**Aaron Ooi, MBChB, DipPaed, PGDipClinEd, FRACP, Brian Banno, MD, FRCPC, Kristen McFee, PhD, RPsych, Dean Elbe, PharmD, BCPP, Robin Friedlander, MD, FRCPC**

# Evaluating and managing irritability and aggression in children and adolescents with autism spectrum disorder: An algorithm

Because the drivers of irritability and aggression in individuals with autism spectrum disorder can be multifactorial, they must be addressed in a stepwise manner or in parallel to identify treatable contributors and institute appropriate management.

*Dr Ooi was a postgraduate fellow in the Neuropsychiatry Clinic at BC Children's Hospital and is a general pediatrician in the Department of Paediatrics at Rotorua Hospital, Rotorua, New Zealand. Dr Banno is a child and adolescent psychiatrist in the Neuropsychiatry Clinic at BC Children's Hospital and a child and adolescent psychiatrist in the Division of Child and Adolescent Psychiatry, Department of Psychiatry, Faculty of Medicine, at the University of British Columbia. Dr McFee is a psychologist in the Neuropsychiatry Clinic at BC Children's Hospital. Dr Elbe is a clinical pharmacy specialist in the Pharmacy Department at BC Children's Hospital and BC Women's Hospital & Health Centre and a clinical pharmacy specialist in the child and adolescent Mental Health Programs at BC Children's Hospital. Dr Friedlander is a child and adolescent psychiatrist in the Neuropsychiatry Clinic at BC Children's Hospital. He is also head of the Neurodevelopmental Disorders program and a clinical professor in the Department of Psychiatry at UBC.*

*This article has been peer reviewed.*

ABSTRACT: A range of maladaptive behaviors, including irritability and aggression, are often encountered in autism spectrum disorder. Challenges in complex clinical decision making and management exist, and off-label antipsychotic prescribing is increasing in Canada. A literature review of various treatments, limited to randomized controlled trials in the pediatric population, was used to develop an algorithm for evaluating and managing irritability and aggression in autism spectrum disorder within a Canadian context, which is supported by expert consensus. Holistic consideration of biomedical, psychiatric, psychosocial, environmental, and developmental factors that affect behavior is emphasized. The algorithm highlights the multifactorial contributors to irritability and aggression in autism spectrum disorder and reserves the use of antipsychotic medication for managing the most severe and refractory cases. A comprehensive evaluation of the drivers of behavior when addressing irritability and aggression in autism spectrum disorder is crucial to identify treatable contributors and institute appropriate management.

Autism spectrum disorder is a complex neurodevelopmental disorder that affects 1 in 32 children and youth in Canada.[1] It is characterized by impairments in social communication and interaction and a pattern of repetitive or restricted activities, interests, or behaviors.[2] A wide range of maladaptive behaviors are commonly encountered, including irritability and aggression, with prevalence estimated at 25% to 68%.[3,4] Irritability can be defined as a mood state characterized by easy annoyance, anger, and the manifestation of temper outbursts; aggression can be defined as intentional verbal or physical threats, attempts to inflict or infliction of bodily harm on another individual, or intentional destruction of property.[5,6] We have excluded self-injurious behavior within the scope of these definitions for the purposes of this article. The causes for irritability and aggression are often multifactorial and can result from difficulties arising from autism spectrum disorder itself, including hypersensitivity to environmental triggers, communication difficulties, and excessive rigidity. Irritability and aggression can also be related to medical symptoms such as pain and discomfort or a symptom of several psychiatric conditions such as attention deficit hyperactivity disorder, anxiety disorders, and mood disorders.[2]

Based on positive clinical trials, the US Food and Drug Administration approved the atypical antipsychotics risperidone and aripiprazole for the treatment of "irritability,

including aggression, deliberate self-injury and temper tantrums" in the autism spectrum disorder population.[7,8] In Canada, no antipsychotic medication is approved for this use. Despite this, off-label antipsychotic prescription rates in the pediatric population in Canada are increasing and present concerns given the known side effects of antipsychotic medications and paucity of data on long-term use and safety.[9]

