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Pharmacological treatment in autism: a proposal for guidelines on common co-occurring psychiatric symptoms

Mariah A. Manter[1,2], Kirstin B. Birtwell[1,3], James Bath[1], Nora D. B. Friedman[1,3], Christopher J. Keary[1,3], Ann M. Neumeyer[1,4], Michelle L. Palumbo[1,5], Robyn P. Thom[1,3], Emily Stonestreet[1,6], Hannah Brooks[1], Kelly Dakin[1], Jacob M. Hooker[1,2,7] and Christopher J. McDougle[1,3*]

Abstract

Background The prevalence of autism spectrum disorder (ASD) has surged, with an estimated 1 in 36 eight-year-olds in the United States meeting criteria for ASD in 2020. Autistic individuals face elevated rates of co-occurring medical, psychiatric, and behavioral conditions compared to non-autistic individuals. The rising ASD-patient demand is increasingly outpacing the capacity of ASD-specialty clinics, resulting in urgent need for autism-competent providers in general practice settings. This work aims to empower healthcare providers, especially primary care providers (PCPs), with guidelines for the recognition and safe pharmacologic management of common co-occurring psychiatric and behavioral conditions in ASD.

Methods Lurie Center for Autism medical providers, who have extensive experience in ASD care, delineated approaches for recognition and pharmacological treatment of sleep disturbances, attention-deficit/hyperactivity disorder (ADHD), anxiety, depression, and irritability tailored to ASD patients. Pharmacological guidelines were iteratively refined until consensus was reached. Treatment differences relative to standard of care (SOC) of non-autistic individuals are noted. Key literature and clinical trial results were reviewed to supplement clinical experience.

Results The pharmacological treatment pathways reflect how appropriate medication options for ASD patients can depend on many factors unique to the patient and can differ from established non-autistic SOC. Key takeaways include: For sleep disturbances in ASD, initial strategies align with non-autistic SOC, emphasizing sleep hygiene and melatonin use. First-line recommendations for treating ADHD, anxiety, and depression in ASD differ from non-autistic SOC; α_2-adrenergic agonists are more suitable than stimulants for some ASD-ADHD patients, buspirone and mirtazapine are preferred to selective serotonin reuptake inhibitors (SSRIs) for anxiety, and duloxetine, mirtazapine, bupropion, and vortioxetine are recommended ahead of SSRIs for depression. Addressing irritability in ASD requires interdisciplinary evaluation of contributing factors, and guanfacine, risperidone, or aripiprazole may be appropriate, depending on severity.

Conclusions Recognition and treatment of co-occurring psychiatric and behavioral conditions in autistic patients must account for differences in clinical presentation and medication effectiveness and tolerability. Drawing on evidence-based clinical insights, these guidelines seek to support PCPs in making informed decisions when prescribing

*Correspondence:
Christopher J. McDougle
cmcdougle@mgh.harvard.edu
Full list of author information is available at the end of the article

medications for ASD patients with co-occurring psychiatric and behavioral conditions, ultimately enhancing access to timely, comprehensive care for all individuals with ASD.

Keywords Autism, Psychopharmacology, Autism-competent care, Guidelines, Primary care, Sleep, ADHD, Anxiety, Depression, Irritability

Background

The escalating prevalence of autism spectrum disorder (ASD) in recent years [1–4] has created an urgent need for additional medical providers capable of delivering autism-competent care [5–7]. While the call for more medical providers could be justified across medical specialties, nowhere is the need greater than in managing co-occurring neuropsychiatric conditions [8–10]. Individuals with ASD have a high prevalence of co-occurring neuropsychiatric conditions, with attention-deficit/hyperactivity disorder (ADHD), depression, and anxiety disorders being among the most common [11]. Left untreated, these co-occuring conditions can have detrimental and potentially catastrophic impacts on ASD individuals and their families, such as decreased quality of life and increased stress, hindered educational and employment opportunities and increased risk of suicidality [12–21]. While in some cases, the standard of care (SOC) for managing these conditions in an individual with ASD is comparable to the SOC for a non-autistic individual, treatment paths can differ significantly due to complex medical and behavioral profiles and differences in medication efficacy and tolerability [22]. Currently, only two drugs have been approved by the United States (U.S.) Food and Drug Administration (FDA) for use in the ASD population: risperidone [23] and aripiprazole [24]. Both drugs are approved for the treatment of irritability in children and adolescents with ASD. Aside from these two exceptions, psychopharmacological treatments for ASD individuals are prescribed off-label. Navigating this treatment landscape can be challenging and time-consuming for providers who have not received specific training in ASD medical care but who nonetheless find themselves with ASD patients amidst the rising need.

In a 2023 study, Hamp and colleagues collected structured interview data from 28 primary care providers (PCPs), and one major theme that emerged was uncertainty among providers with regard to treatment and long-term management in autism care [25]. Another theme of note was a lack of knowledge and general confusion about how systems of care work for patients with ASD, such as navigating the autism evaluation referral network and insurance considerations [25]. In similar interviews with pediatricians and parents from 2016, Levy and colleagues reported ambiguity about the pediatrician's role in ASD management and that pediatricians feel that they lack specific knowledge about diagnosis and treatment [26]. In a 2019 study, medical students and pediatric trainees reported knowledge gaps and discomfort regarding providing basic care to sick children with ASD and expressed a need for increased education and training [27]. These themes are present in healthcare systems outside of the U.S. as well. A 2017 study of 304 general practitioners in the United Kingdom found that nearly 40% had never received formal training in ASD and found a widespread lack of confidence in identifying and managing ASD patients [28]. Relatedly, parents of children with ASD generally do not expect recommendations regarding ASD treatment from their PCP and consistently report that accessible, ASD-specific care is limited [29, 30]. Parents rated their PCP's ability to care for their children's ASD-specific needs as "not good" [29].

Due to the significant increase in the prevalence of ASD, more and more ASD patients are presenting to the PCP with interfering neuropsychiatric symptoms and medical comorbidities. There are not enough ASD specialty clinics to provide satisfactory care for this growing population. This is not a gap that can be filled by psychiatry alone. In a healthcare system where the demand across specialized fields is vastly outpacing the capacity of specialty clinics, the healthcare model must adapt strategically, collaboratively, and creatively to meet the growing care needs of the population. One strategy that begins to bridge this gap in care is to leverage the wealth of knowledge of ASD specialists to provide greater guidance, enabling PCPs to adeptly evaluate and treat mClick or tap here to enter text.ore common medical needs of ASD patients. We believe it is important that PCPs be supported to embrace the opportunity of providing first-line care for the neuropsychiatric and medical comorbidities of their patients with ASD. There are risks involved when non-specialists provide care to individuals with ASD when those providers are not adequately informed to provide quality care. In our opinion, the risk/benefit ratio favors educating general practitioners to provide autism-competent care, as early diagnosis and treatment of presenting interfering neuropsychiatric symptoms will help mitigate the progression of disease and impact the patients' and families' quality of life and long-term outcomes. While acknowledging the risks involved,

empowering general practitioners with ASD expertise represents a pragmatic approach to addressing the pressing need for comprehensive ASD care within the existing healthcare landscape.

Similar treatment guidelines published to date are either now outdated or offer guidance on one co-occurring condition but may not serve as a reference across multiple symptom domains, present which drugs may be used in ASD without walking through the nuanced decision-making process of choosing and prescribing a drug to match the unique needs of individual patients, or do not specifically discuss the ASD landscape and healthcare system in the U.S. [31–34]. In contrast, we aim to provide a prescribing framework that is up to date, relevant across common symptom domains and appropriately nuanced and practical for general practitioners in the U.S. who may be providing care to patients with ASD.

Here, we propose pharmacological treatment guidelines for co-occuring psychiatric and behavioral symptoms in individuals with ASD, based on the clinical expertise of providers from the Lurie Center for Autism and key literature. We focus on five common co-occurring conditions in ASD: sleep disturbances, ADHD, anxiety, depression, and irritability. Key clinical trials and investigative case studies will be discussed for each indication, and pharmacological treatment pathways will be provided and explained. By offering evidence-based insights from the Lurie Center for Autism team, specialists who work almost exclusively with the ASD population, this guide seeks to empower healthcare providers to make informed decisions when prescribing medications to their patients with ASD and co-occurring neuropsychiatric symptoms. By equipping general providers to manage routine ASD care effectively, patients will receive more timely care, and specialist referrals will be more readily available for severe and complex cases. We aim to promote safe and effective prescribing practices grounded in evidence-based insights validated by highly specialized, direct clinical experience, ultimately enhancing access to informed care for all individuals with ASD.

Methods

Collaborative efforts from seasoned clinicians and researchers from the Lurie Center for Autism (see professional backgrounds below), culminated in this set of guidelines on the diagnosis and treatment of sleep disturbances, ADHD, anxiety, depression, and irritability in individuals with ASD. The initial pharmacological treatment pathways for each symptom domain were developed with the clinical expertise of the senior author, CJM, and designed by the first author, MAM. Factors including age, gender, severity of symptoms and combinations of co-occuring conditions were considered. These early drafts went through several rounds of revision with a core team of authors providing feedback and cross-checking with relevant literature, to achieve a desirable format and a solid foundation for the content. The general format for each of these pharmacological treatment pathways includes a box of important factors to consider prior to prescribing medication, followed by a flowchart of psychopharmacological options. After the initial development, interviews were conducted with additional clinician authors, with detailed notetaking and, in some cases, recordings made for future reference. For a given symptom domain, providers were asked to:

- Outline their pharmacological treatment approaches,
- Provide guidance on symptom recognition and diagnosis in the ASD population,
- Identify key differences in care compared to non-autistic SOC.

Secondary versions of the pharmacological treatment pathways were sketched based on insights from these interviews and then compared to the initial drafts. Points of disagreement were noted, prompting additional correspondence between authors, and in some cases, follow-up meetings to allow the authors to discuss until consensus was reached. New versions of each pharmacological treatment pathway were drafted to incorporate the collective input of multiple authors. Text sections on symptom domain background, diagnosis and treatment were either drafted by the provider or a member of their team, or by the lead author based on the interviews, notes and recordings. Prescribing clinicians also provided input and reached consensus on a broad set of principles for responsible prescribing within the ASD population, which were drafted into the Guiding Principles section. The pharmacological treatment pathways also underwent one more round of changes to refine visual design based on feedback from Harvard Library Visualization Specialist Jessica Cohen-Tanugi (no content changes were made at this stage). In addition, a targeted literature search was performed for key clinical trials and current recommendations regarding treatments for these co-occuring conditions in individuals with ASD and SOC for these conditions in populations without ASD. The literature search was conducted through databases including PubMed and Google Scholar using combinations of pertinent keywords and phrases such as autism, psychopharmacology, medication, ADHD, anxiety, sleep, depression, and irritability. In some cases, Lurie Center clinicians also recommended literature they considered essential to a symptom domain. This paper focuses only on seminal and recent publications to capture foundational studies and essential recent advancements in the

treatment landscape. Once pharmacological treatment pathways and text for each symptom domain were ready, a complete manuscript was compiled and circulated for review by all authors leading to additional discourse to reach final consensus. Senior author, CJM, had the ultimate determination of material content on the final revision of the manuscript, which was circulated to all authors before submission.

Clinical Author Backgrounds: JB is the Lurie Center Director of Primary Care and as a board-certified Family Medicine Physician, provides care and coordinates multidisciplinary care for ASD patients across the lifespan. KBB is a Clinical Psychologist at the Lurie Center for Autism and has over 15 years of assessment, treatment, and consultation experience in ASD specifically. NDBF is a child, adolescent, and adult psychiatrist who specializes in the care of patients with ASD and neurodevelopmental disabilities across the lifespan. CJK is a child, adolescent and adult psychiatrist at the Lurie Center with expertise in the treatment of psychiatric and behavioral components of ASD. He is also the Behavioral Director of the MGH Angelman Syndrome Clinic. CJM is the Director of the Lurie Center and the Nancy Lurie Marks Professor of Psychiatry at Harvard Medical School and in addition to his clinical practice is an internationally recognized expert in the neurobiology and neuropsychopharmacology of ASD across the lifespan. AMN is the Medical Director of the Lurie Center for Autism, and a child neurologist who has more than 30 years of experience providing medical and neurological care for patients with ASD. MLP is a triple board trained physician in pediatrics, psychiatry, and child and adolescent psychiatry and has over a decade of experience working with patients and families to develop treatment plans for medical and psychiatric aspects of ASD. RPT is a Lurie Center child, adolescent, and adult psychiatrist who specializes in the diagnosis and treatment of co-occurring psychiatric conditions in individuals with ASD across the lifespan and is the co-director of the MGH Williams Syndrome Program.

Results and discussion

Guiding principles: a preamble to specific recommendations

The risk/benefit ratio of pharmacological treatment of co-occurring psychiatric symptoms in those with ASD can be greatly enhanced by prescribing according to the following principles. Although not unique to psychiatric treatment, these principles are particularly important when prescribing neuropsychiatric medications due to the severity of possible side effects, and when prescribing in the ASD population due to the potential complexity of individuals' medical, behavioral and communication profiles. The four simple principles are:

1. Start Low and Go Slow
2. Monitoring Matters
3. One Size Does Not Fit All
4. Back to the Basics

Start Low and Go Slow

In prescribing medications for individuals with ASD, the principle of "Start Low and Go Slow" guides initial dosing strategies. It advocates for commencing treatment at the lowest practical dose and gradually titrating upward to attain therapeutic efficacy. This approach minimizes the risk of adverse effects while allowing for careful observation of individual responses to medication.

Monitoring Matters

Consistent monitoring for side effects and continued efficacy is paramount in ASD medication management. Some medications may have serious side effects that are challenging to recognize in ASD individuals who may not be able to self-report issues or who may report side effects only through behavioral changes that may appear independent of the side effects listed on the drug insert. This necessitates a thorough understanding of the potential adverse effects of each prescribed medication and familiarity with the presentation of side effects in patients with ASD. Given that individuals with ASD may exhibit atypical responses to medications or difficulties in expressing adverse effects of medications due to challenges with communication, regular check-ups are essential for the timely detection of emerging side effects. Additionally, some medications may lose efficacy over time, or the need for continued treatment may decrease or increase due to factors such as an individual's development or environmental changes. Periodic assessment ensures that the medication remains necessary and continues to have the desired effect.

One Size Does Not Fit All

Tailoring medication treatments to individual needs is essential in ASD management. Recognizing the diversity of ASD presentations, clinicians must acknowledge that "One Size Does Not Fit All." For example, understanding patients' tolerability to different medication formulations is key. Clinicians should be aware of available dosage forms, such as liquids, sprinkles, crushable or chewable formulations, and consider the patient's ability to swallow pills [35]. Moreover, compounding medications into a liquid formulation may offer a tailored alternative when patients are unable to

comply with available formulations. Certain medications require regular blood draws to monitor for therapeutic levels and serious side effects, so it is important to know how well your patient tolerates blood draws before considering such medications. Approaches that account for individual patient needs have the greatest potential for compliance and patient satisfaction, leading to more successful treatment outcomes.

Back to the Basics

Amidst the intricacies of ASD medication management, the principle of "Back to the Basics" serves as a crucial reminder to pay attention to fundamental healthcare needs. Sudden changes in a patient's behavior or the emergence of acute medical or psychiatric conditions may signify underlying basic healthcare issues that have been overlooked. It is imperative for healthcare providers to remain vigilant and consider the possibility of common health concerns that may underlie an individual with ASD's behavioral changes. Regular dental exams, for instance, are indispensable, as issues such as decayed wisdom teeth can lead to significant pain and behavioral changes. Pain or discomfort from gastrointestinal (GI) issues such as constipation or gastroesophageal reflux disease (GERD), which are common in ASD, may manifest as irritability. It is important to ask about constipation and diarrhea, and some cases may warrant a kidney, ureter, and bladder X-RAY (KUB) study. Some additional evaluations to assess basic care needs that should be considered include metabolic panels, Thyroid-Stimulating Hormone (TSH) tests or thyroid function tests (TFTs), blood count, inflammatory markers, Lyme disease panel, and uric acid level. By addressing basic healthcare needs, clinicians can identify when there are underlying medical causes of psychiatric symptoms and behaviors, ensuring appropriate care and optimizing overall well-being for individuals with ASD.

By integrating these four principles into clinical practice, healthcare providers can navigate the complexities of ASD medication management and enhance patient care.

A note on using the pharmacological treatment pathways

The treatment pathways defined later in Figs. 1, 2, 3, 4 and 5 involve a degree of context-dependent decision making due to the limited knowledge base in the literature. When deciding between medications within the same grouping, prescribers can consider factors such as how the medication side effect profiles will interact with patients' unique clinical profiles. Prescribers may also want to consider prior familiarity with a medication as this may impact their proficiency with dosing, assessing efficacy and monitoring for side effects with a given medication.

Sleep disturbances

Background

Sleep difficulties are more common in individuals with ASD than in non-autistics, with reported prevalence rates of 50–80% for children with ASD compared to 9–50% for control groups [36]. Children with ASD between the ages of 2–5 years, experience sleep problems twice as often as their peers in the general population, and sleep difficulties in children of all ages tend to persist compared to typically developing peers [37–39]. A systematic review and meta-analysis of sleep parameters found that adults with ASD also demonstrate significantly impaired sleep compared to controls in most subjective and objective measures of sleep [40]. The prevalence rate of sleep disturbances varies in ASD adults. In one study of adults with ASD, 85% had sleep problems [41] and in adults with ASD and intellectual disability (ID) about 45% were reported to have sleep problems [42]. Even though sleep disturbances are common in ASD across the lifespan, they are reported less often in adults due to adaptation to impaired sleep patterns, and adult ASD sleep disturbances are understudied [43]. Sleep problems in ASD can manifest in many different forms, including difficulties with sleep onset, sleep maintenance, parasomnias (e.g., nightmares, night terrors, enuresis), hypersomnia (excessive sleeping or sleepiness), sleep-related breathing or movement disorders, isolated symptoms like short sleep or early waking, abnormal sleep patterns, and circadian rhythm sleep disorders [36].

