicians often receive limited training in disorders first

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Autism spectrum disorder

Table

Target symptoms and treatment options for patients with ASD

Medication class	Target symptoms	Evidence for use	Adverse effects
Second-generation antipsychotics	Irritability: aggression, self-injury, severe tantrum	Multiple RCTs for risperidone and aripiprazole Other SGAs with small studies, retrospective or prospective open-label studies	Weight gain, increased appetite, sedation
Apha-2 agonists	Inattention, hyperactivity	Several RCTs with relatively small numbers of participants	Sedation, irritability
Stimulants	Inattention, hyperactivity	One moderate-sized RCT, other small studies	Irritability
Selective serotonin reuptake inhibitors	Anxiety-related symptoms	RCTs do not support efficacy in children with ASD Limited evidence for efficacy in adults	Activation and irritability
Antiepileptics	Irritability, repetitive behaviors	Several small RCTs with mixed results	Rash, weight change, irritability

ASD: autism spectrum disorder; RCTs: randomized controlled trials; SGAs: second-generation antipsychotics

Clinical Point

Although symptoms of ASD begin in early childhood, they may become more recognizable later in life with increased social demands

manifesting in childhood and may not consider ASD in patients who have not been previously diagnosed. However, ASD diagnostic criteria have become broader, and public knowledge of the diagnosis has grown. DSM-5 acknowledges that although symptoms begin in early childhood, they may become more recognizable later in life with increasing social demand. The result is that many adults are likely undiagnosed. The estimated prevalence of ASD in adult psychiatric settings range from 1.5% to 4%.[5-7] These patients have different treatment needs and unfortunately are often misdiagnosed with other psychiatric conditions.

A recent study in a state psychiatric facility found that 10% of patients in this setting met criteria for ASD.[8] Almost all of those patients had been misdiagnosed with some form of schizophrenia, including one patient who had been previously diagnosed with autism by the father of autism himself, Leo Kanner, MD. Through the years, this patient's autism diagnosis had fallen away, and at the time of the study, the patient carried a diagnosis of undifferentiated schizophrenia and was prescribed 8 psychotropic medications. The patient had repeatedly denied auditory or visual hallucinations; however, his stereotypies and odd behaviors were taken as evidence that he was responding to internal stimuli. This case highlights the importance of keeping the ASD diagnosis in mind when evaluating and treating patients.

Addressing 3 key symptom clusters

Even for patients with an established ASD diagnosis, comprehensive treatment is complex. It typically involves a multimodal approach that includes speech therapy, occupational therapy, applied behavioral analysis (ABA), and vocational training and support as well as management of associated medical conditions. Because medical comorbidities may play an important role in exacerbation of severe behaviors in ASD, often leading to acute behavioral regression and psychiatric admission, it is essential that they not be overlooked during evaluations.[9,10]

There are no effective pharmacologic treatments for the core social deficits seen in ASD. Novel pharmacotherapies to improve social impairment are in the early stages of research,[11,12] but currently social impairment is best addressed through behavioral therapy and social skills training. Our role as psychiatrists is most often to treat co-occurring psychiatric symptoms so that individuals with ASD can fully participate in behavioral and school-based treatments that lead to improved social skills, activities of daily living, and quality of life. Three of the most

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Comments
Adverse effects are often limiting. Most SGAs have some positive results in literature with exception of lurasidone, which is the only antipsychotic with a published negative placebo-controlled trial
Only methylphenidate has been studied
Adverse events appear more severe in youth

common of these symptoms are irritability, anxiety, and hyperactivity/inattention.

Irritability

Irritability, marked by aggression, self-injury, and severe tantrums, causes serious distress for both patients and families, and this behavior cluster is the most frequently reported comorbid symptom in ASD.[13-15] Nonpharmacologic treatment of irritability often involves ABA-based therapy and communication training.

ABA includes an initial functional behavior assessment (FBA) of maladaptive behavior followed by the application of specific schedules of reinforcement for positive behavior. The FBA allows the therapist to determine what desirable consequences maintain a behavior. Without this knowledge, there is the risk of inadvertently rewarding a maladaptive behavior. For instance, if you are recommending a time-out for escape-motivated aggression, the result will likely be an increase rather than decrease in aggression.