A practice pathway designed to help pediatric primary care practitioners assess and manage irritability and problem behaviors in autism spectrum disorder and a systematic review and meta-analysis of pharmacological management have been published.[10,11] However, to our knowledge, there are no published Canadian guidelines for an area in which frequent challenges exist with regard to decision making. Therefore, our aim was to offer a Canadian perspective that is tailored toward child and adolescent psychiatrists, pediatricians, and family physicians. We conducted a literature review, and, building on our clinical experience in a neuropsychiatry clinic at a quaternary centre, we obtained consensus to produce a clinically useful algorithm to guide decision making for behavioral complexity **[Figure]**. Frequently occurring and treatable comorbid conditions are also discussed, with emphasis on the complexity in psychiatric diagnoses and management. The algorithm highlights the multifactorial contributors to irritability and aggression in autism spectrum disorder and reserves the use of antipsychotic medication for managing the most severe and refractory cases.

## Algorithm

### Comorbidities and links to maladaptive behavior

Patients with autism spectrum disorder often have one or more medical or psychiatric comorbidities and can present to clinicians with a complex interplay of symptoms, including maladaptive behaviors.[10,12] A study of 58 adolescents with autism spectrum disorder who were admitted to a neurobehavioral unit for severe challenging behaviors suggested that 28% and 48% had a primary medical condition or non-autism spectrum disorder psychiatric condition, respectively, that accounted for decompensation.[12,13] Such findings support the need for a comprehensive assessment when patients with autism spectrum disorder present with irritability and aggression, particularly in children who cannot communicate effectively. Identification of underlying comorbid conditions contributing to irritability and aggression permits specific and targeted treatments and may avoid the use of antipsychotics, which carry significant side effects. In contrast, behaviors associated with an unrecognized medical or psychiatric problem are unlikely to improve if the underlying driver of behavior is not addressed and may worsen with nontargeted treatments.

**The algorithm highlights the multifactorial contributors to irritability and aggression in autism spectrum disorder and reserves the use of antipsychotic medication for managing the most severe and refractory cases.**

### Medical comorbidities

Common medical comorbidities encountered in autism spectrum disorder include gastrointestinal dysfunction; feeding disorders; ear, nose, throat, or dental pathology; seizures; and side effects of medications that contribute to symptoms.[13] Although it has been difficult to determine the frequency in which medical factors directly cause or exacerbate maladaptive behaviors, conventional clinical practice and consensus advocate that such potentially reversible causes should be addressed prior to or in parallel with specific treatment that is targeting behaviors.[13] Gastrointestinal dysfunction (such as abdominal pain, gastroesophageal reflux disease, constipation, diarrhea, or abdominal bloating), which occurs in 24% to 79% of the population with autism spectrum disorder, has been associated with behavioral issues.[14] Recognizing that medical evaluations may be poorly tolerated in some children with autism spectrum disorder, it has been suggested that diagnostic trials of empiric therapy for gastroesophageal reflux or constipation may be undertaken to provide diagnostic clarity if supported by history.[15] An evaluation of the ear, nose, throat, and dental health, alongside a medical systems review, is also warranted.[10,13] The presence of seizures in patients with autism spectrum disorder, which has an estimated prevalence of 7% to 46%, is particularly significant, because many anticonvulsant medications such as levetiracetam and clobazam can also adversely affect behavior.[16,17]

### Sleep

Sleep disorders are common in autism spectrum disorder: the estimated prevalence is 50% to 80%.[18] An association between sleep problems and aggression in autism spectrum disorder has been described.[19] A comprehensive evaluation of sleep, including identification of issues related to sleep initiation, maintenance, and nighttime awakenings, is suggested. This should include a review of common causes of nighttime awakenings, such as poor sleep habits, primary sleep disorders (e.g., parasomnias, obstructive sleep apnea, restless legs syndrome), comorbid medical conditions (e.g., seizures, gastroesophageal reflux disease, enuresis), and psychiatric disorders (e.g., anxiety, mood disorders), which may warrant further subspecialist involvement.[13,20]