The psychiatric and medical co-occurring conditions that contribute to sleep problems in ASD include anxiety, depression, ADHD, GI problems, epilepsy, and certain medications that impact sleep [44]. Furthermore, children with ASD are more likely to have difficulty reporting pain, which can disrupt sleep [45]. Sleep issues can lead to challenging daytime behaviors like hyperactivity, inattention, and interfering ritualistic behavior [44]. Other co-occurring behavioral challenges include aggression, irritability, and self-injurious behavior (SIB). Sleep disorders have been correlated with daytime sleepiness, cognitive, attentional, behavioral, and emotional challenges, as well as poorer health-related quality of life for children with ASD [12, 13, 46]. Parents of children with ASD and sleep difficulties suffer a lower quality of life with heightened parent stress, anxiety, and depressive symptoms than average [14, 15]. In adults with ASD, sleep problems are associated with unemployment [47].

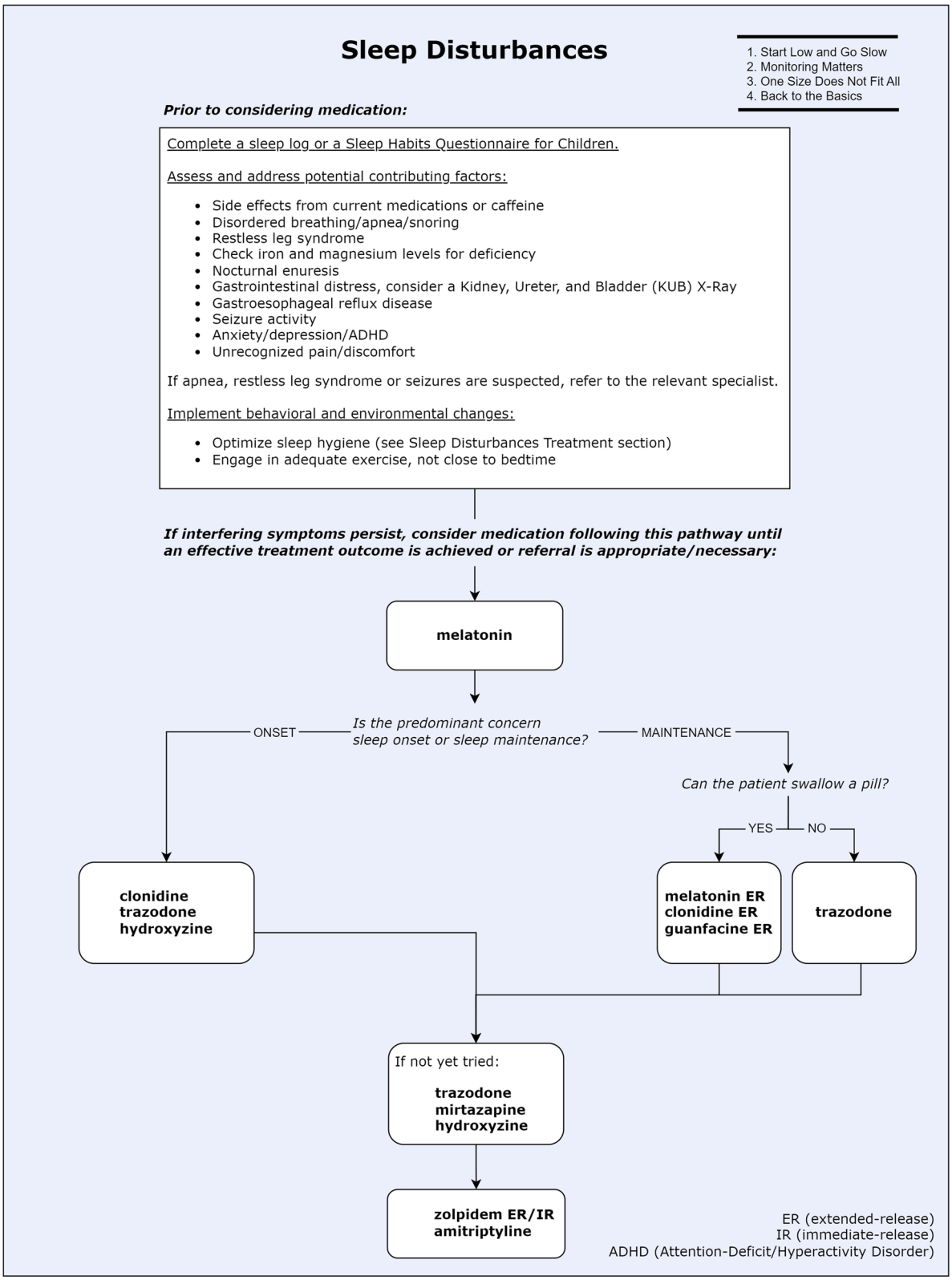

Fig. 1 Pharmacological treatment pathway for sleep disturbances in patients with ASD

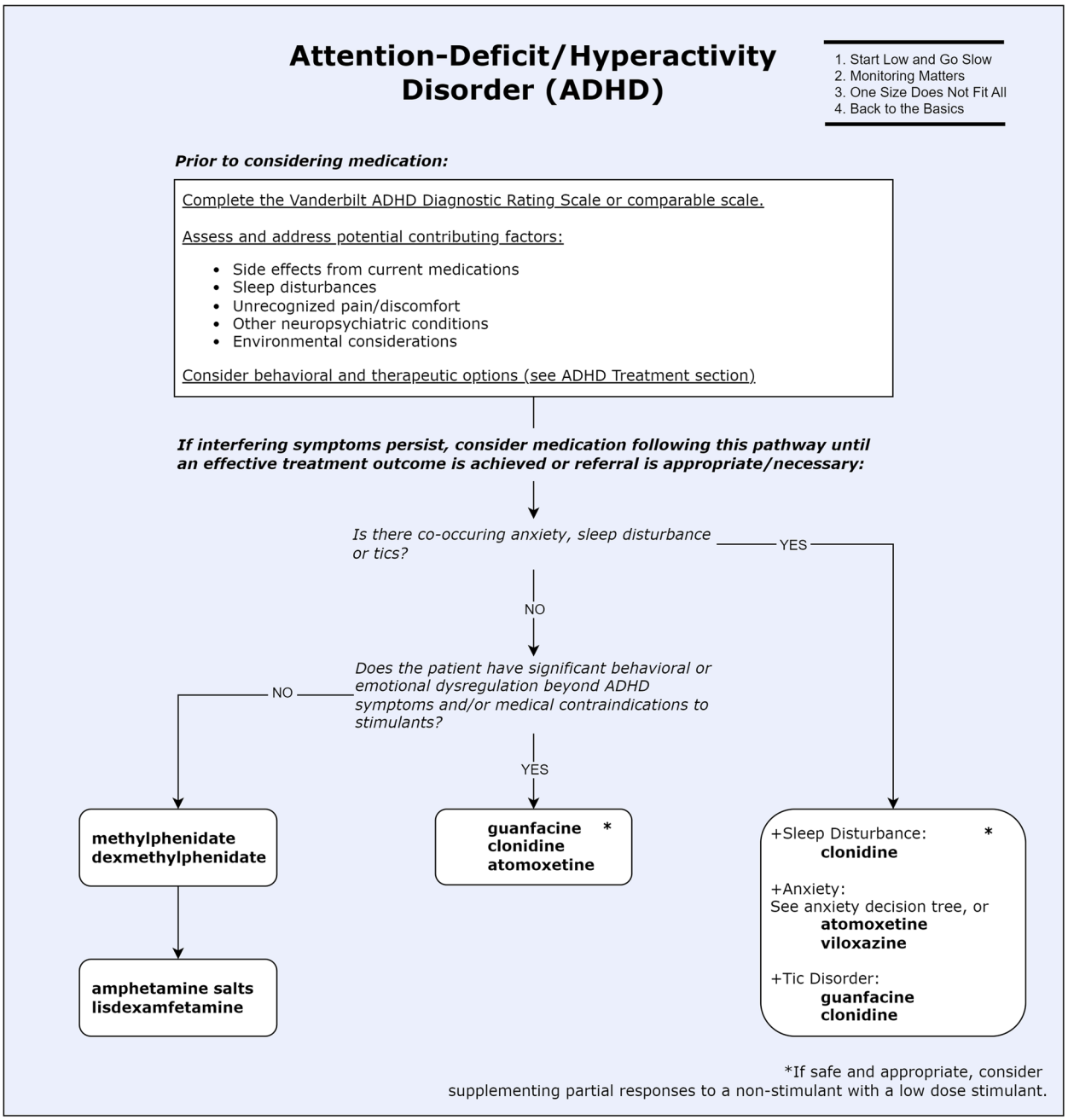

Fig. 2 Pharmacological treatment pathway for ADHD in patients with ASD

Diagnosis

Sleep disturbances can present in many ways (Table 1). Patients with ASD should be screened for insomnia. To best inform treatment strategy, it is important to differentiate between difficulty falling asleep (sleep onset insomnia) and difficulty staying asleep (sleep maintenance insomnia). An individual with problems falling asleep will often also have difficulties staying asleep. To help tease out behavior differences between sleep onset insomnia and sleep maintenance insomnia, the Sleep Habits Questionnaire for Children with ASD (CSHQ-Autism) [48] can be very useful. This questionnaire helps to better understand whether the sleep challenges relate to associations with falling asleep or sleep hygiene. Alternatively, the examiner can ask some key questions such as how long it takes to fall asleep, when the patient wakes

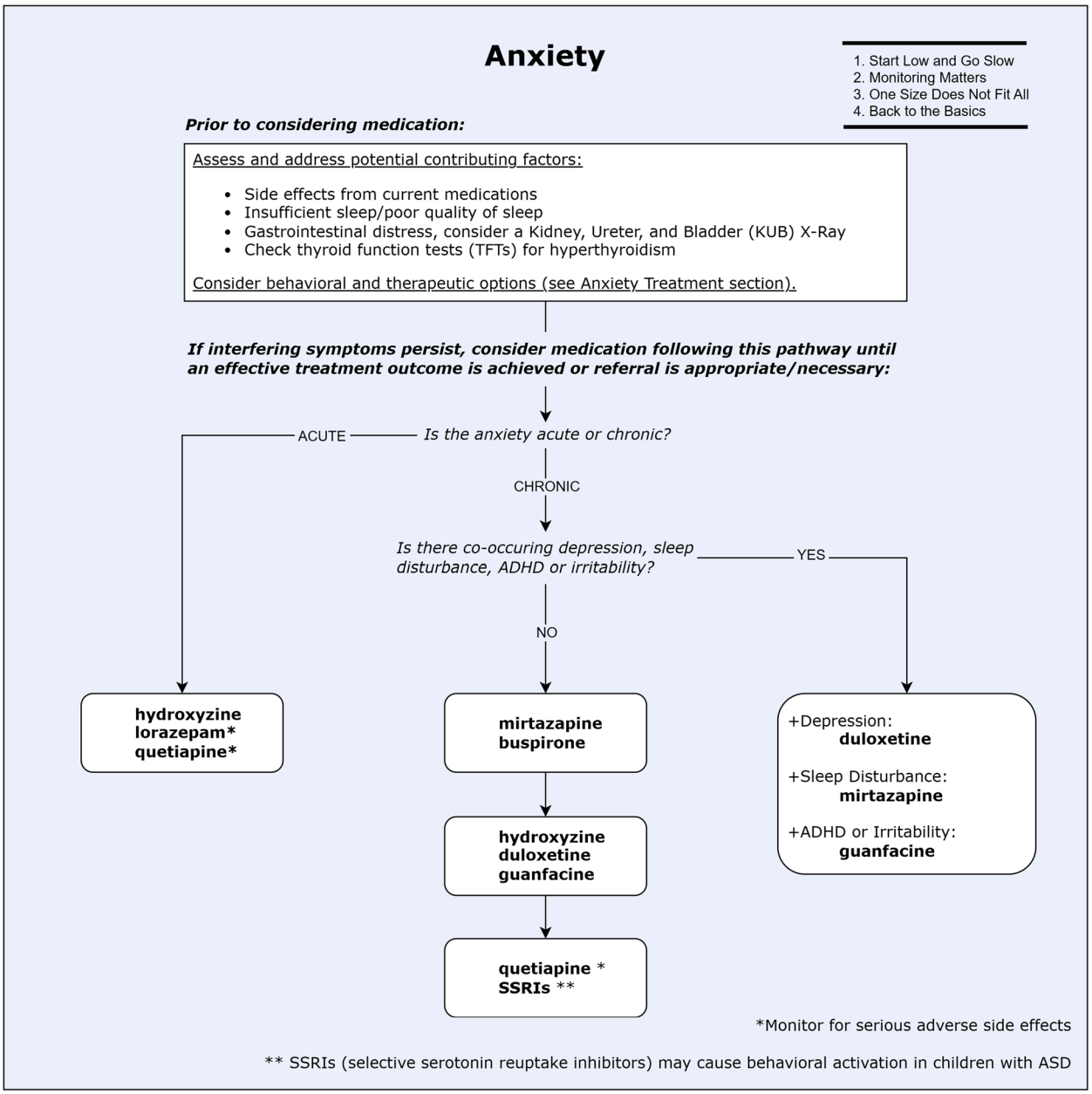

Fig. 3 Pharmacological treatment pathway for anxiety in patients with ASD

up in the morning, when and how many times the patient wakes up during the night, how many hours the patient sleeps, is the patient well rested in the morning, and where does the patient sleep [49]. A sleep log can also be helpful in better understanding when and how frequently a patient sleeps.

Sleep apnea should be ruled out by asking about snoring. The patient who wakes up with headaches and/or snores loudly should be referred for a sleep study (polysomnogram). Sleep studies are often not well tolerated in individuals with ASD. It is important to acknowledge that challenge. In some cases, it is possible to do a sleep study at home. If a sleep study is attempted, a social story, such as the one from the Kennedy Krieger Institute called "The Sleep Study Story" [50] or the one from Boston Children's Hospital called "My Sleep Study" [51], may help patients and families in this process. Many otolaryngologists will preemptively perform surgery to remove the tonsils (tonsillectomy)

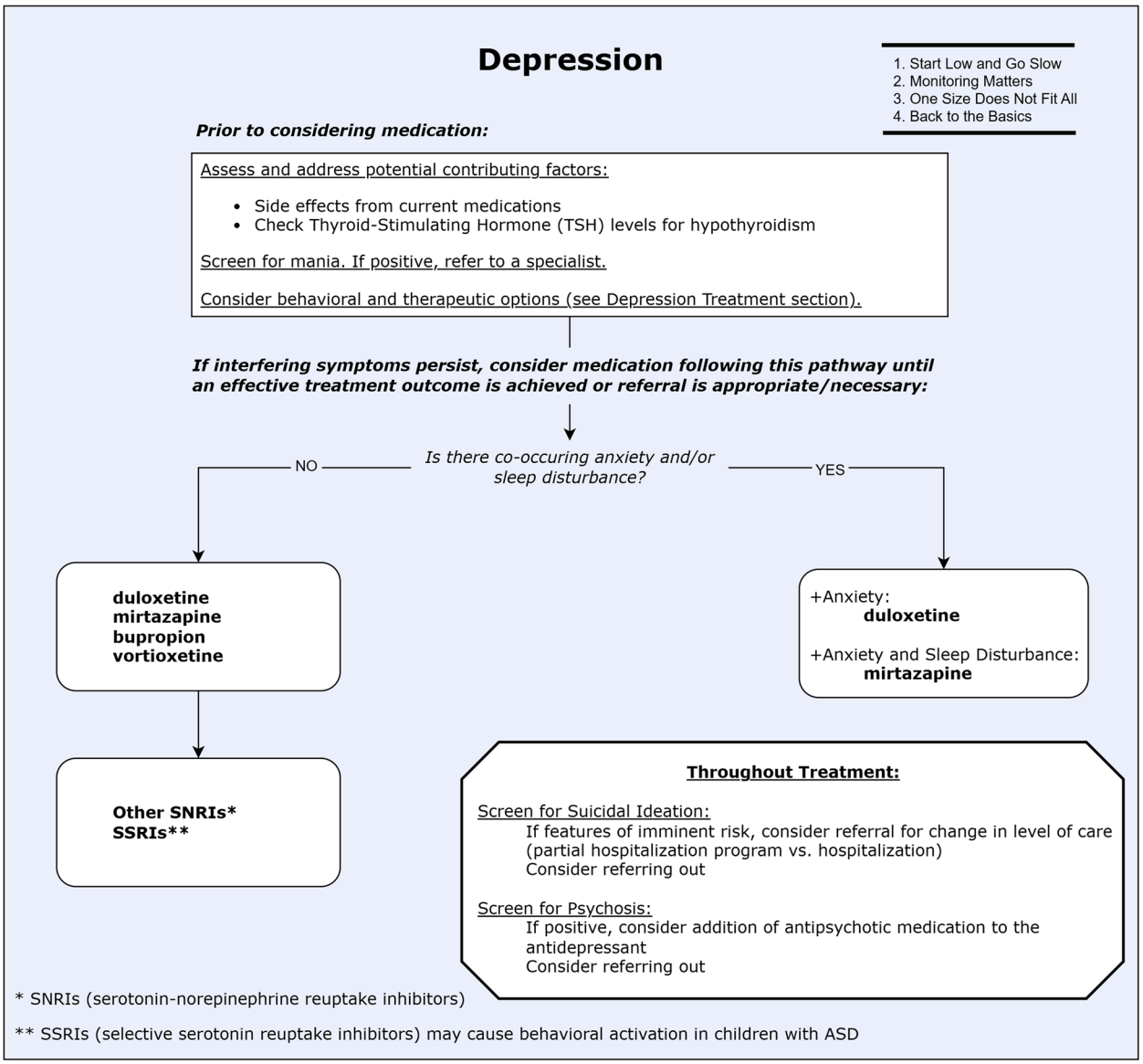

Fig. 4 Pharmacological treatment pathway for depression in patients with ASD

in children with loud snoring and who are presumed to have sleep apnea. Consultation with a sleep specialist can help review all options.

