Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: *Autism Spectrum Disorder*
-April 2026-

Summary/Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) made its initial review of pharmacologic interventions for challenging behaviors and co-occurring conditions in people with Autism Spectrum Disorder (ASD). Medication(s) listed on the National Core Formulary (NCF) relevant to this review include(s) atomoxetine, dextroamphetamine/amphetamine, aripiprazole, fluoxetine, methylphenidate, and sertraline. Following this clinical review, there were **no modifications** to the NCF.

ASD is a neurodevelopmental disorder with a prevalence of 1 in 31 children and 1 in 27 American Indian / Alaska Native (AI/AN) children in the United States aged 8 years.[1] Approximately 50% of AI/AN children with ASD also had an intellectual disability.[1] Combined data from the U.S. Centers for Disease Control and Prevention (CDC) Autism and Developmental Disabilities Monitoring Network show an increase in ASD prevalence since the early 2000s.[2] Prevalence is higher in males than in females at a ratio of approximately 3.4 to 1. Possible factors which may contribute to the increase in prevalence include broader diagnostic criteria, increased screening, greater awareness among parents and pediatricians, reduced stigma and increased acceptance, as well as improved access to specialized services.[1] Standardized screenings at 18 and 24 months of age with ongoing developmental surveillance with age-appropriate standardized autism-specific screening tools is recommended in primary care in order to identify children at risk for ASD that may require additional evaluation for diagnosis; ASD may be diagnosed as young as 18 months of age.[4]

Though there are a multitude of environmental, genetic, and biological factors that may increase the likelihood of ASD development, the exact cause of ASD remains unknown.[5]

ASD is characterized by impairment in two core domains: persistent deficits in social/communication interactions and restrictive, repetitive patterns of behavior, interests and activities.[3,4] Pharmacotherapy is NOT available to treat the core features of ASD for both adults and pediatrics.[4,9-12] Co-occurring behavioral symptoms and mental health disorders tend to be more common in people with ASD vs. those without ASD: ADHD (28% vs 7%), anxiety (20% vs 7%), depressive disorder (11% vs 5%), sleep difficulties (13% vs 5%), epilepsy (21% vs 0.8%).[13] People with ASD and ADHD are 23% more likely to have an intellectual disability compared to 0.7% with ADHD alone.[13] If warranted, guidelines and expert opinion support the use of pharmacotherapy as adjunctive, symptom-targeted, but not first-line; behavioral, developmental, educational, and family-centered interventions make up the foundation of treatment.[4,9-12]

Medications may be used to help manage coexisting behavioral health disorders as well as associated problem behaviors that are causing significant impairment and distress. People with ASD, especially in the pediatric population, can experience more medication side effects than those without ASD; subsequently, dosing should start low (often lower than published recommendations) and upward titration should be slow. Strict monitoring for adverse effects and drugs interaction is essential.[4,11,12] Available data from studies were mainly derived from the pediatric population and were the focus of this review.

Discussion:

Per guidelines, treatment for ADHD (e.g., hyperactivity, impulsivity, inattention and distractibility) in children with ASD does not differ from those without ASD. Stimulants such as methylphenidate and amphetamines are first line.[4,9-11] Stimulants may be less effective in children with comorbid intellectual disability however.[4] Expert opinion states that children with ADHD and ASD may not respond as well to stimulants alone. It is recommended to consider combining alpha agonists such as guanfacine or clonidine along with stimulants for synergistic effect, noting that guanfacine has greater effect than clonidine in managing irritability, impulsivity, and/or hyperactivity.[7] Atomoxetine is a second-line alternative to stimulants and may be considered if hyperactivity coexists with social anxiety.[4]

Aripiprazole and risperidone are the only two FDA-approved drugs for ASD-related irritability.[14,15] Both drugs require periodic monitoring of glucose, lipid, weight, blood pressure, and abnormal involuntary movement scale. Though dosing should be individualized according to patient response and tolerability, according to expert opinion, the pediatric mean dose for aripiprazole (FDA-approved for ≥6 years to <18-years old) is 6.6 mg/day, and the pediatric mean dose for risperidone (FDA-approved for ages ≥ 5-years to <18-years old) is 1.6mg/day.[7] In a systematic review and meta-analysis of 45 randomized controlled trials, aripiprazole and risperidone were associated with greater efficacy as the control event

rate (CER) was set higher (10%, 30% and 50%).[16] In other words, as significant emotional dysregulation and irritability levels increased, the greater the effect was seen in those taking aripiprazole or risperidone [aripiprazole (NNT=4, 95% CI: 4-5 at 30% CER; NNT=3, 95% CI: 2-3 at 50% CER) and risperidone (NNT=4, 95% CI: 4-5 at 30% CER and NNT=3, 95% CI: 2-3 at 50% CER).[16] However, it was observed that a higher rate of comorbid epilepsy was associated with lower efficacy with risperidone or aripiprazole.