In managing sleep disorders in patients with autism spectrum disorder, current recommendations focus on education and implementation of sleep hygiene and behavioral measures as first-line treatment; several resources are available to support this approach.[20,21] Consideration of using melatonin (starting dose 1 mg at bedtime, with a maximum of 10 mg at bedtime) can be made as a second-line recommendation if sleep hygiene and behavioral measures are

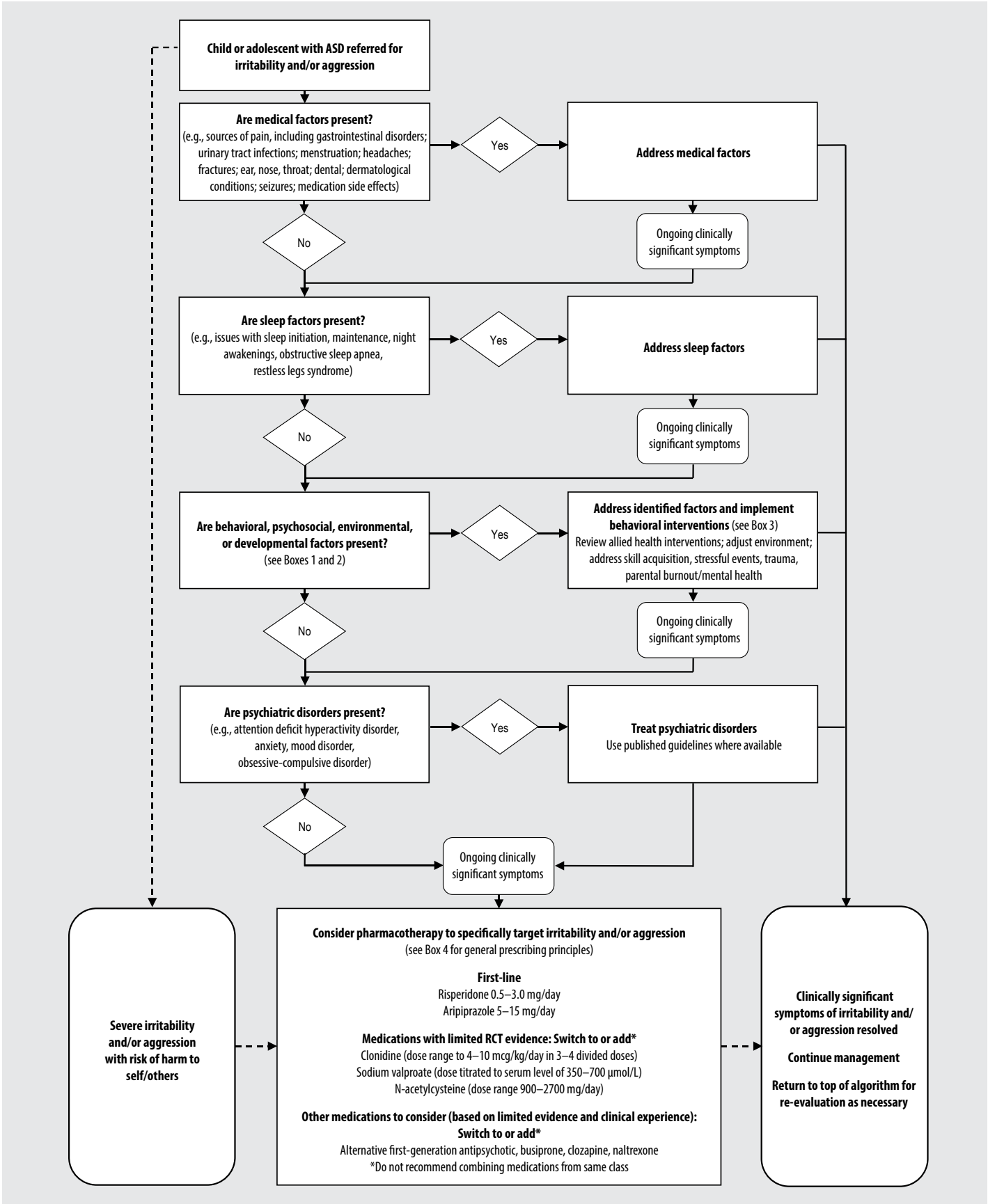


**FIGURE.** Algorithm for assessing and managing irritability and aggression in children and adolescents with autism spectrum disorder (ASD).
RCT = randomized controlled trial.

unsuccessful; a meta-analysis demonstrated increased sleep duration and reduced sleep onset latency but no effect on nighttime awakenings.[22] Third-line treatments may include the use of clonidine, risperidone, or trazodone due to their sedative side effects. Nevertheless, given that there are limited robust data drawn primarily from open-label and observational studies, these medications should be used cautiously.[23,24]

## Behavioral, psychosocial, environmental, and developmental factors

In addition to a history of the behavior itself **[Box 1]**, it is pertinent to explore such behaviors within their broader psychosocial, environmental, and developmental context when evaluating for irritability and aggression **[Box 2]**. In considering psychosocial factors, exploration into parent/caregiver strategies to manage the behavior (such as the ability to consistently implement a routine and the need for front-loading—i.e., preparation for changes ahead of time), their capacity, and adequacy of supports should also be addressed. Stressful events such as bullying and abuse should also be considered, given their increased risks compared with the general pediatric population.[25,26] Developmental factors may include the need for an efficient and effective means of functional communication (e.g., specific communication strategies such as a picture exchange communication system or augmentative communication devices), given that behaviors may arise because of frustration resulting from the inability to communicate needs.