Differential diagnoses

First, medical conditions that could present as sleep dysfunction should be ruled out. These include the common co-occurring conditions seen in ASD, such as GI disorders, including reflux and constipation, sleep apnea, pain, and neuropsychiatric disorders, such as anxiety, depression, and ADHD. Epilepsy can also present as sleep problems, so if this is a concern, a referral for a neurological evaluation is indicated. Medications, including psychostimulants such as methylphenidate and amphetamine salts or daytime cold/flu products, can also impair sleep onset and may be able to be adjusted. Patients with ASD can also have sleep disorders such as parasomnias and restless leg syndrome. Testing for iron deficiency (via a blood ferritin test) is recommended for suspected restless leg syndrome, especially because people with ASD commonly have dietary insufficiencies of vitamins and minerals, including iron, due to selective eating. A ferritin level below 50 mcg/dL suggests iron deficiency and can be

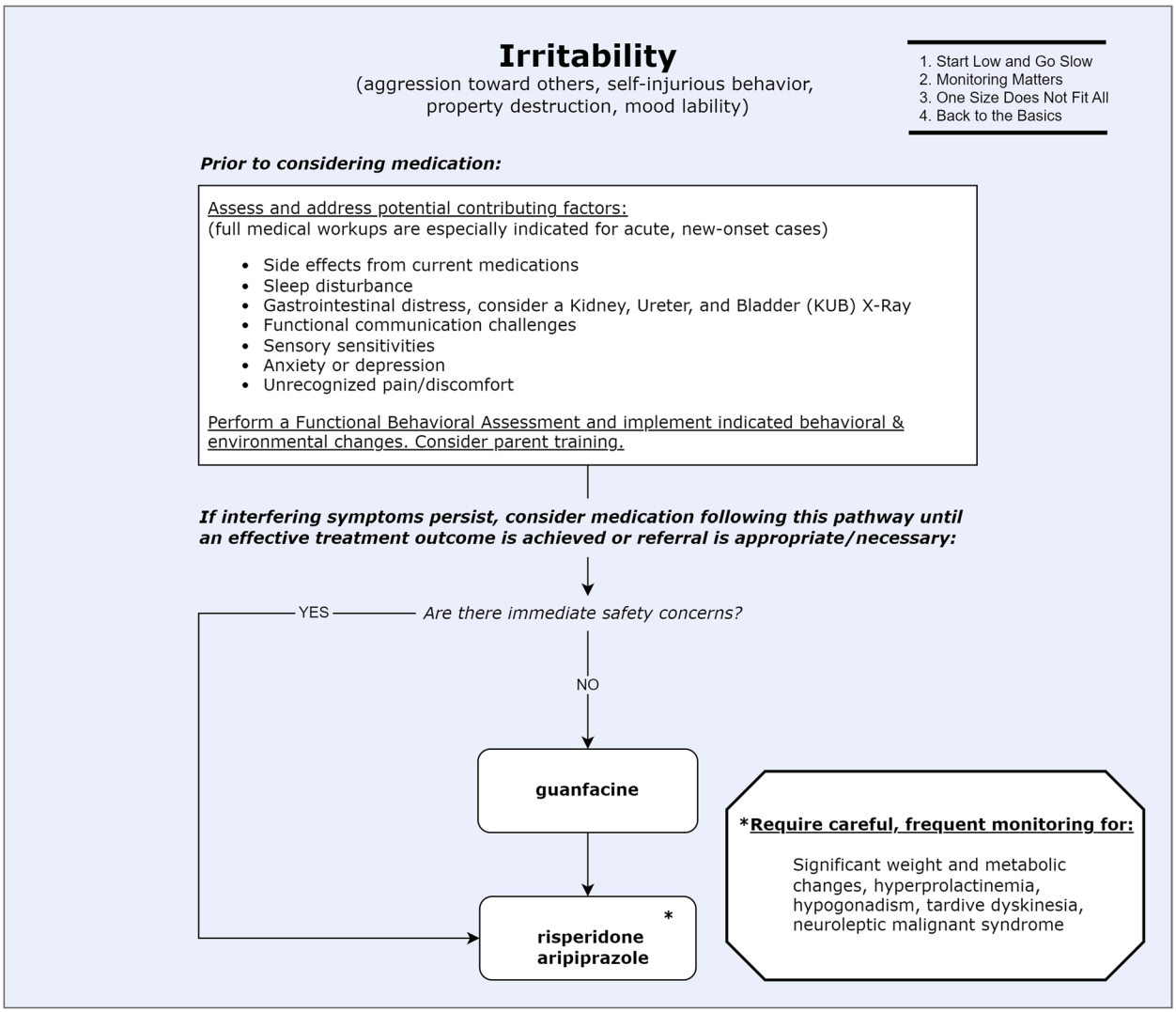

Fig. 5 Pharmacological treatment pathway for irritability in patients with ASD

addressed through diet changes and iron supplementation. Patients and families should be forewarned that iron supplementation products may have a strong smell and can cause constipation, which is a common concern in individuals with ASD.

Treatment

If a patient regularly requires more than 30 min to fall asleep, wakes up during the night and cannot return to sleep, or is not sleeping for an adequate duration, treatment should be considered. First, as stated above, any underlying medical conditions should be addressed. Then, sleep hygiene should be reviewed, including daytime habits, level of physical activity [52], consumption of food and beverages containing caffeine, sleep environment, and screen/device use close to bedtime.

Treatment to improve sleep habits should be established. A general recommendation is to start a brief bedtime routine (less than one hour) with quiet activities on a predictable schedule and ideally away from digital devices and bright lights. There are multiple sleep toolkits available that introduce strategies to improve sleep habits including the Autism Speaks Treatment Network's "Sleep Strategies for Children with Autism" [53] and "Sleep Strategies for Teens with Autism Spectrum Disorder" [54], and the Stanford Medicine Center for Sleep in Autism Spectrum Disorder toolkit on "Interventions for Sleep Problems in Autistic Adolescents and Adults" [55]. For young children and those who are minimally verbal, a social story or a sleep toolkit video can be used, such as the ones available from the Autism Speaks Autism Treatment Network [56]. Importantly, how someone falls asleep is how someone stays asleep. The situation in

Table 1 Behavioral indications of and medical conditions associated with sleep disturbances in ASD

Behavioral	Medical
Refusal to go to bed	GI Issues (reflux and constipation)
Refusal to stay in bed	Sleep apnea/ Snoring
Sleep onset location other than the bedroom	Seizures/ Epilepsy
Delayed sleep onset (> 30 min)	Anxiety
Prolonged bedtime routine	ADHD
Short sleep duration	Depression
Irritable in the morning	Pain
Daytime sleepiness/napping	Incontinence
	Restless leg syndrome

Table 2 Medication options and dosing for sleep disturbances in patients with ASD

Drug	Common US Brand Names	Lurie Center Daily Dose Ranges	Notable Side Effects
Melatonin	Varied	ER/IR | 1–10 mg qHS	Drowsiness, daytime sleepiness, headaches, nausea
Clonidine	Kapvay	ER| 0.1 mg-0.3 mg qHS	Somnolence, abdominal pain, headache, fatigue, nausea, mood lability, constipation, diarrhea, sexual impairment, dizziness, sedation, bradycardia, hypotension
	Catapres	IR | 0.05–0.3 mg qHS	
Trazodone	Desyrel, Desyrel Dividose	IR | 25–150 mg qHS	Drowsiness, fatigue, diarrhea, blurred vision; Rare risk for induction of hypomania, priapism, cardiac arrhythmias, and suicidal ideation
Hydroxyzine	Orgatraz, Vistaril, Atarax	IR | 10–25 mg qHS	Dry mouth, drowsiness, headache
Guanfacine	Intuniv	ER|1–4 mg qHS	Somnolence, fatigue, nausea, constipation, lethargy, insomnia, dizziness, bradycardia, hypotension
	Tenex	IR |0.5–2 mg qHS	
Mirtazapine	Remeron	IR | 3.75–45 mg qHS	Drowsiness, weight gain, dry mouth, constipation, increased appetite, sedation, thrombocytopenia, urinary hesitancy, irritability; Rare risk of induction of hypomania, lowered seizure threshold, and suicidal ideation
Zolpidem	Ambien CR	ER| 6.25–12.5 mg qHS	Drowsiness, dizziness, diarrhea
	Ambien	IR | 5–10 mg qHS	
Amitriptyline	Endep, Elavil, Vanatrip	IR | 5–50 mg qHS	Constipation, heart rate variability, sedation, and metabolic changes; Can lower the seizure threshold

ER Extended-release, *IR* Immediate-release, *qHS* every night before bedtime

which an individual falls asleep the first time should be maintained throughout the night. For example, if someone falls asleep in a room with a light on, that light should be on the whole night.

While improving sleep habits is sufficient in some cases, it may be necessary to consider a medication to help with sleep onset or maintenance. Typically, the stress experienced around sleep (or lack thereof) or the resulting challenges with school, learning or employment might help determine if medication is needed. In addition, if the individual or family is not able or willing to make behavior changes, medication can also be considered. Clinical experience reveals that, for many patients, altering the sleep routine is anxiety-producing, so medications may be a helpful adjunct.

In relation to non-autistic SOC First-line treatment strategies for sleep disturbances in ASD align with non-autistic SOC, focusing on sleep hygiene and melatonin use.

Medication management and dosing for sleep disturbances

When a pharmacological intervention is required, there are several options to consider (Fig. 1, Table 2). Melatonin is generally the first-line approach to treating sleep disruption pharmacologically. Melatonin is produced in the pineal gland and is released as it gets dark. Children with ASD have lower urinary melatonin secretion than typical children, suggesting possibly lower production levels [57, 58]. There are numerous randomized controlled trials (RCTs) of melatonin in people with ASD, including children, showing that melatonin can help with sleep onset and is generally well tolerated with minimal side effects [59, 60]. Out of 18 studies, the average overall improvement rate from melatonin for sleep disturbances in individuals with ASD was over 84% [58]. Melatonin has been shown to reduce sleep latency (the amount of

time it takes to fall asleep) [61]. The effects of melatonin typically last 4–6 h, so while it is helpful for sleep onset, its effect on sleep maintenance is variable [38]. Long-acting melatonin has been shown to increase total sleep time in individuals with ASD across multiple studies [62], but many long-acting formulations require swallowing a pill that is not sized for children. This limitation has led to the development of pediatric-appropriate prolonged-release melatonin (PedPRM), which is a mini-tablet (diameter ≤ 3 mm) designed for children with neurodevelopmental disorders who have difficulty swallowing pills [63]. PedPRM has been shown to be efficacious and safe for the long-term treatment of insomnia in children with ASD in initial research [63]. However, the product is not yet available in the U.S.

It is generally recommended to start with 1–3 mg of melatonin about 30 min prior to the desired onset of sleep. Doses can be increased every 5–7 days in 1–3 mg increments up to 10 mg at bedtime. If no effect is seen after giving 10 mg, melatonin should be discontinued, and a new medication should be considered.

Since melatonin is considered a dietary supplement instead of a drug in the U.S., melatonin products are not subject to FDA oversight. Studies have found considerable variation in product concentrations and ingredients [64, 65]. Because of this, it is important that clinicians educate patients and families to look for supplement products that have received third-party certification from a reputable, independent organization, such as the USP (United States Pharmacopoeia) or NSF (National Sanitation Foundation) International.

Clonidine, an α_2-adrenergic agonist, has been studied for sleep onset, and the long-acting preparation can be used for sleep maintenance [66]. Short-acting clonidine is effective in improving sleep onset. The long-acting formulation however, has not been adequately studied and requires swallowing a pill whole [66]. For sleep onset, it is generally recommended to start with half of the short-acting clonidine 0.1 mg tablet (0.05 mg) 30 min before bedtime and increase the dose by half a pill every 3 to 5 days as tolerated. Typically, if the patient does not fall asleep within 30 min after lights out after increasing their dose up to 0.3 mg, then clonidine should be discontinued, and a different medication should be tried. If the short-acting preparation is effective with sleep onset and the patient can swallow a pill, then clonidine ER can be tried. Dosing of clonidine ER for sleep disturbances should start with 0.1 mg (these tablets cannot be broken or chewed) and can be increased every 5–7 days until achieving the desired clinical response or reaching a maximum daily dose of 0.3 mg.

Guanfacine is a medication in the same drug class as clonidine (α_2-adrenergic agonist), and some practitioners may prefer trying guanfacine before clonidine. Guanfacine is FDA-approved for ADHD in children but is used off-label for sleep disturbances. The short-acting guanfacine can be prescribed at a starting dose of half of a 1 mg tablet (0.5 mg) and can be increased by 0.5–1 mg every 3 to 5 days as tolerated up to 2 mg for sleep disturbances. Long-acting guanfacine preparations can be effective for sleep maintenance. If the short-acting preparation is effective with sleep onset and the patient can swallow a pill, then guanfacine ER can be tried. Dosing of guanfacine ER should start with 1 mg (these tablets cannot be broken or chewed) and can be increased every 5–7 days until achieving the desired clinical response or reaching a maximum dose of 4 mg/day.

Trazodone, a 5-HT_2 antagonist, was initially FDA-approved for the treatment of depression in adults and was found to be too sedating. It is thus frequently used for sleep disturbance in adults and children with mood and anxiety disorders. There are no RCTs of trazodone in children with ASD, yet clinically, it is a very effective medication for improving sleep onset and maintenance. Side effects, including prolonged erection of the penis (priapism), should be explained to patients and families. Start with half of a 50 mg tablet (25 mg) at bedtime and increase weekly by 25 mg to a maximum dosage of 100–150 mg at bedtime, depending on body weight.

Mirtazapine is a central presynaptic α_2-adrenergic antagonist and serotonin $(5\text{-}HT)_{2,3}$ antagonist and is FDA-approved for the treatment of major depressive disorder in adults. There are no RCTs of mirtazapine for sleep, yet this also can be effective for sleep onset and maintenance. Some of the common side effects of mirtazapine include drowsiness, increased appetite, weight gain, and irritability. See the anxiety section for dosing and titration recommendations.

Sleep medications, which are sometimes prescribed for adults with insomnia, such as benzodiazepines or even antihistamines, can cause activation or agitation in some children and should be used with caution. There are no FDA-approved medications for sleep for pediatric insomnia. Antihistamines, such as hydroxyzine, are frequently used by pediatricians for the management of sleep onset difficulties, although they might have a paradoxical effect in children under the age of 5 years. Since the long-term use of these medications in young children has yet to be studied, they are not recommended for long-term use for young children [67]. Hydroxyzine can be started at a dose of 10 mg at bedtime and increased up to a maximum dose of 25 mg.

Zolpidem is a gamma-aminobutyric acid (GABA) A agonist that has received FDA approval for short-term treatment of insomnia in individuals 18 years and older; it can be considered for sleep in teens and adults. Zolpidem

Table 3 Signs and Symptoms of ADHD in ASD

Behavioral	Medical
Careless mistakes	Sleep disturbance
Difficulties with sustained attention	Motor/Coordination Delays
Organizational challenges	Sensory integration difficulties
Refusal behavior	
Distraction by external stimuli	
Forgetfulness	
Overly talkativeness / Frequent interruption of others	
Fidgeting repetitively	
Trouble sitting still	
Restlessness	

is less useful for children who may be at risk for a paradoxical reaction from benzodiazepines. Zolpidem IR can be dosed at 5–10 mg at bedtime, and zolpidem ER can be dosed at 6.25–12.5 mg at bedtime.

Amitriptyline is a tricyclic antidepressant. While there is no data in the literature for children, the use of amitriptyline in low dosages is often effective for insomnia for children and adults with ASD. Start with a low dose of 5 mg at bedtime and increase weekly by 5 mg. Typically, it is effective in doses $\leq$ 50 mg at bedtime. Amitriptyline can cause constipation, which is common in individuals with ASD. Patients with prior heart disease will need an electrocardiogram (ECG) before they take amitriptyline, as it can prolong the time that the heart muscle takes to contract and relax (QTc cardiac interval).

For the patient who does not respond to medication for sleep disturbances, referral to a sleep specialist or psychiatrist is recommended. See Fig. 1 for pharmacological approaches to the treatment of sleep disturbances in individuals with ASD.

Attention-Deficit/Hyperactivity Disorder

Background

The DSM-5-TR defines ADHD as functionally impairing symptoms of inattention and/or hyperactivity and impulsivity, with onset before age 12 years and which occur in two or more settings [68]. While the DSM, Fourth Edition (DSM-IV) [69] and DSM, Fourth Edition, Text Revision (DSM-IV-TR) [70] precluded the co-occurring diagnosis of ADHD in individuals with ASD, the DSM-5, released in 2013, removed this restriction [71]. ADHD is one of the most common co-occurring diagnoses in individuals with ASD, with prevalence estimates ranging from 40–70% [72, 73]. In a 2021 meta-analysis, the pooled current and lifetime prevalence rates of ADHD among those with ASD were 38.5% (95% CI 34.0–43.2) and 40.2% (95% CI 34.9–45.7), respectively [74].

Diagnosis

Due to the overlapping features between ASD and ADHD (e.g., social impairment, executive dysfunction), diagnosing ADHD in patients with ASD can be challenging even for experienced clinicians [75]. A 2020 BMC Medicine publication from Young et al. focused on co-occuring ASD and ADHD offers thorough guidance on identifying and treating ADHD in the ASD population [31]. The diagnosis of ADHD in people with ASD requires a comprehensive, multi-modal evaluation. This determination relies on clinical interviews in combination with reports from collateral sources including rating scales and objective supporting assessments, which are appropriate based on the individual's age and unique presentation [31]. The Strengths and Difficulties Questionnaire (SDQ) and National Institute for Children's Health Quality (NICHQ) Vanderbilt Assessment Scales can be helpful for collecting information from individuals or caregivers and teachers. Whenever possible, neuropsychological testing is highly recommended for its ability to combine direct observation and real-time neurocognitive data (e.g., standardized measures of sustained attention, impulsivity, and executive functioning, such as the Conner's Continuous Performance Test, 3rd Edition) with parent/teacher rating scales and a comprehensive medical record review.

Differential diagnoses

A thorough differential diagnosis should assess for factors that may contribute to the clinical presentation and/or mimic symptoms of inattention, hyperactivity, and impulsivity. These may include other neuropsychiatric conditions, such as anxiety, mood disorders, and tic disorders; medical conditions, such as sleep disturbance and hyperthyroidism; adverse effects of medications, such as movement disorders like akathisia due to an antipsychotic medication; or environmental considerations, such as an unbefitting school placement. In some cases, a medical workup may be indicated to assess for medical causes, such as thyroid function tests to check for endocrine disorders like hyperthyroidism. See Table 3 for signs and symptoms to assist with recognition of ADHD in individuals with ASD.