Communication training teaches the patient to use communicative means to request a desired outcome to reduce inappropriate behaviors and improve independent functioning. Communication training can include speech therapy, teaching sign language, using picture exchange programs, or navigating communication devices. Consideration of nonpharmacologic management is vital in treatment planning. Continual inadvertent reward of behaviors will limit the effects of medications. Evidence suggests that pharmacotherapy is more effective when it occurs in the context of appropriate behavioral management techniques.[16]

Irritability has been the focus of significant pharmacotherapy research in ASD. Second-generation antipsychotics (SGAs) are first-line pharmacotherapy for severe irritability. Risperidone and aripiprazole are both FDA-approved for addressing irritability in youth with ASD. Their efficacy has been established in several large, placebo-controlled trials.[17-23]

Given issues with tolerability and cases refractory to the use of first-line agents,[24] other SGAs are frequently used off-label for this indication with limited safety or efficacy data. Olanzapine demonstrated high response rates in early open-label studies,[25,26] followed by efficacy over an 8-week double-blind placebo-controlled trial, although with significant weight gain.[27] No other SGAs have been examined in double-blind placebo-controlled trials. Paliperidone demonstrated a particularly high response rate (84%) in a prospective open-label study of 25 adolescents and young adults with ASD.[28] In a retrospective study of ziprasidone in 42 youth with ASD and irritability, we reported a response rate of 40%, which is lower than that seen for some other SGAs; however, ziprasidone can be an appealing option for patients for whom SGA-associated weight gain has been significant, because it is much more likely to be weight-neutral.[29,30] Open-label studies with quetiapine in ASD have generally revealed only minimal efficacy for aggression,[31,32] although sleep improvement may be more substantial.[32] The safety and tolerability of lurasidone in treating irritability in youth with ASD has yet to be established.[33] It is the only SGA with a published negative placebo-controlled trial in ASD.[34] Use of SGAs may be limited by adverse effects, including weight gain, increased appetite, sedation, enuresis, and elevated prolactin. Monitoring of body mass index and metabolic profiles is indicated with all SGAs.

continued

Clinical Point

Our role usually is to treat psychiatric symptoms so patients can fully participate in other therapies

Autism spectrum disorder

Clinical Point

Second-generation antipsychotics are first-line pharmacotherapy for addressing irritability in youth with ASD

Haloperidol is the only first-generation antipsychotic with significant evidence (from multiple studies dating back to 1978) to support its use for ASD-associated irritability.[35] However, due to the high incidence of dyskinesias and potential dystonias, use of haloperidol is reserved for severe treatment-refractory symptoms that have often not improved after multiple SGA trials.

When severe self-injury and aggression fail to improve with multiple medication trials, the next steps include combination treatment with multiple antipsychotics,[36] followed by clozapine, often as a last option.[37] Research suggests that clozapine is effective and well-tolerated in ASD[38-42]; however, it has many potential severe adverse effects, including cardiomyopathy, lowered seizure threshold, severe constipation, weight gain, and agranulocytosis; due to risk of the latter, patients require regular blood draws for monitoring.

There is very little evidence to support the use of antiepileptic medications (AEDs) and mood stabilizers for irritability in ASD.[43] Placebo-controlled trials have had mixed results. Some evidence suggests that AEDS may have more utility in individuals with ASD and abnormal EEGs without epilepsy[44] or as an adjunct to SGA treatment.[45] One study found that lithium may be beneficial for patients with ASD whose clinical presentation includes 2 or more mood symptoms.[46]

Anxiety

Anxiety is a significant issue for many individuals with ASD.[47] Anxiety symptoms and disorders, including specific phobias, obsessive-compulsive disorder (OCD), social anxiety, and generalized anxiety disorder, are commonly seen in persons with ASD.[48] Anxiety is often combined with restricted, repetitive behaviors (RBs) in ASD literature. Some evidence suggests that in individuals with ASD, sameness behaviors may limit sensory input and modulate anxiety.[49] However, the core RBs symptom domain may not be related solely to anxiety, but rather represents deficits in executive processes that include cognitive flexibility and inhibitory control seen across multiple disorders with prominent RBs.[50-54] Research indicates that anxiety is an independent and separable construct in ASD.[55]

Studies of treatments for both RBs and anxiety have focused primarily on selective serotonin reuptake inhibitors (SSRIs), hoping that the promising results for anxiety and OCD behaviors seen in neurotypical patients would translate to patients with ASD.[56] Unfortunately, there is little evidence for effective pharmacologic management of ASD-associated anxiety.[57] Large, randomized controlled trials (RCTs) are lacking. A Cochrane Database review of SSRIs for ASD[58] examined 9 RCTs with a total of 320 patients. The authors concluded that there is no evidence to support the use of SSRIs for children with ASD, and limited evidence of utility in adults. Youth with ASD are particularly vulnerable to adverse effects from SSRIs, specifically impulsivity and agitation.[57,59] However, SSRIs are among the most commonly prescribed medications for youth with ASD. Because there is limited evidence supporting SSRIs' efficacy for this indication and issues with tolerability, there is significant concern for the overprescribing of SSRIs to patients with ASD. In comparison, there is some compelling evidence of efficacy for modified cognitive-behavioral therapy (CBT) for patients with high-functioning ASD. Seven RCTs have shown that CBT is superior to treatment as usual and waiting list control groups, with most effect sizes >0.8 and with no treatment-associated adverse effects.[57]