[27] Play skills, the ability to self- or emotionally regulate, and the ability to wait are additional developmental factors that warrant attention **[Box 2]**. Several general preventive and environmental strategies can also be considered to aid aspects of behavioral management **[Box 3]**.

## Psychiatric comorbidities

A significant number of children and adolescents with autism spectrum disorder have at least one identifiable psychiatric comorbidity, which evidence suggests is linked to irritability and maladaptive behaviors. The *Diagnostic and Statistical Manual for Mental Disorders*, fifth edition (*DSM-5-TR*), reports rates of psychiatric comorbidity in autism spectrum disorder as approximately 70%, including attention deficit hyperactivity disorder, anxiety disorders, mood disorders, and obsessive-compulsive disorder.[2] This suggests that psychiatric comorbidity is usually present in clinical populations and highlights the importance of looking for potentially modifiable psychiatric pathology in patients with autism spectrum disorder who present with irritability and aggression.

**A significant number of children and adolescents with autism spectrum disorder have at least one identifiable psychiatric comorbidity.**

**Diagnostic evaluation and management of comorbid psychiatric conditions.** Psychiatric comorbidities in autism spectrum disorder can be challenging to recognize and diagnose, particularly in the context of cognitive, language, or communication impairments and inherent difficulties in reporting emotional states. This subsequently necessitates reliance on parent/caregiver reports and clinician observations and is compounded by a lack of standardized tools for making psychiatric diagnoses in populations with autism spectrum disorder. Additional challenges can arise due to diagnostic overshadowing, whereby emotional and behavioral symptoms are frequently attributed to autism spectrum disorder itself—for example, when distinguishing overlapping symptoms such as social anxiety and social deficits or obsessive-compulsive disorder and repetitive stereotypical behaviors.[28]