Table 4 Medication options and dosing for ADHD in patients with ASD

Drug	Common US Brand Names	Lurie Center Daily Dose Ranges	Notable Side Effects
Methylphenidate	Ritalin LA/SR, Methylin ER, Metadate CD, Daytrana	ER| 2.5–30 mg	Slowing of growth in children, reduced appetite, insomnia, emotional lability, depression, anxiety; Rare risk of priapism; Consider avoiding in patients with marked anxiety or agitation
	Concerta	ER| 18–72 mg	
	Ritalin, Methylin	IR | 2.5–35 mg; >25 kg may require/tolerate up to 60 mg	
Dexmethylphenidate	Focalin XR	ER| 10–40 mg; Some patients may require/tolerate up to 50 mg	Slowing of growth in children, reduced appetite, insomnia, emotional lability, depression, anxiety; Can activate hypomania and lower the seizure threshold; Consider avoiding in patients with marked anxiety or agitation
	Focalin	IR | 5–40 mg (may be divided across two administrations)	
Amphetamine salts	Adderall XR	ER| 5–60 mg	Slowing of growth in children, reduced appetite, insomnia, emotional lability, depression, anxiety; Consider avoiding in patients with marked anxiety or agitation
	Adderall	IR | 2.5–40 mg; >50 kg may require/tolerate up to 60 mg	
Lisdexamfetamine	Vyvanse	IR | 10–70 mg	Slowing of growth in children, reduced appetite, insomnia, emotional lability, depression, anxiety; Consider avoiding in patients with marked anxiety or agitation
Guanfacine	Intuniv	ER| 1–4 mg	Somnolence, fatigue, nausea, constipation, lethargy, insomnia, dizziness, bradycardia, hypotension
	Tenex	IR |0.5–4 mg (may be divided across two or more administrations; daily max. dose varies by weight: 2 mg for 27–40.5 kg, 3 mg for 40.5–45 kg, 4 mg for >45 kg)	
Clonidine	Kapvay	ER| 0.1 mg-0.4 mg (may be divided across two administrations)	Somnolence, abdominal pain, headache, fatigue, nausea, mood lability, constipation, diarrhea, sexual impairment, dizziness, sedation, bradycardia, hypotension
	Catapres	IR | 0.05 mg-0.4 mg	
Atomoxetine	Strattera	IR | 10–100 mg	Headache, insomnia, nausea, reduced appetite, early morning awakenings; Rare risk of liver injury, suicidal ideation
Viloxazine	Qelbree	ER| 100–600 mg	Somnolence, reduced appetite, fatigue, nausea, vomiting, insomnia, irritability; Rare risk of suicidal ideation

ER Extended-release, *IR* Immediate-release

Treatment

There are differences of opinion as to whether to first initiate pharmacologic or non-pharmacologic interventions in the treatment of ADHD [76]. The American Academy of Pediatrics (AAP) Clinical Practice Guideline on ADHD in the general population identifies parent-training behavior management (PTBM) as the first-line approach for preschool-aged children and medication management in conjunction with PTBM and behavioral classroom interventions for youth ages six years or older [77]. Young et al. outline many non-pharmacological avenues through which to support children and adults with co-occuring ASD and ADHD and how to tailor these to meet the needs of the individual [31]. Their practice recommendations echo the AAP guideline's focus on education for parents, along with career and occupational skills training, cognitive behavioral therapy (CBT), and other behavioral and educational approaches both for individuals with ASD and ADHD and their families [31].

Medications approved by the FDA to treat ADHD include psychostimulants (methylphenidate, amphetamine salts), selective norepinephrine reuptake inhibitors, and α_2-adrenergic agonists (Fig. 2, Table 4). The data examining the effectiveness of these medications in patients with ASD and ADHD is more limited.

In relation to non-autistic SOC While stimulants are the first-line pharmacological treatment for ADHD in non-autistic populations, non-stimulants may be more suitable than stimulants for many autistic patients based on their unique clinical profiles.

Medication management and dosing for ADHD

Whether a stimulant or a non-stimulant should be the first-line pharmacotherapy approach for managing ADHD in ASD depends on the profile of the individual

patient. Methylphenidate (MPH) and amphetamine (AMP) are the first-line treatments for ADHD in typically developing children and adolescents. Clinicians can choose from among a variety of immediate-release (IR) and extended-release (ER) formulations of MPH and AMP.

Non-stimulants such as α_2-adrenergic agonists may be preferable for patients with any of the following: significant behavioral or emotional dysregulation beyond ADHD symptoms, anxiety, sleep disturbance, tics, or medical contraindications such as cardiovascular disease or low body weight that stimulants could exacerbate. Although FDA labeling on stimulants warns of their association with the onset or worsening of tics, a 2015 meta-analysis did not substantiate this relationship [78]. Nonetheless, α_2-adrenergic agonists, which are a first-line treatment for tics, may be preferred for patients with ADHD and co-occuring tic disorders.

Stimulants: Operating through different mechanisms, MPH and AMP increase synaptic extracellular dopamine and norepinephrine levels.

The Research Units on Pediatric Psychopharmacology (RUPP) Autism Network conducted a randomized, placebo-controlled, 4-week crossover trial of MPH in 72 children ages 5 to 14 years [79]. Subjects carried a DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder-not otherwise specified (PDD-NOS) and had significant interfering symptoms of hyperactivity and/or impulsiveness present for at least six months [71, 79]. The researchers investigated three dosage levels of MPH: 0.125, 0.25, and 0.5 mg/kg per dose administered in the morning and at noontime and a half-dose administered in the late afternoon. All three dosage levels improved teacher and parent ratings on the Aberrant Behavior Checklist (ABC)-Hyperactivity subscale. Effect sizes ranged from 0.20 to 0.54 depending on the dose and rater, smaller than those seen in studies of typically developing children with ADHD. Nine of the 58 subjects (15.5%) who completed the crossover phase were deemed placebo responders. Thirty-five of the 72 total participants (49%) qualified as MPH responders [79]. The RUPP trial had an 18% discontinuation rate due to adverse events, compared with a 1.4% discontinuation rate in the Collaborative Multisite Multimodal Treatment Study of Children with ADHD, a landmark study of ADHD treatments in typically developing children with ADHD [79, 80]. In the RUPP trial, irritability, reduced appetite, difficulty with sleep onset, and emotional outbursts were more frequent with MPH than with placebo [79].

There are no RCTs of AMP treatment for ADHD symptoms in the ASD population.

Earlier research suggested that stimulants had lower efficacy and were less well tolerated in children with ASD and ADHD compared to children with ADHD alone [81]. A recent non-randomized, prospective observational cohort study evaluated 323 children with ADHD who were initiating pharmacotherapy and who also demonstrated either high or low ASD symptoms [82]. The majority of these children were started on MPH, and the data showed no difference in treatment effect or rates of adverse events between the groups with high and low ASD symptoms [82]. MPH products may rarely cause prolonged erection of the penis (priapism).

Methylphenidate IR is available in 5 mg, 10 mg, and 20 mg tablets; 2.5 mg, 5 mg, and 10 mg chewable tablets; and 5 mg/5 ml and 10 mg/5 ml solutions. We recommend starting with a dose of 2.5 mg in the morning and increasing after a few days to 2.5 mg twice daily, administered in the morning and at lunchtime. We continue titrating by 2.5 to 5 mg increments every 5 to 7 days as needed. The usual maximum daily dose is 35 mg for patients weighing $\leq$ 25 kg and 60 mg for those weighing > 25 kg. Please refer to specific dosing instructions for MPH ER formulations, which include tablets, capsules, a suspension, and a transdermal patch.

Non-stimulants: Clonidine and guanfacine are α_2-adrenergic agonists that exert their action primarily by stimulating presynaptic α_2 receptors in the central nervous system. Their effects on noradrenergic transmission in the locus coeruleus and the prefrontal cortex are postulated to underlie their benefits on cognition and behavior [83, 84]. Clonidine and guanfacine were initially used as antihypertensive agents. ER formulations of these drugs carry FDA approval as monotherapy or adjunctive therapy to stimulants for the treatment of ADHD in patients ages 6–17 years.

Sixty-two subjects, ages 5–14 years, diagnosed with autistic disorder, Asperger's disorder, or PDD-NOS, participated in an 8-week RCT of guanfacine ER to target symptoms of hyperactivity, impulsiveness, and distractibility [83]. Doses ranged from 1 to 4 mg/day. ABC-Hyperactivity subscale scores fell by 43.6% in the active treatment group and 13.2% in the placebo group. The guanfacine group had a 50% positive response rate on the Clinical Global Impressions-Improvement (CGI-I) scale compared to 9.4% for placebo. Drowsiness, fatigue, emotional/tearful presentation, dry mouth, and irritability were the most common side effects in the active treatment arm. In the guanfacine group, systolic and diastolic blood pressures and pulse decreased in the first four weeks. By week eight, however, blood pressure parameters had returned close to baseline, while pulse was a little under 10 points below baseline. The results of this trial indicated that guanfacine ER is safe and efficacious

for the short-term treatment of ADHD symptoms in children and adolescents with ASD [83].

One small, placebo-controlled trial demonstrated that transdermal clonidine reduced hyperarousal symptoms in patients with ASD [85]. A small, placebo-controlled study of oral clonidine in children with ASD had mixed findings [86]. There are no RCTs of clonidine ER in the ASD population. Potential side effects of clonidine include somnolence, fatigue, and reductions in pulse and blood pressure. Clonidine tends to be more sedating than guanfacine. Of note, α_2-adrenergic agonists can worsen constipation, which is a common issue in the ASD population. Patients can experience rebound hypertension with abrupt discontinuation of α_2-adrenergic agonists.

Research indicates that α_2-adrenergic agonists have a lower effect size than psychostimulants for treating symptoms of ADHD in non-autistic children and adolescents [77]. Nonetheless, they can be attractive options for patients presenting with significant co-occurring issues, such as irritability, anxiety, disruptive behavior, tics, and sleep disturbances. Start with the IR preparations of guanfacine or clonidine for patients who cannot swallow tablets whole or who require a smaller initial dose.

Guanfacine IR is available in 1 mg and 2 mg tablets. The starting dose for ADHD is 0.5 mg (half of a 1 mg tablet), administered in the morning. The medication can be titrated up by 0.5 mg every few days as tolerated and divided into twice daily dosing. Some individuals may respond better to three or four times daily dosing. The maximum daily dose varies by weight and is 2 mg/day for patients weighing 27 to 40.5 kg, and 3 mg/day for patients weighing 40.5 to 45 kg, and 4 mg/day for patients weighing more than 45 kg.

Guanfacine ER is available in 1 mg, 2 mg, 3 mg, and 4 mg tablets. The starting dose for ADHD is 1 mg daily, which can be administered in the morning or at night. The medication can be increased by 1 mg weekly until achieving the desired clinical response or reaching a maximum dose of 4 mg/day. Although doses up to 7 mg/day have been studied in adolescents ages 13 to 17 years old, we do not typically use doses higher than 4 mg/day at the Lurie Center for Autism.

Clonidine IR is available in 0.1 mg, 0.2 mg, and 0.3 mg tablets, as well as 0.1 mg/24 h, 0.2 mg/24 h, and 0.3 mg/24-h patches. The starting dose of oral clonidine for ADHD is 0.05 mg, administered in the morning. The medication can be increased by 0.05 mg, divided into twice daily dosing, every few days as tolerated. Some individuals may respond better to three or four times daily dosing. Weight-based guidelines exist for the maximum daily dose of clonidine: 0.2 mg/day for patients weighing between 27 and 40.5 kg, 0.3 mg/day for patients weighing between 40.5 and 45 kg, and 0.4 mg/day for patients weighing more than 45 kg.

Clonidine ER is available in 0.1 mg tablets. The starting dose is 0.1 mg, administered at night. The medication can be increased by 0.1 mg in weekly intervals up to a maximum dose of 0.4 mg daily for ADHD. Doses higher than 0.1 mg are often split into twice-daily dosing.

Atomoxetine and viloxazine are selective norepinephrine reuptake inhibitors. Atomoxetine raises synaptic norepinephrine and dopamine concentrations in the prefrontal cortex [87], while viloxazine modulates serotonin and norepinephrine [88].

A RCT in 97 children, ages 6–17 years, with ASD and ADHD found that atomoxetine improved ADHD symptoms [89]. The active group had an average 8.2-point reduction in ADHD Rating Scale total scores from baseline, compared to a 1.2-point decrease in the placebo group. This reflects a smaller magnitude of the effect of atomoxetine for ADHD in children with ASD than that reported in studies of atomoxetine in typically developing children with ADHD. In this trial, there was no significant difference in the number of patients who were "much improved" or "very much improved" on the medication compared to placebo, as measured by the CGI-I. Commonly reported side effects included nausea, reduced appetite, fatigue, and early morning awakenings [89]. Atomoxetine also carries the rare risks of liver injury and prolonged erection of the penis (priapism). While a recent review of non-ASD trials suggests that atomoxetine is efficacious for co-occurring anxiety and ADHD, these findings have not been replicated in the ASD population [90].

Viloxazine received FDA approval for ADHD in children and adolescents in the general population in 2021 [91]. Currently, there are no published studies evaluating viloxazine in the management of ADHD symptoms in patients with ASD.

Both atomoxetine and viloxazine carry FDA black box warnings about the risk of suicidal thinking and behavior in children, adolescents, and young adults who are treated with antidepressants.

Atomoxetine is available in 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, and 100 mg capsules. For patients weighing $\leq$70 kg, the suggested starting dose is 0.5 mg/kg/day, administered once daily. After a week, the medication can be titrated to 1.2 mg/kg/day, usually divided into two daily doses. For patients in this weight class, we typically begin 10 mg daily, titrating by that amount every week or two as indicated. For patients >70 kg, we recommend starting at 18 mg daily and increasing to 25 mg or 36 mg daily after one week. After two to three weeks, the dose can be titrated to 80 mg/day. The recommended

Table 5 Signs and Symptoms of Anxiety in ASD

Behavioral	Medical
Crying	Changes in appetite
Distractibility/inattention	GI distress
Escaping or running away	Increased heart rate
Increased stereotypies (repetitive, ritualistic movements and vocalizations)	Insomnia
Meltdowns/tantrums	
Nail or skin picking/biting	
Pacing/restlessness	
Repetitive questioning	
Rocking	
Rubbing hands on arms or legs	
SIB	

maximum daily dose is 1.4 mg/kg/day, up to a total of 100 mg/day.

Viloxazine is available in 100 mg, 150 mg, and 200 mg capsules. The starting dose for children ages 6 to 11 years is 100 mg daily. The dose can be titrated by 100 mg weekly until reaching a maximum of 400 mg/day. Older children and adolescents can start at 200 mg daily and increase after one week to 400 mg/day. For adult patients, the starting dose is 200 mg daily, and the maximum dose is 600 mg/day.

Some patients with ASD and significant inattention, hyperactivity, and/or impulsivity may not respond to typical ADHD medications. For these challenging cases, cautious use of atypical antipsychotics may be appropriate, particularly if they are targeting additional symptoms like irritability or behavioral dysregulation.

See Fig. 2 for pharmacological approaches to the treatment of ADHD in individuals with ASD.

Anxiety

Background

Co-occurring anxiety is common among children and adolescents with ASD. A prospective study from 2021 demonstrated that 69% of youth with ASD had clinically significant anxiety, compared to 8% of typically developing children [92]. The anxiety signs and symptoms observed among children with ASD were highly varied, both corresponding and contrasting with the specified anxiety disorders of the DSM [68, 70, 92]. Fear of change, uncommon phobias, and social fears are all ASD-specific presentations of anxiety that can significantly impact daily functioning. Fear of change can manifest as distress or anxiety, especially when routines or familiar environments are disrupted. People with ASD may develop uncommon phobias of stimuli that are atypical compared to those seen in the general population (i.e., fears of toilets or specific songs). Social fears in ASD tend to pertain more to underlying social performance challenges rather than to interfering thoughts of others' negative perceptions, as observed in non-autistic social anxiety. This confusion can arise due to challenges in understanding social cues, norms, and expectations. Psychosocial factors that lead to challenges in relationship development and academic and vocational success may play a role in anxiety disorders among individuals with ASD [93]. According to a meta-analysis, 39.6% of youth with ASD have at least one co-occurring anxiety disorder based on the DSM-IV criteria [71, 94]. Specific phobia (29%), obsessive–compulsive disorder (OCD) (17.4%), and social anxiety disorder (16.6%) were the three most commonly observed anxiety disorders in ASD youth [94]. Anxiety levels are positively associated with ASD severity [16], and severe anxiety in ASD youth has also been associated with aggression, decreased participation in social activities, and poor social relationships [95].

Diagnosis

Family members and patients may use different words to refer to "anxiety." It can be helpful to explain that "anxiety," "worry," and "nervousness" refer to the same condition. This helps to bring the clinician, patient, and family members to a more consistent understanding of the interfering signs and symptoms (disorder) we are trying to diagnose or rule out. Because individuals with ASD may have limited communicative ability and/or ID, it can be difficult for them to describe their mood or how they feel. Therefore, clinicians need to ask about and look for signs and symptoms of anxiety that may be present beyond an internal feeling state. Table 5 lists signs and symptoms of anxiety disorders that are commonly present in individuals with ASD. These signs and symptoms, along with the DSM-5-TR criteria [68], can be used to make the diagnosis of an anxiety disorder.

Differential diagnoses

Prior to making the diagnosis of an anxiety disorder, it is important to consider factors that may contribute to the clinical presentation and/or may mimic anxiety. These can include medical conditions, like sleep disturbance,

hyperthyroidism, or GI dysfunction (e.g., constipation, GERD); adverse effects of medications; or environmental stress, such as overstimulating sensory stimuli in daily living spaces or a school placement that is not adequately addressing a patient's learning style or educational needs, or a group home with limited staffing, for example. Further complicating the differential diagnoses are overlapping phenotypes with OCD, where obsessions in OCD and fixated interests in ASD exhibit similarities in repetitive thoughts but differ in subjective experiences [96]. Obsessions in OCD are typically intrusive and distressing, contrasting with fixated interests in ASD, which may be enjoyed by the individual and/or may serve a self-soothing purpose but can cause distress when disrupted [96, 97]. Accurately discerning between these presentations becomes crucial in delineating anxiety manifestations within ASD. If true co-occurring ASD and OCD are suspected, then referral to a specialist may be warranted.