Risperidone has been shown to reduce RBs[17,60] and anxiety[17] in patients with ASD. In young children with co-occurring irritability, risperidone monotherapy is likely best to address both symptoms. When anxiety occurs in isolation and is severe, clinical experience suggests that SSRIs can be effective in a limited percentage of cases, though we recommend starting at low doses with frequent monitoring for activation and irritability. Treatment of anxiety is further complicated by the significant challenges presented by the diagnosis of true anxiety in the context of ASD.

Hyperactivity and impulsivity

Hyperactivity and impulsivity are common among patients with ASD, with rates estimated from 41% to 78%.[61] Hyperactivity

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Related Resources

- National Institute of Mental Health. Autism spectrum disorder. https://www.nimh.nih.gov/health/publications/autism-spectrum-disorder/index.shtml.
- Centers for Disease Control and Prevention. Autism spectrum disorder (ASD). https://www.cdc.gov/ncbddd/autism/index.html.

Drug Brand Names

Aripiprazole • Abilify
Clonidine • Catapres
Clozapine • Clozaril
Guanfacine • Tenex
Guanfacine Extended Release • Intuniv
Haloperidol • Haldol
Lithium • Eskalith, Lithobid
Lurasidone • Latuda
Methylphenidate • Ritalin
Olanzapine • Zyprexa
Paliperidone • Invega
Quetiapine • Seroquel
Risperidone • Risperdal
Ziprasidone • Geodon

Clinical Point

Risperidone has been shown to reduce repetitive behaviors and anxiety in patients with ASD

and inattention are treated with a variety of medications. Research examining methylphenidate in ASD has demonstrated modest effects compared with placebo, though with frequent adverse effects, such as increased irritability and insomnia[62,63] Other smaller studies have confirmed these results.[64-66] One additional study found improvements not only in hyperactivity but also in joint attention and self-regulation of affective state following stimulant treatment.[67] There is limited data on the efficacy and tolerability of amphetamine for treating hyperactivity and impulsivity in ASD. Stimulant medications often are avoided as the first-line treatment for hyperactivity because of concerns about increased irritability. Alpha-2 adrenergic receptor agonists often are used before stimulants because of their relatively benign adverse effect profile. Clonidine, guanfacine, and guanfacine ER all have demonstrated effectiveness in double-blind, placebo-controls trials in patients with ASD.[68-70] In these trails, sedation was the most common adverse effect, although some studies have reported increased irritability with guanfacine.[70,71]

The ***Table*** (***page 18***) provides a summary of the target symptoms and their treatment options for patients with ASD.

Improved diagnosis, but few evidence-based treatments

The rise in ASD cases observed over the past 20 years can be explained in part by a broader diagnostic algorithm and increased awareness. We are better at identifying ASD; however, there are still considerable gaps in identifying ASD in high-functioning patients and adults. One percent of the population has ASD,[72,73] and this group is overrepresented in psychiatric clinic and hospital settings.[74] Therefore, we must be aware of and understand the diagnosis.

Medication treatments are often less effective and less tolerable in patients with ASD than in patients without neurodevelopmental disability. There are differences in pharmacotherapy response and tolerability across development in ASD and limited evidence to guide prescribing in adults with ASD. SGAs appear to be effective across multiple symptom domains, but carry the risk of significant adverse effects. For anxiety and irritability, there is compelling evidence supporting the use of nonpharmacologic treatments.

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Bottom Line

A subset of patients seen in psychiatry will have undiagnosed autism spectrum disorder (ASD). When evaluating worsening behaviors, first rule out organic causes. Second-generation antipsychotics have the most evidence for efficacy in ASD across multiple symptom domains. To sustain improvement in symptoms, it is vital to incorporate nonpharmacologic treatments.

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Clinical Point

The rise in ASD cases over the past 20 years can be explained in part by a broader diagnostic algorithm and increased awareness

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Clinical Point

For anxiety and irritability, there is compelling evidence supporting the use of nonpharmacologic treatments

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