Several strategies can be used in differentiating diagnostic dilemmas and symptom overlap. A comprehensive history from multiple perspectives is paramount, including the child, where possible, the parents/caregivers, and other key individuals, such as teachers. Emphasis should be placed on elucidating baseline behaviors and how current behaviors differ from baseline in relation to the child's level of functioning and their psychosocial, environmental, and developmental context **[Boxes 1 and 2]**. Particular attention to the history of the behavior itself, including the age of onset and variation in symptoms over time, is pertinent. For example, a 7-year-old boy with autism spectrum disorder who presents with a 1-month history of behavioral escalations in the morning before going to school in a new school environment, despite significant transition planning, may suggest an evolving anxiety disorder rather than symptoms attributed to autistic rigidity. Similarly, a 14-year-old boy with autism spectrum disorder and previous repetitive behaviors who presents with a 3-month history of increasing time spent per day performing new ritualistic and repetitive behaviors, and becoming aggressive whenever he is unable to perform such rituals, may suggest evolving obsessive-compulsive disorder. The examination should also include general observations and a mental status examination, ideally within a familiar environment, to watch for behaviors that may help provide diagnostic clarity. This may include observations of a child's ability to sit still, their reported mood or observed affect, and their speech.

Given the paucity of randomized controlled trials published to date that have reviewed psychotropic medications to treat comorbid psychiatric conditions in populations with autism spectrum disorder, guidelines and reviews have suggested adapting treatments based on evidence from the general pediatric population for treating psychiatric comorbidities in autism spectrum disorder.[10,13] Careful attention should be paid to monitoring for side effects whenever psychiatric medication is prescribed.[13,29] Psychiatric medication may also cause irritability or maladaptive behaviors, such as akathisia, with antipsychotic treatment and activation with antidepressant treatment.

**BOX 1.** Behavioral history.

**What is the behavior and what is the context in which it occurs, what function might the behavior serve, or what is behind the behavior?**

1. Tell me about the behavior that concerns you.
2. What does it look like, including topography, intensity, frequency, duration, and time trends (increasing, decreasing, or stable)?
3. What is the context in which the behavior occurs? Is there a predictable trigger (antecedents)? Things that make the behavior better/worse?
   a. External setting events that might be related (e.g., home/school/community, specific activities, following specific instructions/demands, with specific people, time of day)?
   b. Internal factors that might be related (e.g., mood, fatigue, hunger, boredom, frustration, pain, sensory aversions/seeking)?
4. What happens after the behavior (consequences)?
   a. Does the behavior lead to avoidance or delay of a nonpreferred activity (i.e., escape motivated)?
   b. Does the child gain access to something desirable (motivated by attention, either positive or negative; access to a preferred item or activity)?
5. What are the child's baseline behaviors? Does the behavior represent an escalation of baseline behaviors or an onset of new behaviors (if the latter, how is this different)?

**BOX 2.** Behavioral, psychosocial, environmental, and developmental factors.

**Behavioral, psychosocial, and environmental factors**

1. Parents/caregivers
   a. What strategies have been useful in managing behavior? What has not worked thus far?
   b. How successful have you been in altering the environment to avoid known triggers?
   c. Have rewards and incentives been tried?
      i. Does the child like the reward?
      ii. Is the reward tied specifically to the target behavior, or can the child access the reward in other situations?
      iii. Has the reward been used consistently?
   d. Are the parents/caregivers burned-out? Do they have access to sufficient respite services/other supports (e.g., extended family, support workers, church, professional support)?
   e. Is there parental/caregiver mental illness that needs to be addressed?
2. Other systems/supports
   a. Have stressful events, including bullying and abuse, been dealt with?
   b. Is a behavior consultant involved? If yes, does the behavioral approach target the child's current challenging behaviors? Has the behavioral approach been changed or modified in the past year to adapt to the child's ongoing behavioral challenges?

**Developmental factors and skill acquisition**

What skill areas need to be addressed to help meet the needs of the child and make the challenging behavior redundant?