Treatment

If the symptoms of anxiety are interfering with daily life and treatment is required, behavioral therapy and educational approaches may be appropriate for some individuals. Non-pharmacological treatment options for anxiety can include modified CBT [98], psychosocial education, parent training, social recreational programs, and mindfulness techniques, either alone or in combination, that have been tailored to meet the needs and strengths of the patient [95, 98, 99].

If therapeutic approaches have been attempted without adequate improvement or do not seem appropriate for the patient, pharmacological treatment should be considered (Fig. 3, Table 6). For non-autistic children and adolescents, the first-line medication approach for the treatment of anxiety is the administration of SSRIs (e.g., fluoxetine and sertraline, among others). However, larger-scale, double-blind, placebo-controlled trials of SSRIs for youth with ASD have not found the drug to be better than placebo, and significant adverse effects are common. Most trials of SSRIs in youth with ASD have targeted interfering repetitive and ritualistic behavior rather than anxiety specifically. For example, King et al. 2009 completed a 12-week RCT of the SSRI citalopram in 149 youth with ASD (mean age = 9.4 years, range 5–17 years) [100]. Citalopram was found to be no more efficacious than placebo at reducing repetitive behaviors, and the drug was associated with significantly more adverse effects, including behavioral activation, characterized by increased energy, impulsiveness, hyperactivity, decreased concentration, stereotypy, and insomnia, among others [100]. The Study of Fluoxetine in Autism (SOFIA) was a 14-week RCT of the SSRI fluoxetine (2–18 mg/day) in 158 youth with ASD, ages 5–17 years [101]. The results showed that fluoxetine was no more efficacious than placebo for repetitive behavior. High rates of behavioral activation were reported in both groups [101].

In relation to non-autistic SOC Buspirone and mirtazapine are preferred first-line medications for anxiety in individuals with ASD, compared to SSRIs, which are commonly used in non-autistic SOC but can cause behavioral activation in those with ASD.

Medication management and dosing for anxiety disorders

To date, there has been only one published RCT of a medication, mirtazapine, for the treatment of anxiety in youth with ASD [102]. Mirtazapine is a central presynaptic α_2-adrenergic antagonist that increases norepinephrine release, which results in increased synaptic serotonin (5-HT) levels facilitated by the stimulation of α_1-adrenergic receptors on 5-HT neuron cell bodies. Mirtazapine also blocks 5-HT_2 and 5-HT_3 receptors [103], a mechanism likely responsible for the anxiolytic and hypnotic effects of the drug [104]. Mirtazapine is FDA-approved for the treatment of major depressive disorder in adults. The study was a 10-week RCT comparing mirtazapine (mean dosage = 41.8 ± 5.2 mg/day) with placebo in youth with ASD ages 5–17 years [102]. Thirty subjects were randomly assigned to mirtazapine versus placebo in a 2:1 ratio, with the CGI-I and the Pediatric Anxiety Rating Scale (PARS) as the primary outcome measures. A non-significant trend toward superiority of mirtazapine compared with placebo was observed with the PARS (effect size = 0.63). For 47% of participants assigned to mirtazapine, symptoms of anxiety were considered "much improved" (CGI-I = 2) or "very much improved" (CGI-I = 1) compared to 20% of those assigned to placebo. The most common adverse effects of mirtazapine were sedation/drowsiness, appetite increase/weight gain, and irritability; however, there was no statistically significant difference in the frequency of adverse effects between mirtazapine and placebo [102].

Mirtazapine is available in 7.5 mg, 15 mg, and 30 mg tablets and a 15 mg dissolvable wafer. We recommend starting with a dosage of 3.75 mg at bedtime. We then increase the dosage by 3.75 mg each week, giving all medication at bedtime, until the symptoms of anxiety are "much improved" or "very much improved"; the patient develops interfering side effects (see above), that limit further dose escalation; or we reach a maximum dose of 45 mg/day. Mirtazapine can be given in two divided doses if clinically indicated. Common side effects of mirtazapine include drowsiness, increased appetite, weight gain, and irritability.

Buspirone is a 5-HT_{1A} receptor partial agonist and dopamine (D_2) antagonist. Buspirone is FDA-approved

Table 6 Medication options and dosing for anxiety in patients with ASD

Drug	Common US Brand Names	Lurie Center Daily Dose Ranges	Notable Side Effects
Mirtazapine	Remeron	IR | 3.75–45 mg (may be divided across two administrations)	Drowsiness, weight gain, dry mouth, constipation, increased appetite, sedation, thrombocytopenia, urinary hesitancy, irritability; [a]Rare risk of induction of hypomania and suicidal ideation, and lowered seizure threshold
Buspirone	BuSpar, BuSpar Dividose, Vanspar	IR | 5–30 mg (divided across two administrations)	Drowsiness, dizziness, headache, blurred vision, tinnitus, diarrhea, nausea
Lorazepam	Ativan	Acute | 0.5–1 mg (children), 0.5–2 mg (adult) Short term | 0.5–3 mg (divided across 2–3 administrations)	Sedation, drowsiness, ataxia, appetite changes, tachycardia, irritability, constipation, sexual impairment
Hydroxyzine	Orgatraz, Vistaril, Atarax	IR | 10–200 mg (divided across 2–4 administrations)	Dry mouth, drowsiness, headache
Duloxetine	Cymbalta	IR | 20–90 mg (may be divided across two administrations)	Headache, drowsiness, fatigue, nausea, sexual impairments, constipation, reduced appetite, diarrhea, hyponatremia; [a]
Guanfacine	Intuniv	ER| 1–4 mg	Somnolence, fatigue, nausea, constipation, lethargy, insomnia, dizziness, bradycardia, hypotension
	Tenex	IR |0.5–4 mg (may be divided across two or more administrations; daily max. dose varies by weight: 2 mg for 27–40.5 kg, 3 mg for 40.5–45 kg, 4 mg for > 45 kg)	
Quetiapine	Seroquel XR	ER| 25–200 mg (acute) 25–300 mg (chronic)	Somnolence, dry mouth, dizziness, constipation, metabolic changes, increased appetite, weight gain, lethargy, tachycardia, tardive dyskinesia
	Seroquel	IR | 25–200 mg (acute) 25–300 mg (chronic, divided across 2–3 administrations)	
Citalopram	Celexa	IR | 5–40 mg	Drowsiness, insomnia, dizziness, headache, nausea, vomiting, constipation, sexual impairments, weight changes, QTc prolongation; [a]
Escitalopram	Lexapro	IR | 5–20 mg	Insomnia, sexual impairments, nausea, sweating, fatigue, sedation; [a]
Fluoxetine	Prozac	IR | 5–80 mg	Anxiety, hyperhidrosis, diarrhea, dry mouth, sexual impairments, nausea, sedation; [a]
Fluvoxamine	Luvox	IR | 12.5–300 mg	Nausea, somnolence, insomnia, sexual impairments, vomiting, dry mouth; [a]
Paroxetine	Paxil, Seroxat	IR | 5–50 mg	Drowsiness, dry mouth, weight gain, insomnia, sexual impairments, tachycardia, constipation, diarrhea, hyperhidrosis; [a]
Sertraline	Zoloft	IR | 12.5–200 mg	Nausea, diarrhea, tremors, dyspepsia, reduced appetite, hyperhidrosis, sexual impairment; [a]

ER Extended-release, *IR* Immediate-release

[a] Medications carry rare risks for induction of hypomania and suicidal ideation

for the treatment of generalized anxiety disorder (GAD) in adults. To date, there are no published RCTs of buspirone for the treatment of anxiety in ASD. In an open-label trial, 22 children and adolescents with ASD (ages 6–17 years) received buspirone (15–45 mg/day) for 6–8 weeks [105]. Nine patients (41%) showed a "marked response," and seven participants (32%) showed a "moderate response," addressing target symptoms of anxiety and irritability as measured with the CGI-I [105]. In a retrospective chart review including 31 ASD youth (ages 8–17 years) without co-occurring ID or impaired language skills, treatment with buspirone for co-occurring anxiety disorders led to 18 of the subjects (58%) rated as "much improved" or "very much improved" on the CGI-I [106]. Nine of the subjects (29%) were "minimally improved" [106]. There are very few clinically significant side effects with buspirone. Possible side effects include a sensation of dizziness, sedation, behavioral activation, and increased appetite and weight gain.

Buspirone is available in 5 mg, 10 mg, 15 mg, and 30 mg tablets. We recommend starting with a dosage of 2.5 mg (half of a 5 mg tablet) given each morning. We then

increase the dosage by 2.5 mg weekly, in the morning and at "after school" time points. We continue in this manner until the symptoms of anxiety are "much improved" or "very much improved," the patient develops interfering side effects (see above) that limit further dose escalation, or we reach a target dose of 15 mg twice a day.

While no published trials have been completed in ASD, benzodiazepines can be highly effective for acute episodes of anxiety (i.e., as needed for acute panic attacks) but can also be used as a short-term treatment of anxiety while waiting for a primary medication to take effect. Lorazepam dosing depends on its specific intent (acute administration or as a short-term treatment) and the age of the individual. Minimal dose is typically initiated to achieve efficacy without sedation or dizziness. For acute dosing, which is the most common use of lorazepam, children can be given 0.25 mg up to 1 mg, and adults can be given 0.5 mg up to 2 mg. However, in some cases, it may be advantageous to start at an even lower dose (0.125 in children and 0.25 in adults). For short-term daily treatment, with the intended action of 4–6 h, the frequency of administration would be 2–3 times/day with a total maximum daily dose of 1–3 mg. Clinical exceptions may require higher dosing. Side effects include sedation, dizziness, impaired muscle coordination (ataxia), and confusion. A less common yet notable side effect may include misuse or development of addiction (with increased risk in individuals who have a history of substance misuse). To protect against misuse, clinicians may consider short-term usage only or increase the monitoring of refill durations. Benzodiazepines can act with other sedating medications (to increase the risk of sedation), and at high dosages, risks include suppression of respiration drive, which is contraindicated for treating sleep in patients with sleep apnea. In addition, patients taking more than 3 mg in 24 h are at risk for seizure if medication is stopped suddenly. Prescribers are advised to taper down as the safest way to discontinue use. Finally, benzodiazepines also carry a risk of paradoxical reactions in those with neurodevelopmental disorders (again emphasizing the need to start low and go slow).

Hydroxyzine is an antihistamine that is described in the sleep disturbances section, which can also be an effective option for acute anxiety or for chronic anxiety. For acute use, on an as-needed basis, 10 mg is an appropriate starting dose and can be given up to 3 times per day. For chronic anxiety, 10 mg twice daily is an appropriate starting dose, and this can be increased by 10 mg per day until an effective dose is reached or until the maximum daily dose is reached. The recommended maximum daily dose for patients younger than six years is 25 mg up to 2 times/day. The recommended maximum daily dose for patients between 6–12 years is 25 mg up to 4 times/day. For patients 12 years and older, the recommended maximum daily dose is 50 mg up to 4 times/day. As noted previously, the safety of long-term use of antihistamines in young children has yet to be studied, and thus, hydroxyzine is not recommended for long-term use for young children [67].

Duloxetine is a serotonin-norepinephrine reuptake inhibitor (SNRI) that is FDA-approved for the treatment of Major Depressive Disorder (MDD) in non-autistic adults and GAD in non-autistic children, adolescents and adults. Currently, there are no published RCTs evaluating the use of duloxetine in the ASD population. Duloxetine is recommended as a first-line option for co-occurring anxiety and depression and as a second-line option for anxiety alone. Side effects of duloxetine may include headache, drowsiness, fatigue, nausea, sexual impairments, constipation, reduced appetite, diarrhea, low blood sodium (hyponatremia), and, more rarely, risk of induction of hypomania, lowered seizure threshold, and suicidal ideation. Duloxetine is available in capsules of 20 mg, 30 mg, 40 mg, and 60 mg and must be swallowed whole. The recommended starting dosage is 20 mg/day, and this can be increased by 10 mg every 1–2 weeks to reach a target dosage between 20–90 mg a day in 1–2 divided dosages.

Guanfacine, which was previously discussed in the sleep disturbances and ADHD sections, is also recommended for anxiety with co-occurring sleep disturbance or ADHD or as a second-line option for anxiety alone. Appropriate dosing of guanfacine IR for anxiety can start with 0.5 mg (half of a 1 mg tablet) and can be titrated up by 0.5 mg every few days as tolerated and may be divided across two or more administrations. This can continue until an effective treatment response or the maximum daily dose (2–4 mg depending on weight, see Table 6) is reached. Guanfacine ER can be started at 1 mg daily and titrated up by 1 mg weekly until achieving the desired clinical response or reaching 4 mg, the maximum daily dose for anxiety.

Quetiapine is an atypical antipsychotic with a good effect size for anxiety but a poor side effect profile [107], and it may be considered for patients with severe anxiety who have not responded to other treatments. It is thought that quetiapine provides relief from anxiety through its actions on dopaminergic, serotonergic, and noradrenergic systems [108]. Similarly to lorazepam, quetiapine can be prescribed on an as-needed basis for acute anxiety or as a standing dose for chronic anxiety. For both acute and chronic use, total daily doses of quetiapine may be given divided across 2–3 administrations per day or once per day for ER formulations. For acute use, on an as-needed basis, starting doses of 25 are recommended and can be divided across 2–3 administrations. This can be increased

by 25 mg/day until an effective treatment response is reached or a total maximum dose of 200 mg per day for acute dosing is reached. For chronic use, daily doses can start at 25 mg per day and can be divided across 2–3 administrations. This can be increased by 25 mg every 5–7 days until an effective treatment response is reached or a maximum dose of 300 mg per day for chronic dosing is reached [107], though doses as high as 800 mg have been studied for the treatment of psychosis and some patients may be able to tolerate higher doses. Common side effects include sedation, dizziness, constipation, increased appetite, weight gain, and elevated cholesterol and blood sugar (metabolic syndrome). Other rare side effects that can be seen include neuroleptic malignant syndrome, tardive dyskinesia (slow onset, potentially irreversible movement disorder), and extrapyramidal side effects (tremor, dystonia). Quetiapine also has a black box warning regarding the risk of stroke in elderly patients with dementia-related psychosis.

See Fig. 3 for pharmacological approaches to the treatment of anxiety in individuals with ASD.

Depressive disorders

Background

Depression is characterized by a clear-cut change in affect and functioning accompanied by depressed mood or anhedonia, the reduced ability to experience pleasure. Major depressive disorder (MDD), the primary depressive disorder, includes discrete episodes of at least two weeks' duration of depressed mood and/or loss of interest or pleasure along with four or more of the following neurovegetative symptoms: changes in appetite/weight, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or guilt, decreased concentration, and recurrent thoughts of death or suicidality [68]. Compared to their typically developing peers, individuals with ASD are four times more likely to experience depression in their lifetime [109]. The prevalence of depression in adults with ASD is higher in populations without co-occurring ID [110], and depression rates among youth with ASD increase with age and intelligence quotient (IQ) [111]. Due to overlapping symptomology and difficulties of diagnosis in this population, depression may be underdiagnosed in ASD [20]. Without accurate intervention, depression symptoms often worsen over time [17].

Failure to treat co-occurring depression in ASD can be life-threatening, with a 2014 systematic review finding suicidality present in 10.9–50% of samples with ASD [21]. A recent meta-analysis of data from over 48,000 autistic and possibly autistic individuals without co-occurring ID reported pooled prevalence rates of suicidal ideation to be 34% and suicidal attempts and behaviors to be 24% [112]. Gender was an important moderating factor; suicidal ideation was higher in samples from individuals who are transgender or gender non-conforming, and meta-regression results showed that as the proportion of male participants decreased, suicide plan prevalence increased [112], partially supporting previous research that suicidality is more prevalent in ASD females [113].

Table 7 Signs and Symptoms of Depression in ASD

Behavioral	Medical
Loss of interest in preferred activities[a]	Increased or decreased sleep[a]
Guilty thoughts	Changes in appetite[a]
Low self-esteem	Psychomotor retardation[a]
Decreased energy[a]	
Decreased concentration	
Suicidal thoughts	
Crying episodes[a]	
Sustained sad mood[a]	
Increased irritability or aggression[a]	
Regression in activities of daily living[a]	
Anhedonia[a]	

[a] Items with an asterisk are especially crucial for recognizing depression in minimally verbal patients

Diagnosis

Identifying symptoms of depression in ASD (Table 7) (i.e., distinguishing symptoms of depression from the functional and adaptive impairments inherent in ASD) can be challenging. First, traditional measures of depression are not well-validated in the ASD population [114]. Moreover, identifying core symptoms of depression relies at least partially on self-report [114]. Social communication difficulties (including fundamental communication impairments) may prevent even a skilled clinician from gathering the information necessary to make an accurate diagnosis. A co-occurring diagnosis may be further complicated by the ways in which the symptoms and features overlap (e.g., social withdrawal) and by the atypical manifestation of depression symptoms in ASD [115].