Evidence on the use of SSRIs for treatment of anxiety and depression for children with ASD is limited. This recommendation is based largely on data extrapolated from non-ASD depression trials as there is no rigorous ASD specific trials identified.[9] Anxiety is harder to identify in the ASD population, especially in non-verbal children. Some patients may be slow metabolizers so it is important to initiate therapy at half the lowest-starting SSRI dose and titrate slowly to effect. Monitor for "activation syndrome" which includes hyperactivity, irritability, impulsive behavior and sleep disturbance.[4] Per expert opinion, consider adding guanfacine, clonidine or propranolol for physiological symptoms or consider adding hydroxyzine as needed for situational anxiety.[7]

Also per guidelines, melatonin is recommended for insomnia or sleep onset delay.[4,9,17] Notably, there is no FDA-approved medication for insomnia in children with ASD. For both children and adults, it is recommended that behavioral intervention be provided as first-line therapy, and as adjunct to the use of melatonin.[4,9] Melatonin may be dosed at 1–3 mg, 30–60 min before bedtime, or initiated at 0.5 mg, given 3 hours before bedtime if there is a circadian rhythm issue. It is not recommended to dose higher than 10 mg.[7] Due to its short half-life (40 minutes), immediate-release melatonin formulations may be helpful with sleep onset insomnia while the controlled-release melatonin formulation may be helpful for sleep maintenance. Adverse effects reported with melatonin include morning drowsiness, increased enuresis, headache, dizziness, diarrhea, rash, and hypothermia.[17] Melatonin's long-term effects in the pediatric population have not been studied, but its ability to suppress the hypothalamic–gonadal axis may potentially initiate precocious puberty.[17]

Findings:

Current studies on ASD have largely been heterogenous and standardization issues are compounded with the inclusion of older studies that utilized previous versions of the American Psychiatric Associations' Diagnostic and Statistical Manual for Mental Disorders (DSM). The evolution of ASD diagnosis in the DSM from its historical origins (linked to schizophrenia) to its own broad category has improved surveillance and is a factor for ASD's increased prevalence. Pharmacotherapy for treating symptoms associated with ASD and possible comorbidities is not considered first line. Additionally, adverse effects of treatment must be weighed against the short-term benefit of treatment, as long-term use of pharmacotherapy has not been studied.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

References:

1. Shaw KA, Williams S, Patrick ME, et al. Prevalence and Early Identification of Autism Spectrum Disorder Among Children Aged 4 and 8 Years — Autism and Developmental Disabilities Monitoring Network, 16 Sites, United States, 2022. MMWR Surveill Summ. 2025;74(2):1–22.
2. U.S. Centers for Disease Control and Prevention. Data and Statistics on Autism Spectrum Disorder. May 2025. Accessed April 14, 2026.
3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorder, 5th edition Text Revision 2022 (DSM-5-TR). March 2022.
4. Hyman SL, Levy SE, Myers SM, et al. Identification, evaluation, and management of children with autism spectrum disorder. Pediatrics. 2020; 145(1):e20193447.
5. National Institute of Health. National Institute of Environmental Health Sciences. Autism. Updated March 6, 2026. Accessed March 27, 2026.
9. Howes OD, Rogdaki M, Findon JL, et al. Autism spectrum disorder: Consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology. J Psychopharmacol. 2017;32(1):3-29.
10. Ip A, Zwaigenbaum L, Brian JA, et al. Canadian Paediatric Society, Autism Spectrum Disorder Guidelines Task Force. Paediatr Child Health. 2019; 24(7):461-68.
11. William B, Campbell L, Diekroger EA, et al. Society for Developmental and Behavioral Pediatrics Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents with Complex Attention-Deficit/Hyperactivity Disorder. J Dev Behav Pediatr. 2020; 41:S35-S57.
12. National Institute for Health and Excellence. Autism spectrum disorder in adults: diagnosis and management. Updated June 14, 2021. NICE; 2021.
13. Hirota T, King BH. Autism Spectrum Disorder: A Review. JAMA. 2023;329(2):157-68.
14. U.S. Food and Drug Administration. ABILIFY (aripiprazole) medication guide. Updated Jan 2025.
15. U.S. Food and Drug Administration. RISPERDAL (risperidone) medication guide. Updated Jan 2025.
16. de Pablo GS, Jordá CP, Vaquerizo J, et al. Systematic Review and Meta-analysis: Efficacy of Pharmacological Interventions for Irritability and Emotional Dysregulation in Autism Spectrum Disorder and Predictors of Response. *J Am Acad of Child Adolesc Psychiatry.* 2023; 62(2):151-68.
17. Buckley AW, Hirtz D, Oskoui M, et al. Practice guideline: Treatment for insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2020; 94(9):392-404.