1. Do the parents/caregivers have a realistic understanding of the child's developmental level and trajectory (e.g., level of support child will likely require, expectations consistent with child's ability level)?
2. Communication
   a. Does your child use an alternative/augmentative communication system?
   b. If yes, where do they use it (school, home, community)?
   c. If yes, can they use it independently (initiate without prompting/help)?
   d. If yes, do you find it useful?
   e. How does your child indicate:
      i. That they want something (food item, activity, person).
      ii. That they want a break or want to stop an activity.
      iii. Choice (among multiple items).
      iv. Yes/No.
3. Play
   a. What does your child like to do when given free time? Do they have preferred activities?
   b. Can your child play on their own? For how long?
   c. Can your child play with other children without support?
4. Self-regulation/emotion regulation
   a. How does your child let you know that they are upset (e.g., with words like "I'm angry," with behavior, by running away, by crying)?
   b. How does your child self-soothe?
   c. Are there strategies that help your child calm down when upset?
5. Wait
   a. Can your child wait to obtain/delay obtaining an item or activity?
   b. Are there strategies that help your child wait (e.g., a visual timer, distraction using an alternative activity, visual schedule indicating when they will access the item/activity, use of "when/then" instructions)?

**BOX 3.** General environmental/preventive strategies.

**What can we do to provide increased support and prevent challenging behavior from occurring?**

1. Is there a clear and predictable schedule that is displayed and referenced daily?
2. Is there sufficient structure and routine, minimizing the amount of stressful transitions?
3. Is there front-loading prior to activities and transitions (e.g., what is going to happen next, expectations for behavior and rewards/consequences)?
4. Is time externalized through the use of visual schedules and visual timers?
5. Are behavioral expectations made clear prior to activities and new contexts?
6. Are behavioral expectations realistic and developmentally appropriate? Do demands exceed skill/ability level (self-help, academics)?
7. Are expectations for behavior consistent across caregivers and settings?
8. Does the child have sufficient access to enjoyable/preferred activities throughout the day?
9. Is the child provided with choice throughout the day?
10. Are difficult/nonpreferred tasks interspersed with easy/preferred tasks?
11. Are appropriate/replacement behaviors rewarded quickly and consistently?
12. Have known sensory triggers been addressed (e.g., loud noises, tactile aversions)? Or has a similar sensory experience been created through an enriched environment (e.g., oral stimulation with appropriate oral motor toys)?

**Attention deficit hyperactivity disorder.** The *DSM-5-TR* permits the diagnosis of comorbid attention deficit hyperactivity disorder in autism spectrum disorder.[2] Nevertheless, several challenges can exist in the diagnostic process for attention deficit hyperactivity disorder in the context of autism spectrum disorder, including the need to consider cognitive and developmental levels and the similarities in behavioral phenotypes to other common comorbid conditions such as anxiety.[13] For example, a 10-year-old boy with an intellectual disability who is given tasks beyond his cognitive level without educational support and adaptations may present with behaviors such as inattention, hyperactivity, and aggression. Management in such instances should first be centred on psychoeducation and initiation of supports and accommodations rather than pharmacological therapy for attention deficit hyperactivity disorder.

Guidelines are available for the evaluation and pharmacotherapy of attention deficit hyperactivity disorder symptoms in autism spectrum disorder.[30,31] The use of methylphenidate in populations with autism spectrum disorder has been explored in several randomized controlled trials; a meta-analysis noted it to be efficacious on the symptomatology of attention deficit hyperactivity disorder.[32] Two randomized controlled trials have supported the use of atomoxetine in populations with autism spectrum disorder.[33,34] Although Canadian manufacturer labeling advises against opening atomoxetine capsules, a formula for compounded atomoxetine suspension for children who are unable to swallow atomoxetine capsules has been published, and specialty compounding pharmacies may have other proprietary recipes available.[35] A randomized controlled trial showed guanfacine extended-release to be safe and effective for the reduction of hyperactivity, impulsivity, and distractibility symptoms in the autism spectrum disorder population, although use of this formulation requires the child to be able to swallow tablets whole.[36] Although limited evidence exists, our clinical experiences suggest that the use of clonidine immediate-release in a carefully titrated manner is a useful adjunct or alternative and can be considered in cases where guanfacine extended-release tablets may not be an option.[37] An immediate-release guanfacine formulation is not available in Canada. Several randomized controlled trials support the efficacy of risperidone and aripiprazole on hyperactivity and impulsivity; nevertheless, these study populations were selected for irritability, and attention deficit hyperactivity disorder symptoms were not the primary outcomes for the studies.[38-40] It is our clinical experience that treatment for attention deficit hyperactivity disorder should also be revisited if it is identified as a contributor to irritability and aggression following initiation of risperidone or aripiprazole because these medications may ameliorate stimulant-induced dysregulation, and subsequent improvements in behavior can sometimes be observed in such cases, which will eventually permit weaning of the antipsychotic **[Figure]**.