Differential diagnoses

Ruling out the effects of substance-induced depression (e.g., intoxication or withdrawal from drugs of abuse), medication side effects (e.g., fatigue from beta-blocker or anti-epileptic medications), or another.

underlying medical condition (e.g., hypothyroidism or conditions that cause pain or delirium) is critical for the accurate diagnosis of depressive disorders. Moreover, clinicians must rule out separate mental health diagnoses that warrant different approaches to treatment. Specifically, clinicians should screen for hallucinations or delusions that may suggest a psychotic disorder or depression with psychotic features. Additionally, clinicians should screen for mania (currently or in the past) and active

Table 8 Medication options and dosing for depression in patients with ASD

Drug	Common US Brand Names	Lurie Center Daily Dose Ranges	Notable Side Effects
Duloxetine	Cymbalta	IR | 20–90 mg (may be divided across two administrations)	Headache, drowsiness, fatigue, nausea, sexual impairments, constipation, reduced appetite, diarrhea, hyponatremia; [a]
Mirtazapine	Remeron	IR | 3.75–45 mg (may be divided across two administrations)	Drowsiness, weight gain, dry mouth, constipation, increased appetite, sedation, thrombocytopenia, urinary hesitancy, irritability; [a]
Bupropion	Wellbutrin SR, Wellbutrin XL, Forfivo XL	ER|150–450 mg	Insomnia, headache, decreased appetite, dizziness, hypertension, constipation, nausea, dry mouth, tinnitus; Can lower the seizure threshold, contraindicated in patients with seizure disorder; [a]
	Wellbutrin, Aplenzin	IR |37.5–450 mg	
Vortioxetine	Trintellix, Brintellix	IR | 5–20 mg	Nausea, constipation, vomiting; [a]
Venlafaxine	Effexor	IR | 25–375 mg	Nausea, diarrhea, reduced appetite, hyperhidrosis, sexual impairments, headache, insomnia, sedation, hyponatremia, hypertension; [a]
Citalopram	Celexa	IR | 5–40 mg	Drowsiness, insomnia, dizziness, headache, nausea, vomiting, constipation, sexual impairments, weight changes, QTc prolongation; [a]
Escitalopram	Lexapro	IR | 5–20 mg	Insomnia, sexual impairments, nausea, sweating, fatigue, sedation; [a]
Fluoxetine	Prozac	IR | 5–80 mg	Anxiety, hyperhidrosis, diarrhea, dry mouth, sexual impairments, nausea, sedation; [a]
Fluvoxamine	Luvox	IR | 12.5–300 mg	Nausea, somnolence, insomnia, sexual impairments, vomiting, dry mouth; [a]
Paroxetine	Paxil, Seroxat	IR | 5–50 mg	Drowsiness, dry mouth, weight gain, insomnia, sexual impairments, tachycardia, constipation, diarrhea, hyperhidrosis; [a]
Sertraline	Zoloft	IR | 12.5–200 mg	Nausea, diarrhea, tremors, dyspepsia, reduced appetite, hyperhidrosis, sexual impairments; [a]

ER Extended-release, *IR* Immediate-release

[a] All medications carry rare risks for induction of hypomania and suicidal ideation

substance abuse. Periods of depressed mood that are milder, self-limited without sustained duration, and without neurovegetative features should prompt the clinician to consider adjustment disorder or normative sad mood and may benefit from more conservative management with therapy, exercise, or other psychosocial supports. The treatment of co-occurring issues such as ADHD, anxiety, or irritability may result in a more stable mood and a reduction in the frequency and intensity of brief periods of sad affect.

Treatment

Therapeutic approaches that have been tailored to meet the unique needs of individuals with ASD, such as modified CBT, are options for depression treatment in ASD [116]. Social skills interventions [117] have shown success, as well as mindfulness-based stress reduction techniques and coaching to address functional challenges [98]. As a guiding principle, if a patient is able to identify mood states and associate those mood states with life events, then one of the above therapies is likely a good first step in treatment.

Pharmacological treatments may also be required (Fig. 4, Table 8). In the psychopharmacological treatment of depression, there have been no RCTs in ASD. Some trials of SSRIs evaluated depression as a secondary outcome measure, but they did not recruit for clinically significant depression in their participant cohort [118]. In the general population, SSRIs are the common first-line pharmacological treatment for depression. However, increased rates of behavioral activation, impulsiveness, and stereotypy have been observed in studies examining the use of SSRIs among patients with ASD for the treatment of restricted and repetitive behaviors [118]. This raises the concern for there being an increased risk for behavioral side effects in patients with ASD using SSRIs. Clinicians may consider non-SSRI medications as first-line options in the treatment of depression in patients with ASD to avoid this risk. Duloxetine, mirtazapine, bupropion, and vortioxetine are suitable first-line medications for depression in ASD, as described below. If patients achieve remission with one of the first-line medications, the drug should be continued for a minimum of one year with monitoring every 3–6 months depending on stability for side effects and effectiveness. If a medication results in a partial response, then augmentation with bupropion or lithium may help achieve remission. If a patient has no response or does not tolerate a medication, then the medication should be tapered off, and the next option should be tried.

Selective serotonin reuptake inhibitors can be considered as second-line treatment options. It is important to note that both SSRIs and SNRIs carry an FDA black box warning to monitor for suicidal ideation when used in patients ages 25 years or younger. This black box warning also exists for proposed first-line treatment options of mirtazapine, bupropion, and vortioxetine. However, recent research has suggested that SSRI treatment may actually reduce the risk of suicidal behavior [119]. Patients should be monitored for suicidality throughout treatment regardless of medication choice. For patients who are at imminent risk for suicidality or self-harm, it may be necessary to consider hospitalization or inpatient management to achieve acute stability.

For severe or treatment-refractory depression, options such as transcranial magnetic stimulation, electroconvulsive therapy (ECT), or ketamine may be considered in concert with psychiatric consultation if available.

In relation to non-autistic SOC Duloxetine, mirtazapine, bupropion, and vortioxetine are recommended first-line medications for depression in individuals with ASD, ahead of non-autistic SOC, SSRIs which can cause behavioral activation in individuals with ASD.

Medication management and dosing for depressive disorders

Duloxetine, which was described above in the anxiety section, is FDA-approved for MDD in non-autistic adults and GAD in non-autistic children, adolescents and adults. Duloxetine can be started at 20 mg/day, and this can be increased by 10 mg every 1–2 weeks until a target dosage between 20–90 mg a day in 1–2 divided dosages is reached.

Mirtazapine, fully described previously in the anxiety section, is FDA-approved for MDD in adults. It has shown good tolerability in an RCT for anxiety in youth with ASD [102]. For use in the treatment of depression in ASD, the recommended starting dose is 3.75 mg, which can be increased by 3.75 mg weekly until depression symptoms are resolved. The maximum recommended dosage of mirtazapine is 45 mg daily in 1–2 divided doses.

Bupropion is an aminoketone antidepressant that is believed to act by inhibiting dopamine and norepinephrine reuptake. Bupropion is FDA-approved for adult MDD, seasonal affective disorder (SAD), and nicotine addiction. Bupropion is available in IR (three times a day), sustained-release (twice a day), and ER (once a day) formulations. Typical starting dosages are 37.5 mg a day for IR and 150 mg a day for ER and may be increased by 37.5 mg a week for IR or 150 mg every 1–2 weeks for ER until a target dose of 150 mg to 450 mg a day is reached. Bupropion can lower the seizure threshold and should not be used for patients with a seizure disorder.

Vortioxetine is a serotonin modulator that has received FDA approval for MDD in individuals 18 years and older. Vortioxetine has not been studied for the treatment of depression in an RCT in the ASD population. Vortioxetine IR tablets are available in 5 mg, 10 mg, 15 mg, and 20 mg doses. The recommended starting dose is 5 mg daily, which can be increased by 5 mg every week to a target dosage between 10 and 20 mg daily in once-daily dosing.

See Fig. 4 for pharmacological approaches to the treatment of depressive disorders in individuals with ASD.

Irritability

Background

Irritability in the DSM-5 is defined as "persistent anger, a tendency to respond to events with angry outbursts or blaming others, an exaggerated sense of frustration over minor matters" [103]. Irritability is often used as an umbrella term for behavioral symptoms associated with various disorders, including ASD, which can consist of one or a combination of the following: extreme tantrums, aggression towards people or property, severe mood lability, and SIB. The DSM-5-TR lists irritability as a symptom of various mood and behavioral disorders such as depression, posttraumatic stress disorder, disruptive mood dysregulation disorder, and oppositional defiant disorder (ODD) [68]. Within the context of ASD, irritability may be a manifestation of an additional psychiatric condition such as ADHD or a mood disorder for example. Irritability may also be a symptom of underlying medical issues such as GI discomfort or related to difficulty communicating. Irritability is common in ASD. Parent reports of physical aggression in a cohort of 1,380 children and adolescents with ASD showed that 35% were currently exhibiting significant aggression towards a caregiver or another person and that 49% had demonstrated some form of aggression towards others in the past [120]. A recent meta-study reported that prevalence rates of SIB in the ASD population may be as high as 42% [121]. Severe irritability can impact relationships, access to educational programming and therapeutic/behavioral services, and work opportunities and can lead to stress and reduced quality of life for individuals, family members, and caregivers [18, 19, 122–124].

Irritability is a complex symptom domain, and it can be difficult to determine the underlying cause among the wide array of potential sources. Additional challenges are posed by balancing safety concerns related to irritability behaviors themselves and those related to pharmacological treatment options for irritability. Ideally, specialized medical experts, such as a psychiatrist,

will be involved in the assessment and treatment of individuals with severe irritability, as irritability can be a symptom of multiple psychiatric conditions, including ADHD, depression, mania, psychosis, or a potential medication side effect. However, we recognize that access to specialized care is not always attainable, and there may be cases where the treatment of irritability through general practice providers is necessary and warranted. With this in mind, we include a brief section that offers insight into the ways that Lurie Center for Autism providers approach the treatment of irritability in ASD.

Defining and recognizing irritability

Unlike the first four co-occurring conditions discussed in these guidelines, irritability is an umbrella term rather than a diagnosis. There are many terms and concepts related to irritability that have been used in clinical and research applications through the years, such as aggression, problem behaviors, maladaptive behaviors, and mood/emotional dysregulation [124–127]. However, as the two drugs that have received FDA approval for use in ASD, risperidone, and aripiprazole, are both for the indication of "irritability" [23, 24], we chose this language for the purposes of our prescribing practices guidelines.

While irritability may be hard to define and interpret, the signs of irritability are more overt than many other interfering behaviors. The Aberrant Behavior Checklist (ABC)-Irritability subscale can be helpful in identifying these signs including inappropriate yelling or crying, banging objects, deliberate self-injury, showing aggression towards others (either physical or verbal aggression), and tantrums/meltdowns [128]. Self-injurious behavior may involve head banging, hair pulling, eye pressing, self-biting/scratching, and other behaviors individuals do to themselves that can result in physical injury [122]. Patient, caregiver, and teacher reports, with subsequent clinician interviews/impressions, typically comprise the process of assessing if a patient has irritability.

Differential diagnoses

In individuals with ASD, it can be challenging to determine the underlying cause of irritability, which is a crucial first step for determining the appropriate treatment. Unrecognized or untreated medical/physical issues may be at the root of irritability in some cases. Possible medical issues include but are not limited to headaches, oral abscesses, ear infections, constipation, GERD, etc. In such cases, proper medical attention can alleviate irritability. Similarly, irritability may be a manifestation of an additional psychiatric condition, in which case treatment should target that condition. In these cases, there are typically more symptoms than just irritability, such as sleep, appetite, and/or concentration changes. For example, mood disorders such as depression, bipolar disorder, or anxiety disorders may present as irritability in ASD, and ADHD-related impulsivity may be driving emotional dysregulation that manifests as irritability. A clinical data review of 123 psychiatrically referred youth with ASD suggested that complaints of irritability may be a primary presentation of depression in this population [20]. It is important to assess early on whether one or more of these physical or psychiatric factors or behavioral or communicative needs are underlying or exacerbating irritability to treat the root cause. Considering the number and complexity of potential underlying causes of irritability, an ideal assessment pathway involves multidisciplinary, expert input. An extensive practice pathway for irritability was described by McGuire et al. 2016, which includes comments on potential contributors such as medical problems, functional communication challenges, psychosocial stressors, maladaptive reinforcement patterns, and co-occurring psychiatric disorders [125]. Potential medical or physical causes should be evaluated by the appropriate medical professional, whether that be in general practice, gastroenterology, dental care, etc. When the general practitioner is unclear about the diagnosis or is concerned that there may be additional psychiatric conditions, referral to a psychiatrist is advised.

Treatment

Behavioral and educational strategies can be implemented to assist in the management of irritability. A functional behavioral assessment from a school behavioralist can offer helpful insight into the function of disruptive behaviors, such as escaping aversive stimuli like a loud room or accessing rewarding or soothing stimuli like getting caregiver attention. When the function of a behavior can be determined, a behavioral team can develop a plan to reduce the frequency of maladaptive behaviors through adjustments to the environment and caregiver response patterns that aim to decrease the persistence of the behavior. Parent training, namely targeted skill development for caregivers in addressing maladaptive behavior, has shown potential to reduce irritability [129–131]. The RUBI Parent Training for Disruptive Behavior was specifically endorsed by Lurie Center providers and preliminary efficacy findings in recent feasibility studies are promising [132].

When behavioral options are ineffective, or irritability is in the moderate to severe range [133], providers may turn to pharmacological treatments for non-specific irritability (Fig. 5, Table 9). The ABC-Irritability subscale is important to obtain at baseline and throughout the course of treatment of irritability in ASD [133].

Table 9 Medication options and dosing for irritability in patients with ASD

Drug	Common US Brand Names	Lurie Center Daily Dose Ranges	Notable Side Effects
Guanfacine	Intuniv	ER| 1–4 mg	Somnolence, fatigue, nausea, constipation, lethargy, insomnia, dizziness, bradycardia, hypotension
	Tenex	IR | 1–4 mg (may be divided across two or more administrations)	
Risperidone	Risperdal	IR | 0.25–4 mg	Somnolence, increased appetite, weight gain, fatigue, urinary incontinence, constipation, anxiety, nausea, dizziness, akathisia, tardive dyskinesia, priapism, hyperprolactinemia
Aripiprazole	Abilify	IR | 1–15 mg	Somnolence, increased appetite, weight gain, nausea, akathisia, tardive dyskinesia, metabolic changes

ER Extended-release, *IR* Immediate-release

Medication management and dosing for irritability

When pharmacological treatments are appropriate, α_2-adrenergic agonists such as guanfacine are a good option to begin with based on their safety and side effect profiles. For irritability, guanfacine IR tablets can be started at a daily dose of 1 mg, given as 0.5 mg (half of a 1 mg tablet) twice daily, and increased up to a maximum daily dose of 4 mg across two or more administrations. Guanfacine ER can be started at 1 mg daily and increased up to a maximum daily dose of 4 mg for irritability.

In extreme cases of irritability where behaviors pose a significant threat to the safety of an individual or others, one may consider beginning with the atypical antipsychotics, risperidone and aripiprazole, which are both FDA-approved for irritability in children and adolescents with ASD [23, 24]. While antipsychotic medications show efficacy and general tolerability [134], they can lead to serious physiological effects such as changes in bodyweight, body mass index, triglycerides, cholesterol, prolactin and heart rate [135], and thus require careful, frequent monitoring.

Risperidone and aripiprazole have shown similar efficacy and safety profiles in comparison clinical trials [136, 137], though one meta-analysis on pharmacological treatment of irritability and problem behaviors in ASD did report that the number of subjects needed to treat was lower for risperidone [138]. However, these drugs differ in a few key areas worth considering when choosing the best first-line option for a particular patient. Risperidone can increase prolactin levels (hyperprolactinemia), which can lead to breast tissue development (gynecomastia) and milk production (galactorrhea), which may be distressing to patients. Aripiprazole can lower prolactin levels, which will help avoid the risks of gynecomastia and galactorrhea. Hypogonadism, which is another potential side effect that is more common with risperidone than aripiprazole, can lead to decreased libido, erectile dysfunction, menstrual irregularities, decreased muscle mass, and low bone density.

Risperidone can be slightly more sedating than aripiprazole. Both antipsychotics come with the risk of serious side effects such as neuroleptic malignant syndrome and tardive dyskinesia, a slow onset, sometimes irreversible movement disorder. Profound metabolic side effects, including weight gain, increased chance of diabetes, hyperlipidemia, and high blood pressure, are also common with risperidone and aripiprazole [139–141]. Data from drug naïve patients with psychosis showed significant weight and metabolic changes after one year of treatment with either risperidone or aripiprazole [142]. Risperidone can be started at a dose of 0.25 mg per day and increased as needed up to 4 mg per day. Aripiprazole can be started at a dose of 1 mg per day and increased as needed up to 10–15 mg per day.

See Fig. 5 for pharmacological approaches to the treatment of irritability in individuals with ASD.

Conclusion

Current ASD prevalence estimates are now 1 in 36 for children in the U.S. [1] and in the last decade the global median prevalence of ASD children and adults is 10 per 1000 [3]. This jump in ASD rates is partly attributable to increased reporting and diagnosis [143], especially with the expanded Autism Spectrum Disorder diagnosis of the DSM-5 [103, 144]. There is also evidence to suggest a true increase in global ASD occurrence, potentially relating to environmental exposures [145, 146] or reproductive health factors [147]. A compelling recent BMC Medicine review outlines evidence for an array of prenatal environmental risk factors that are contributing to ASD prevalence [148]. As we experience a rising number of new ASD patients entering the healthcare system and a growing cohort of young adults and aging adults, the limited availability of ASD specialists in the U.S. and significant disparities in access to care [149] are

raising systemic alarms. The current climate of ASD care absolutely requires that general practitioners receive the knowledge and training necessary to increase familiarity and comfort with ASD-specific prescribing practices, as referring to specialists for every case is no longer a sustainable model.

In the guidelines presented herein, experts in the field were asked to combine their years of highly specialized ASD medication management experience with findings from updated scientific literature reviews to educate all providers on specialty prescribing guidelines. Common co-occurring symptom domains were discussed, with ASD-specific prescribing recommendations and clinical considerations for each problem. The ambiguity of which patients to treat "in-house" was addressed by discussing specific thresholds of when to refer out to specialists.

It is important to recognize the limitations of these clinical guidelines. Our findings are based on the consensus among prescribers from a single site, many of whom have received similar clinical training or have mentored one another, thereby limiting the breadth of perspectives included in this study. Additionally, because we are a highly specialized ASD clinic, there may be a bias in the patient population that our providers have experience working with. Furthermore, due to the necessity of maintaining a manageable scope, this manuscript primarily focuses on psychopharmacology and does not encompass the extensive realm of behavioral and therapeutic treatment approaches which are a critical aspect of the treatment landscape. Our recommendations also do not encompass considerations of the additionally complex and unique needs of individuals with ASD and a co-occurring genetic disorder such as Rett Syndrome or Fragile X syndrome. In the future, we hope to adapt the content of this paper into educational materials and in doing so, would love to connect with outside experts in the field, to add to the diversity of perspectives and potentially incorporate a wider variety of treatment approaches.

Our work is also limited by the dearth of FDA-approved medications, conclusive, replicated clinical trials and validated diagnostic and outcome measures for co-occuring conditions in individuals with ASD. The limited experimental evidence for medication treatment options results in lingering ambiguity in our pharmacological treatment pathways. Outside of specific use cases that account for a patient's unique clinical profile and a prescriber's experience, there is not sufficient information to inform whether to choose one medication or another within groupings of medication options in our treatment pathways. The paucity of approved medications for ASD underscores the pressing need for further research into the pharmacotherapy of common co-occurring conditions linked to ASD. Additional RCTs are greatly needed, as are clinical outcome measures validated in ASD to assist with co-occuring diagnoses and assess treatment efficacy. Additional research across the ASD lifespan is especially needed as the vast majority of research to date has focused on ASD youth which limits the relevance of guidance to younger and aging adults with ASD. This future research is essential, but will take time, and meanwhile there is an ever-pressing need for access to ASD-competent care.

In summary, the number of ASD patients in the U.S. far exceeds the capacity of the current subspecialty care model. General practitioners are both highly capable and willing to fill in this gap in ASD care if given sufficient education and resources to do so. This manuscript presents relevant, easy-to-reference prescribing guidelines on the treatment of sleep disturbances, ADHD, anxiety, depression, and irritability in ASD, based on expert opinion combined with current research. Our hope is that empowering general providers to manage first-line care for patients with ASD and interfering neuropsychiatric symptoms and disorders, will give these patients faster access to competent care and will increase specialist time to provide care to patients with more complex conditions. The goal is to improve access to timely, safe and informed care, ultimately improving treatment outcomes for all individuals with ASD seeking medical care.

Abbreviations

ABC	Aberrant Behavior Checklist
AAP	American Academy of Pediatrics
AMP	Amphetamine
ADHD	Attention-deficit/hyperactivity disorder
ASD	Autism spectrum disorder
CGI-I	Clinical Global Impressions-Improvement
CBT	Cognitive behavioral therapy
DSM-5-TR	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision
DSM-IV	DSM, Fourth Edition
DSM-IV-TR	DSM, Fourth Edition, Text Revision
ECG	Electrocardiogram
ER	Extended-release
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
GAD	Generalized anxiety disorder
IR	Immediate-release
ID	Intellectual disability
IQ	Intelligence quotient
KUB	Kidney, ureter, and bladder X-RAY
MDD	Major Depressive Disorder
MPH	Methylphenidate
NICHQ	National Institute for Children's Health Quality
OCD	Obsessive-compulsive disorder
ODD	Oppositional defiant disorder
PTBM	Parent-training behavior management
PARS	Pediatric Anxiety Rating Scale
PedPRM	Pediatric-appropriate prolonged-release melatonin
PDD-NOS	Pervasive developmental disorder-not otherwise
PCP	Primary care provider
RCT	Randomized controlled trial

RUPP	Research Units on Pediatric Psychopharmacology
SAD	Seasonal affective disorder
SSRI	Selective serotonin reuptake inhibitor
SIB	Self-injurious behavior
SNRI	Serotonin-norepinephrine reuptake inhibitor
CSHQ-Autism	Sleep Habits Questionnaire for Children with ASD
SOC	Standard of care
SDQ	Strengths and Difficulties Questionnaire
SOFIA	Study of Fluoxetine in Autism
TFTs	Thyroid function tests
TSH	Thyroid-Stimulating Hormone
U.S.	United States

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Authors' contributions
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Declarations

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Author details
[1]Lurie Center for Autism, Massachusetts General Hospital, Lexington, MA 02421, USA. [2]Athinoula A. Martinos Center for Biomedical Imaging, Mass General Research Institute, Charlestown, MA 02129, USA. [3]Department of Psychiatry, Harvard Medical School, Boston, MA 02215, USA. [4]Department of Neurology, Harvard Medical School, Boston, MA 02215, USA. [5]Department of Pediatrics, Harvard Medical School, Boston, MA 02215, USA. [6]Beth Israel Deaconess Medical Center, Boston, MA 02215, USA. [7]Department of Radiology, Harvard Medical School, Boston, MA 02215, USA.

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References

1. Maenner MJ, Warren Z, Williams AR, Amoakohene E, Bakian AV, Bilder DA, et al. Prevalence and characteristics of Autism spectrum disorder among children aged 8 years - Autism and Developmental Disabilities Monitoring network, 11 sites, United States, 2020. MMWR Surveill Summ. 2023;72(2):1–14.
2. Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marcín C, et al. Global prevalence of autism and other pervasive developmental disorders. Autism Res. 2012;5(3):160–79.
3. Zeidan J, Fombonne E, Scorah J, Ibrahim A, Durkin MS, Saxena S, et al. Global prevalence of autism: A systematic review update. Autism Res. 2022;15(5):778–90.
4. Salari N, Rasoulpoor S, Rasoulpoor S, Shohaimi S, Jafarpour S, Abdoli N, et al. The global prevalence of autism spectrum disorder: a comprehensive systematic review and meta-analysis. Ital J Pediatr. 2022;48(1):112.
5. Malik-Soni N, Shaker A, Luck H, Mullin AE, Wiley RE, Lewis MES, et al. Tackling healthcare access barriers for individuals with autism from diagnosis to adulthood. Pediatr Res. 2022;91(5):1028–35.
6. Gilmore D, Longo A, Krantz M, Radford D, Hand BN. Five ways providers can improve mental healthcare for autistic adults: A review of mental healthcare use, barriers to care, and evidence-based recommendations. Curr Psychiatry Rep. 2022;24(10):565–71.
7. Finding Autism-Competent Health Care. Available from: https://www.adult-autism.health.harvard.edu/resources/finding-autism-competent-health-care/.
8. Bishop TF, Seirup JK, Pincus HA, Ross JS. Population of US practicing psychiatrists declined, 2003–13, which may help explain poor access to mental health care. Health Aff Millwood. 2016;35(7):1271–7.
9. Satiani A, Niedermier J, Satiani B, Svendsen DP. Projected workforce of psychiatrists in the United States: A population analysis. Psychiatr Serv. 2018;69(6):710–3.
10. Cai A, Mehrotra A, Germack HD, Busch AB, Huskamp HA, Barnett ML. Trends in mental health care delivery by psychiatrists and nurse practitioners in Medicare, 2011–19. Health Aff Millwood. 2022;41(9):1222–30.
11. Lugo-Marín J, Magán-Maganto M, Rivero-Santana A, Cuellar-Pompa L, Alviani M, Jenaro-Rio C, et al. Prevalence of psychiatric disorders in adults with autism spectrum disorder: A systematic review and meta-analysis. Res Autism Spectr Disord. 2018;2019(59):22–33.
12. Limoges É, Bolduc C, Berthiaume C, Mottron L, Godbout R. Relationship between poor sleep and daytime cognitive performance in young adults with autism. Res Dev Disabil. 2013;34(4):1322–35.
13. Sadikova E, Dovgan K, Mazurek MO. Longitudinal examination of sleep problems and symptom severity in children with autism spectrum disorder. J Autism Dev Disord. 2023;53(4):1673–81.
14. Leader G, Glynn C, Kirkpatrick B, Chen JL, O'Súilleabháin PS, Mannion A. Familial sleep and autism spectrum disorder: a pilot actigraphy study of sleep quality, quality of life and psychological distress. Ir J Psychol Med. 2022;39(3):261–71.
15. Hoffman CD, Sweeney DP, Lopez-Wagner MC, Hodge D, Nam CY, Botts BH. Children with autism: Sleep problems and mothers' stress. Focus Autism Dev Disabl. 2008;23(3):155–65.
16. van Steensel FJA, Bögels SM, Dirksen CD. Anxiety and quality of life: clinically anxious children with and without autism spectrum disorders compared. J Clin Child Adolesc Psychol. 2012;41(6):731–8.

17. Gadke DL, McKinney C, Oliveros A. Autism spectrum disorder symptoms and comorbidity in emerging adults. Child Psychiatry Hum Dev. 2016;47(2):194–201.
18. Carr EG, Taylor JC, Robinson S. The effects of severe behavior problems in children on the teaching behavior of adults. J Appl Behav Anal. 1991;24(3):523–35.
19. McIntyre LL, Blacher J, Baker BL. Behaviour/mental health problems in young adults with intellectual disability: the impact on families. J Intellect Disabil Res. 2002;46(Pt 3):239–49.
20. Henry CA, Nowinski L, Koesterer K, Ferrone C, Spybrook J, Bauman M. Low rates of depressed mood and depression diagnoses in a clinic review of children and adolescents with autistic disorder. J Child Adolesc Psychopharmacol. 2014;24(7):403–6.
21. Segers M, Rawana J. What do we know about suicidality in autism spectrum disorders? A systematic review: Systematic review of suicidality in ASD. Autism Res. 2014;7(4):507–21.
22. Bowers K, Lin PI, Erickson C. Pharmacogenomic medicine in autism: challenges and opportunities. Paediatr Drugs. 2015;17(2):115–24.
23. McCracken JT, McGough J, Shah B, Cronin P, Hong D, Aman MG, et al. Risperidone in children with autism and serious behavioral problems. N Engl J Med. 2002;347(5):314–21.
24. Blankenship K, Erickson CA, Stigler KA, Posey DJ, McDougle CJ. Aripiprazole for irritability associated with autistic disorder in children and adolescents aged 6–17 years. Ped Health. 2010;4(4):375–81.
25. Hamp N, DeHaan SL, Cerf CM, Radesky JS. Primary care pediatricians' perspectives on autism care. Pediatrics. 2023;151(1). Available from: https://doi.org/10.1542/peds.2022-057712.
26. Levy SE, Frasso R, Colantonio S, Reed H, Stein G, Barg FK, et al. Shared decision making and treatment decisions for young children with autism spectrum disorder. Acad Pediatr. 2016;16(6):571–8.
27. Austriaco K, Aban I, Willig J, Kong M. Contemporary trainee knowledge of autism: How prepared are our future providers? Front Pediatr. 2019;7:165.
28. Unigwe S, Buckley C, Crane L, Kenny L, Remington A, Pellicano E. GPs' confidence in caring for their patients on the autism spectrum: an online self-report study. Br J Gen Pr. 2017;67(659):e445–52.
29. Carbone PS, Murphy NA, Norlin C, Azor V, Sheng X, Young PC. Parent and pediatrician perspectives regarding the primary care of children with autism spectrum disorders. J Autism Dev Disord. 2013;43(4):964–72.
30. Russell S, McCloskey CR. Parent perceptions of care received by children with an autism spectrum disorder. J Pediatr Nurs. 2016;31(1):21–31.
31. Young S, Hollingdale J, Absoud M, Bolton P, Branney P, Colley W, et al. Guidance for identification and treatment of individuals with attention deficit/hyperactivity disorder and autism spectrum disorder based upon expert consensus. BMC Med. 2020;18(1):146.
32. Juneja M, Sairam S, Jain R, Gupta A. Practical aspects of ASD management-what pediatricians should know. Indian J Pediatr. 2023;90(4):369–76.
33. Howes OD, Rogdaki M, Findon JL, Wichers RH, Charman T, King BH, et al. Autism spectrum disorder: Consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology. J Psychopharmacol. 2018;32(1):3–29.
34. Subramanyam AA, Mukherjee A, Dave M, Chavda K. Clinical practice guidelines for autism spectrum disorders. Indian J Psychiatry. 2019;61(Suppl 2):254–69.
35 Schirm E, Tobi H, de Vries TW, Choonara I, De Jong-van Berg LTW, den. Lack of appropriate formulations of medicines for children in the community. Acta Paediatr. 2003;92(12):1486–9.
36. Richdale AL, Schreck KA. Sleep problems in autism spectrum disorders: prevalence, nature, & possible biopsychosocial aetiologies. Sleep Med Rev. 2009;13(6):403–11.
37 Malow BA, Katz T, Reynolds AM, Shui A, Carno M, Connolly HV, et al. Sleep difficulties and medications in children with autism spectrum disorders: A registry study. Pediatrics. 2016;137 Suppl 2(Supplement_2):S98–104.
38. Galion AW, Farmer JG, Connolly HV, Allhusen VD, Bennett A, Coury DL, et al. A practice pathway for the treatment of night wakings in children with autism spectrum disorder. J Autism Dev Disord. 2024;54(8):2926–45.
39. Mazurek MO, Dovgan K, Neumeyer AM, Malow BA. Course and predictors of sleep and co-occurring problems in children with autism spectrum disorder. J Autism Dev Disord. 2019;49(5):2101–15.
40. Morgan B, Nageye F, Masi G, Cortese S. Sleep in adults with Autism Spectrum Disorder: a systematic review and meta-analysis of subjective and objective studies. Sleep Med. 2020;65:113–20.
41. Charlton RA, McQuaid GA, Bishop L, Lee NR, Wallace GL. Predictors of sleep quality for autistic people across adulthood. Autism Res. 2023;16(4):757–71.
42. Matson JL, Ancona MN, Wilkins J. Sleep disturbances in adults with autism spectrum disorders and severe intellectual impairments. J Ment Health Res Intellect Disabil. 2008;1(3):129–39.
43. Oyane NMF, Bjorvatn B. Sleep disturbances in adolescents and young adults with autism and Asperger syndrome. Autism. 2005;9(1):83–94.
44. Maxwell-Horn A, Malow BA. Sleep in autism. Semin Neurol. 2017;37(4):413–8.
45. Reynolds A, Katz T, Richdale A. CHAPTER 3: Medical Issues Affecting Sleep in Children With Autism Spectrum Disorder. In: Sleep Difficulties and Disorders in Autism Spectrum Disorder. Charlotte: Information Age Publishing; 2020. p. 51–9.
46. Fadini CC, Lamônica DA, Fett-Conte AC, Osório E, Zuculo GM, Giacheti CM, et al. Influence of sleep disorders on the behavior of individuals with autism spectrum disorder. Front Hum Neurosci. 2015;9(JUNE):347.
47. Baker EK, Richdale AL, Hazi A. Employment status is related to sleep problems in adults with autism spectrum disorder and no comorbid intellectual impairment. Autism. 2019;23(2):531–6.
48. Shui AM, Richdale AL, Katz T. Evaluating sleep quality using the CSHQ-Autism. Sleep Med. 2021;87:69–76.
49. Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. Sleep. 2000;23(8):1043–51.
50. The Sleep Study Story. Available from: https://www.kennedykrieger.org/sites/default/files/library/documents/patient-care/centers-and-programs/sleep-disorders-clinic-and-lab/sleep-story.pdf.
51. G. Weintraub A. Lombardo E.J. Davidson. My Sleep Study. 2011. Available from: https://www.childrenshospital.org/sites/default/files/media_migration/0a332357-f97c-4448-9f6c-297676b4ed8f.pdf.
52. Benson S, Bender AM, Wickenheiser H, Naylor A, Clarke M, Samuels CH, et al. Differences in sleep patterns, sleepiness, and physical activity levels between young adults with autism spectrum disorder and typically developing controls. Dev Neurorehabil. 2019;22(3):164–73.
53. Weiss SK, Malow BA. Sleep Strategies for Children with Autism. 2018. Available from: https://www.autismspeaks.org/sites/default/files/2018-08/Sleep%20Tool%20Kit.pdf.
54. Autism Speaks Autism Treatment Network. ATN/AIR-P Sleep Strategies for Teens with Autism. Available from: https://www.autismspeaks.org/tool-kit/atnair-p-sleep-strategies-teens-autism.
55. Interventions. Available from: https://med.stanford.edu/csasd/education/adolescent-adult-toolkit/parent-interventions.html.
56. ATN/AIR-P Strategies to Improve Sleep in Children with Autism. Available from: https://www.autismspeaks.org/tool-kit/strategies-improve-sleep-children-autism.
57. Goldman SE, Adkins KW, Calcutt MW, Carter MD, Goodpaster RL, Wang L, et al. Melatonin in children with autism spectrum disorders: endogenous and pharmacokinetic profiles in relation to sleep. J Autism Dev Disord. 2014;44(10):2525–35.
58. Rossignol DA, Frye RE. Melatonin in autism spectrum disorders: a systematic review and meta-analysis. Dev Med Child Neurol. 2011;53(9):783–92.
59 Hanish A, Jo Klein A, Mathews T, Berger A, Kupzyk K, Ellis C, et al. 631 sleep SMART in adolescents with neurodevelopmental disorders. Sleep. 2021;44(Supplement_2):A247–8.
60. Yuge K, Nagamitsu S, Ishikawa Y, Hamada I, Takahashi H, Sugioka H, et al. Long-term melatonin treatment for the sleep problems and aberrant behaviors of children with neurodevelopmental disorders. BMC Psychiatry. 2020;20(1):445.
61 Malow B, Adkins KW, McGrew SG, Wang L, Goldman SE, Fawkes D, et al. Melatonin for sleep in children with autism: a controlled trial examining dose, tolerability, and outcomes. J Autism Dev Disord. 2012;42(8):1729–37 (**author reply 1738**).