**Current guideline recommendations centre on psychoeducation, modified cognitive-behavioral therapy, and pharmacological agents such as selective serotonin reuptake inhibitors used in anxiety in neurotypical populations.**

**Anxiety disorders.** Anxiety disorders are highly comorbid with autism spectrum disorder. Clinical recommendations on assessing anxiety in pediatric populations with autism spectrum disorder have been published.[41] The complexity of delineating core autism spectrum disorder symptoms from those of anxiety has been recognized. For example, repetitive behaviors that improve with front-loading and transition planning may suggest an autism spectrum disorder phenotype, compared with repetitive behaviors associated with anxiety that continue to escalate despite using such an approach.

Several open trials and randomized controlled trials have used cognitive-behavioral therapy for anxiety in youth with high-functioning autism spectrum disorder, and a recent meta-analysis found a moderate treatment effect size for that therapy.[42,43] To our knowledge, no randomized controlled trials have examined the use of pharmacotherapy for anxiety disorders in children and adolescents with autism spectrum disorder. Nevertheless, current guideline recommendations centre on psychoeducation, modified cognitive-behavioral therapy, and pharmacological agents such as selective serotonin reuptake inhibitors used in anxiety in neurotypical populations.[41]

**Mood disorders.** Current guidelines drawn from the general pediatric population suggest screening for depression in patients older than 12 years of age.[44] While symptoms of depressed mood and guilt are frequently cited in neurotypical populations with depression, challenges in expressing complex emotions in patients with autism spectrum disorder often necessitate reliance on parent/caregiver reports or observed behaviors by others.[45] Symptoms of social withdrawal and a flattened affect that can present in autism spectrum disorder can often be confused with symptoms of depression, thereby necessitating a comprehensive history in relation to the time course and the nature of other core symptoms of a mood disorder, such as anhedonia or sleep or appetite disturbances. Specifically, in nonverbal populations, less-typical presentations of depression in autism spectrum disorder may be observed, including increased irritability, aggression, self-injury, crying, repetitive behaviors, a sad or miserable facial appearance, or regressive behavior.[45,46]

In terms of treatment options, a recent systematic review highlighted the paucity of data in evaluating the efficacy of

psychosocial interventions and pharmacological therapy in populations with depression and autism spectrum disorder.[47] Nevertheless, current expert opinion and recommendations centre on supportive therapy, cognitive-behavioral therapy, and pharmacological therapy with selective serotonin reuptake inhibitors based on general pediatric population data.[13]

**Obsessive-compulsive disorder.** Comorbid obsessive-compulsive disorder should also be considered in individuals with autism spectrum disorder who present with an escalation of restricted and repetitive behaviors or the development of new-onset ritualistic behaviors after the preschool period, given its potential for treatment. By definition, obsessive-compulsive disorder involves obsessions (recurrent, unwanted, and intrusive thoughts or urges) that are usually followed by compulsions (behaviors that are performed to ameliorate the anxiety arising from an obsession).[48] Difficulties in language skills may add to the complexity of obtaining an obsessive-compulsive disorder diagnosis. In contrast to the stereotyped, restricted, and repetitive behaviors seen in autism spectrum disorder, which are often pleasurable to the individual, compulsions in obsessive-compulsive disorder are often egodystonic and perceived as distressing or anxiety-provoking. Qualitatively, in evaluating the nature of the repetitive behaviors to help distinguish both diagnoses, checking, excessive cleaning, and repetitive behaviors to protect against harm have been determined to be more common in neurotypical children with obsessive-compulsive disorder and relatively uncommon in populations with autism spectrum disorder.[49]