62. Lalanne S, Fougerou-Leurent C, Anderson GM, Schroder CM, Nir T, Chokron S, et al. Melatonin: From pharmacokinetics to clinical use in autism spectrum disorder. Int J Mol Sci. 2021;22(3):1490.
63. Maras A, Schroder CM, Malow BA, Findling RL, Breddy J, Nir T, et al. Long-term efficacy and safety of pediatric prolonged-release melatonin for insomnia in children with autism spectrum disorder. J Child Adolesc Psychopharmacol. 2018;28(10):699–710.
64. Doyen C, Mighiu D, Kaye K, Colineaux C, Beaumanoir C, Mouraeff Y, et al. Melatonin in children with autistic spectrum disorders: recent and practical data. Eur Child Adolesc Psychiatry. 2011;20(5):231–9.
65. Cohen PA, Avula B, Wang YH, Katragunta K, Khan I. Quantity of melatonin and CBD in melatonin gummies sold in the US. JAMA. 2023;329(16):1401–2.
66. Ming X, Gordon E, Kang N, Wagner GC. Use of clonidine in children with autism spectrum disorders. Brain Dev. 2008;30(7):454–60.
67. Gober HJ, Li KH, Yan K, Bailey AJ, Carleton BC. Hydroxyzine use in preschool children and its effect on neurodevelopment: A population-based longitudinal study. Front Psychiatry. 2021;12:721875.
68. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fifth edition, text revision (DSM-5-TR®): Test questions for the diagnostic criteria. Muskin PR, Dickerman AL, Drysdale A, Holderness CC, editors. Arlington, TX: American Psychiatric Association Publishing; 2023. 1120 p.
69. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, 4th Ed. Washington, DC; 1994.
70 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. DC: Text Revision. Washington; 2001.
71. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, 5th ed. Washington, DC; 2013.
72. Salazar F, Baird G, Chandler S, Tseng E, O'sullivan T, Howlin P, et al. Co-occurring psychiatric disorders in preschool and elementary school-aged children with autism spectrum disorder. J Autism Dev Disord. 2015;45(8):2283–94.
73. Joshi G, Faraone SV, Wozniak J, Tarko L, Fried R, Galdo M, et al. Symptom profile of ADHD in youth with high-functioning autism spectrum disorder: A comparative study in psychiatrically referred populations. J Atten Disord. 2017;21(10):846–55.
74. Rong Y, Yang CJ, Jin Y, Wang Y. Prevalence of attention-deficit/hyperactivity disorder in individuals with autism spectrum disorder: A meta-analysis. Res Autism Spectr Disord. 2021;83(101759):101759.
75. Antshel KM, Russo N. Autism spectrum disorders and ADHD: Overlapping phenomenology, diagnostic issues, and treatment considerations. Curr Psychiatry Rep. 2019;21(5):34.
76. Shrestha M, Lautenschleger J, Soares N. Non-pharmacologic management of attention-deficit/hyperactivity disorder in children and adolescents: a review. Transl Pediatr. 2020;9(Suppl 1):S114–24.
77. Wolraich ML, Chan E, Froehlich T, Lynch RL, Bax A, Redwine ST, et al. ADHD diagnosis and treatment guidelines: A historical perspective. Pediatrics. 2019;144(4):e20191682.
78. Cohen SC, Mulqueen JM, Ferracioli-Oda E, Stuckelman ZD, Coughlin CG, Leckman JF, et al. Meta-analysis: Risk of tics associated with psychostimulant use in randomized, placebo-controlled trials. J Am Acad Child Adolesc Psychiatry. 2015;54(9):728–36.
79. Research Units on Pediatric Psychopharmacology Autism Network. Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. Arch Gen Psychiatry. 2005;62(11):1266–74.
80 The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD. Arch Gen Psychiatry. 1999;56(12):1073–86.
81. Reichow B, Volkmar FR, Bloch MH. Systematic review and meta-analysis of pharmacological treatment of the symptoms of attention-deficit/hyperactivity disorder in children with pervasive developmental disorders. J Autism Dev Disord. 2013;43(10):2435–41.
82. Lilja MM, Sandblom E, Lichtenstein P, Serlachius E, Hellner C, Bhagia J, et al. The effect of autistic traits on response to and side-effects of pharmacological ADHD treatment in children with ADHD: results from a prospective clinical cohort. J Neurodev Disord. 2022;14(1):17.
83. Scahill L, McCracken JT, King BH, Rockhill C, Shah B, Politte L, et al. Extended-release guanfacine for hyperactivity in children with autism spectrum disorder. Am J Psychiatry. 2015;172(12):1197–206.
84. Mechler K, Banaschewski T, Hohmann S, Häge A. Evidence-based pharmacological treatment options for ADHD in children and adolescents. Pharmacol Ther. 2022;230(107940):107940.
85. Fankhauser MP, Karumanchi VC, German ML, Yates A, Karumanchi SD. A double-blind, placebo-controlled study of the efficacy of transdermal clonidine in autism. J Clin Psychiatry. 1992;53(3):77–82.
86. Jaselskis CA, Cook EH Jr, Fletcher KE, Leventhal BL. Clonidine treatment of hyperactive and impulsive children with autistic disorder. J Clin Psychopharmacol. 1992;12(5):322–7.
87. Fu D, Wu DD, Guo HL, Hu YH, Xia Y, Ji X, et al. The mechanism, clinical efficacy, safety, and dosage regimen of atomoxetine for ADHD therapy in children: A narrative review. Front Psychiatry. 2021;12:780921.
88. Yu C, Garcia-Olivares J, Candler S, Schwabe S, Maletic V. New insights into the mechanism of action of viloxazine: Serotonin and norepinephrine modulating properties. J Exp Pharmacol. 2020;12:285–300.
89. Harfterkamp M, van de Loo-Neus G, Minderaa RB, van der Gaag RJ, Escobar R, Schacht A, et al. A randomized double-blind study of atomoxetine versus placebo for attention-deficit/hyperactivity disorder symptoms in children with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. 2012;51(7):733–41.
90. Khoodoruth MAS, Ouanes S, Khan YS. A systematic review of the use of atomoxetine for management of comorbid anxiety disorders in children and adolescents with attention-deficit hyperactivity disorder. Res Dev Disabil. 2022;128(104275):104275.
91. Lamb YN. Viloxazine: Pediatric first approval. Paediatr Drugs. 2021;23(4):403–9.
92. Kerns CM, Winder-Patel B, Iosif AM, Nordahl CW, Heath B, Solomon M, et al. Clinically significant anxiety in children with autism spectrum disorder and varied intellectual functioning. J Clin Child Adolesc Psychol. 2021;50(6):780–95.
93. Kirsch AC, Huebner ARS, Mehta SQ, Howie FR, Weaver AL, Myers SM, et al. Association of comorbid mood and anxiety disorders with autism spectrum disorder. JAMA Pediatr. 2020;174(1):63–70.
94. van Steensel FJA, Bögels SM, Perrin S. Anxiety disorders in children and adolescents with autistic spectrum disorders: a meta-analysis. Clin Child Fam Psychol Rev. 2011;14(3):302–17.
95. Delli CKS, Polychronopoulou SA, Kolaitis GA, Antoniou ASG. Review of interventions for the management of anxiety symptoms in children with ASD. Neurosci Biobehav Rev. 2018;95:449–63.
96. Wu MS, Rudy BM, Storch EA. Obsessions, compulsions, and repetitive behavior: Autism and/or OCD. In: Davis TE, White SW, Ollendick TH, editors. Handbook of Autism and Anxiety. Cham: Springer International Publishing; 2014. p. 107–20. Available from: https://doi.org/10.1007/978-3-319-06796-4_8.
97. Turner-Brown L, Frisch M. Understanding and addressing restricted and repetitive behaviors in children with autism. In: Vivanti G, Bottema-Beutel K, Turner-Brown L, editors. Best Practices in Child and Adolescent Behavioral Health Care. Cham: Springer International Publishing; 2020. p. 61–77. Available from: https://doi.org/10.1007/978-3-030-41160-2_4.
98. Linden A, Best L, Elise F, Roberts D, Branagan A, Tay YBE, et al. Benefits and harms of interventions to improve anxiety, depression, and other mental health outcomes for autistic people: A systematic review and network meta-analysis of randomised controlled trials. Autism. 2023;27(1):7–30.
99. Parr JR, Brice S, Welsh P, Ingham B, Le Couteur A, Evans G, et al. Treating anxiety in autistic adults: study protocol for the Personalised Anxiety Treatment-Autism (PAT-A©) pilot randomised controlled feasibility trial. Trials. 2020;21(1):265.
100. King BH, Hollander E, Sikich L, McCracken JT, Scahill L, Bregman JD, et al. Lack of efficacy of citalopram in children with autism spectrum disorders and high levels of repetitive behavior: citalopram ineffective in children with autism: Citalopram ineffective in children with autism. Arch Gen Psychiatry. 2009;66(6):583–90.
101. Herscu P, Handen BL, Arnold LE, Snape MF, Bregman JD, Ginsberg L, et al. The SOFIA study: Negative multi-center study of low dose fluoxetine on repetitive behaviors in children and adolescents with autistic disorder. J Autism Dev Disord. 2020;50(9):3233–44.

102. McDougle CJ, Thom RP, Ravichandran CT, Palumbo ML, Politte LC, Mullett JE, et al. A randomized double-blind, placebo-controlled pilot trial of mirtazapine for anxiety in children and adolescents with autism spectrum disorder. Neuropsychopharmacology. 2022;47(6):1263–70.
103. Salzman C. Manual of clinical psychopharmacology, 5th ed. J Clin Psychiatry. 2006;67(04):678.
104. de Boer T. The pharmacologic profile of mirtazapine. J Clin Psychiatry. 1996;57 Suppl 4(Suppl 4):19–25.
105. Buitelaar JK, van der Gaag RJ, van der Hoeven J. Buspirone in the management of anxiety and irritability in children with pervasive developmental disorders: results of an open-label study. J Clin Psychiatry. 1998;59(2):56–9.
106. Ceranoglu TA, Wozniak J, Fried R, Galdo M, Hoskova B, DeLeon FM, et al. A retrospective chart review of buspirone for the treatment of anxiety in psychiatrically referred youth with high-functioning Autism Spectrum Disorder. J Child Adolesc Psychopharmacol. 2019;29(1):28–33.
107. Maneeton N, Maneeton B, Woottiluk P, Likhitsathian S, Suttajit S, Boonyanaruthee V, et al. Quetiapine monotherapy in acute treatment of generalized anxiety disorder: a systematic review and meta-analysis of randomized controlled trials. Drug Devel Ther. 2016;10:259–76.
108. Katzman MA, Brawman-Mintzer O, Reyes EB, Olausson B, Liu S, Eriksson H. Extended release quetiapine fumarate (quetiapine XR) monotherapy as maintenance treatment for generalized anxiety disorder: a long-term, randomized, placebo-controlled trial. Int Clin Psychopharmacol. 2011;26(1):11–24.
109. Hudson CC, Hall L, Harkness KL. Prevalence of depressive disorders in individuals with autism spectrum disorder: A meta-analysis. J Abnorm Child Psychol. 2019;47(1):165–75.
110. Sterling L, Dawson G, Estes A, Greenson J. Characteristics associated with presence of depressive symptoms in adults with autism spectrum disorder. J Autism Dev Disord. 2008;38(6):1011–8.
111. Mayes SD, Calhoun SL, Murray MJ, Zahid J. Variables associated with anxiety and depression in children with autism. J Dev Phys Disabil. 2011;23(4):325–37.
112. Newell V, Phillips L, Jones C, Townsend E, Richards C, Cassidy S. A systematic review and meta-analysis of suicidality in autistic and possibly autistic people without co-occurring intellectual disability. Mol Autism. 2023;14(1):12.
113. Hirvikoski T, Boman M, Chen Q, D'Onofrio BM, Mittendorfer-Rutz E, Lichtenstein P, et al. Individual risk and familial liability for suicide attempt and suicide in autism: a population-based study. Psychol Med. 2020;50(9):1463–74.
114. Gotham K, Unruh K, Lord C. Depression and its measurement in verbal adolescents and adults with autism spectrum disorder. Autism. 2015;19(4):491–504.
115. Magnuson KM, Constantino JN. Characterization of depression in children with autism spectrum disorders. J Dev Behav Pediatr. 2011;32(4):332–40.
116. Kerns CM, Roux AM, Connell JE, Shattuck PT. Adapting cognitive behavioral techniques to address anxiety and depression in cognitively able emerging adults on the autism spectrum. Cogn Behav Pr. 2016;23(3):329–40.
117. Schiltz HK, McVey AJ, Dolan BK, Willar KS, Pleiss S, Karst JS, et al. Changes in depressive symptoms among adolescents with ASD completing the PEERS® social skills intervention. J Autism Dev Disord. 2018;48(3):834–43.
118. Hollander E, Soorya L, Chaplin W, Anagnostou E, Taylor BP, Ferretti CJ, et al. A double-blind placebo-controlled trial of fluoxetine for repetitive behaviors and global severity in adult autism spectrum disorders. Am J Psychiatry. 2012;169(3):292–9.
119. Lagerberg T, Fazel S, Sjölander A, Hellner C, Lichtenstein P, Chang Z. Selective serotonin reuptake inhibitors and suicidal behaviour: a population-based cohort study. Neuropsychopharmacology. 2022;47(4):817–23.
120. Kanne SM, Mazurek MO. Aggression in children and adolescents with ASD: prevalence and risk factors. J Autism Dev Disord. 2011;41(7):926–37.
121. Steenfeldt-Kristensen C, Jones CA, Richards C. The prevalence of self-injurious behaviour in autism: A meta-analytic study. J Autism Dev Disord. 2020;50(11):3857–73.
122. Minshawi N, Hurwitz S, Fodstad J, Biebl S, Morris D, McDougle C. The association between self-injurious behaviors and autism spectrum disorders. Psychol Res Behav Manag. 2014;7:125.
123. Kurtz PF, Leoni M, Hagopian LP. Behavioral approaches to assessment and early intervention for severe problem behavior in intellectual and developmental disabilities. Pediatr Clin North Am. 2020;67(3):499–511.
124. Roy AK, Lopes V, Klein RG. Disruptive mood dysregulation disorder: a new diagnostic approach to chronic irritability in youth. Am J Psychiatry. 2014;171(9):918–24.
125. McGuire K, Fung LK, Hagopian L, Vasa RA, Mahajan R, Bernal P, et al. Irritability and problem behavior in autism spectrum disorder: A practice pathway for pediatric primary care. Pediatrics. 2016;137 Suppl 2(Supplement_2):136–48.
126. Cai RY, Richdale AL, Uljarević M, Dissanayake C, Samson AC. Emotion regulation in autism spectrum disorder: Where we are and where we need to go. Autism Res. 2018;11(7):962–78.
127. Im DS. Treatment of aggression in adults with autism spectrum disorder: A review. Harv Rev Psychiatry. 2021;29(1):35–80.
128. Aman MG, Singh NN, Stewart AW, Field CJ. The aberrant behavior checklist: a behavior rating scale for the assessment of treatment effects. Am J Ment Defic. 1985;89(5):485–91.
129. Choi H, Kim JH, Yang HS, Kim JY, Cortese S, Smith L, et al. Pharmacological and non-pharmacological interventions for irritability in autism spectrum disorder: a systematic review and meta-analysis with the GRADE assessment. Mol Autism. 2024;15(1):7.
130. Burrell TL, Postorino V, Scahill L, Rea HM, Gillespie S, Evans AN, et al. Feasibility of group parent training for children with autism spectrum disorder and disruptive behavior: A demonstration pilot. J Autism Dev Disord. 2020;50(11):3883–94.
131. Stone-Heaberlin M, Blackburn A, Hoffman EK, Esbensen AJ. Feasibility study of a parent-driven intervention for youth with Down syndrome. J Intellect Disabil Res. 2024;68(9):1077–86.
132. Shanok NA, Lozott EB, Sotelo M, Bearss K. Community-based parent-training for disruptive behaviors in children with ASD using synchronous telehealth services: A pilot study. Res Autism Spectr Disord. 2021;88:101861.
133. Volkmar F, Siegel M, Woodbury-Smith M, King B, McCracken J, State M, et al. Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. 2014;53(2):237–57.
134. D'Alò GL, De Crescenzo F, Amato L, Cruciani F, Davoli M, Fulceri F, et al. Impact of antipsychotics in children and adolescents with autism spectrum disorder: a systematic review and meta-analysis. Health Qual Life Outcomes. 2021;19(1):33.
135. Rogdaki M, McCutcheon RA, D'Ambrosio E, Mancini V, Watson CJ, Fanshawe JB, et al. Comparative physiological effects of antipsychotic drugs in children and young people: a network meta-analysis. Lancet Child Adolesc Health. 2024;8(7):510–21.
136. Ghanizadeh A, Sahraeizadeh A, Berk M. A head-to-head comparison of aripiprazole and risperidone for safety and treating autistic disorders, a randomized double blind clinical trial. Child Psychiatry Hum Dev. 2014;45(2):185–92.
137. DeVane CL, Charles JM, Abramson RK, Williams JE, Carpenter LA, Raven S, et al. Pharmacotherapy of autism spectrum disorder: Results from the randomized BAART clinical trial. Pharmacotherapy. 2019;39(6):626–35.
138 Fung LK, Mahajan R, Nozzolillo A, Bernal P, Krasner A, Jo B, et al. Pharmacologic treatment of severe Irritability and problem behaviors in autism: A systematic review and meta-analysis. Pediatrics. 2016;137 Suppl 2(Supplement_2):S124–35.
139 Rotella F, Cassioli E, Calderani E, Lazzeretti L, Ragghianti B, Ricca V, et al. Long-term metabolic and cardiovascular effects of antipsychotic drugs. A meta-analysis of randomized controlled trials. Eur Neuropsychopharmacol. 2020;32:56–65.
140. Henderson DC, Vincenzi B, Andrea NV, Ulloa M, Copeland PM. Pathophysiological mechanisms of increased cardiometabolic risk in people with schizophrenia and other severe mental illnesses. Lancet Psychiatry. 2015;2(5):452–64.
141. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol. 2011;8(2):114–26.
142 Vázquez-Bourgon J, de la Ortiz-GarcíaFoz V, Gómez-Revuelta M, van Mayoral Son J, Juncal-Ruiz M, Garrido-Torres N, et al. Aripiprazole and risperidone present comparable long-term metabolic profiles: Data from a pragmatic randomized controlled trial in drug-naïve first-episode psychosis. Int J Neuropsychopharmacol. 2022;25(10):795–806.
143. Russell G, Stapley S, Newlove-Delgado T, Salmon A, White R, Warren F, et al. Time trends in autism diagnosis over 20 years: a UK population-based cohort study. J Child Psychol Psychiatry. 2022;63(6):674–82.

144. Chahboun S, Stenseng F, Page AG. The changing faces of autism: The fluctuating international diagnostic criteria and the resulting inclusion and exclusion-A Norwegian perspective. Front Psychiatry. 2022;13:787893.
145. Volk HE, Ames JL, Chen A, Fallin MD, Hertz-Picciotto I, Halladay A, et al. Considering toxic chemicals in the etiology of autism. Pediatrics. 2022;149(1):e2021053012.
146. Symeonides C, Vacy K, Thomson S, Tanner S, Chua HK, Dixit S, et al. Male autism spectrum disorder is linked to brain aromatase disruption by prenatal BPA in multimodal investigations and 10HDA ameliorates the related mouse phenotype. Nat Commun. 2024;15(1):6367.
147. Al-Salihy AARS. Longitudinal trends and correlation between autism spectrum disorder prevalence and sperm quality parameters (2000–2024): a comprehensive statistical analysis. Front Reprod Health. 2024;6:1438049.
148. Love C, Sominsky L, O'Hely M, Berk M, Vuillermin P, Dawson SL. Prenatal environmental risk factors for autism spectrum disorder and their potential mechanisms. BMC Med. 2024;22(1):393.
149. McBain RK, Kareddy V, Cantor JH, Stein BD, Yu H. Systematic review: United States workforce for autism-related child healthcare services. J Am Acad Child Adolesc Psychiatry. 2020;59(1):113–39.

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