Treatment approaches include cognitive-behavioral therapy (including exposure/response prevention), which has been shown to be efficacious for obsessive-compulsive disorder in youth with autism spectrum disorder, although an adapted program may be required depending on the individual's language and cognition level.[50] Empiric treatment of obsessive-compulsive disorder based on evidence in the general pediatric population is recommended, given the paucity of literature on this topic. One randomized controlled trial showed significantly greater reductions in obsessive-compulsive disorder symptoms and repetitive behaviors with the use of fluoxetine compared with placebo in children with autism spectrum disorder and comorbid obsessive-compulsive disorder, while a systematic review that evaluated pharmacological therapies for obsessive-compulsive disorder in populations with autism spectrum disorder suggested that fluvoxamine and risperidone were likely efficacious.[51,52]

## Treatment of irritability and aggression

**Behavioral and psychosocial interventions.** There is a considerable body of literature on the assessment and intervention of challenging behavior based on the principles of learning and behavioral theory.[53,54] Several modalities of intervention have been proposed, including applied behavior analytic interventions, developmental relationship-focused interventions, naturalistic developmental behavioral interventions, and parent-mediated training.[13] We discuss applied behavior analytic theory, which most evidence-based treatment models are based on.

According to this theory, all behavior serves a function.[55] The function can be analyzed by operationalizing the behavior in question (e.g., hitting the table with an open hand) and gaining clarification of the antecedents and consequences of the behavior. Antecedents refer to factors that influence the behavior in advance, including environmental factors (e.g., specific people, activities, setting, time of day, specific instructions/demands) and internal variables (e.g., boredom, stress, anxiety, pain, hunger, fatigue, sensory experiences). Consequences broadly refer to outcomes that follow the behavior (e.g., access to desired items or social attention, escape from the situation).

Understanding the antecedent-behavior-consequence relationship (e.g., the caregiver instructs the child to clean up their toys, the child hits the table with an open hand, and the caregiver says, "Okay, you have 10 more minutes") can help elucidate the particular function(s) of behavior. Behavior often serves one of four functions: (1) to obtain social attention, (2) to obtain access to desirable items or activities, (3) to avoid or escape an undesirable demand or situation, or (4) to obtain sensory stimulation.[56,57] There are several direct and indirect assessment methods, including experimental functional analysis, for gathering information on the function of behavior and contingencies surrounding the behavior **[Boxes 1 and 2]**.[58,59] A referral to a board-certified behavior analyst may be warranted to better understand the function of behavior and support related intervention plans.

The intervention plan should always target the function of behavior. When intervention plans do not adequately address function, challenging behavior is likely to continue or be replaced with new behavior. For example, a child with autism spectrum disorder who responds with aggression due to frustration at being unable to communicate demands is unlikely to improve with an intervention plan that teaches social skills until a consistent plan is developed to address the child's communication needs. Similarly, if escape from an activity does not occur when the child flips the table, they may attempt aggression toward others.

Based on applied behavior analytic theory, a well-designed intervention plan targets problem behavior by manipulating the antecedent and consequent variables that strengthen or weaken the behavior. Three categories of behavioral interventions are often used: (1) prevent: manipulate antecedent and environmental variables (e.g., identify triggers and prevent the behavior from occurring), (2) teach: use instructional strategies focused on teaching skills and behaviors that serve as effective replacements for the challenging behavior (e.g., asking for help, asking for a break, requesting play time), and (3) reinforce: adjust the consequences with an emphasis on positive reinforcement of more appropriate behaviors.[53,60]

Antecedent-based strategies often include altering or eliminating the demand that triggers the behavior altogether or temporarily, enriching the environment to make it more engaging, providing a similar sensory experience, and reducing overall stress levels. For example, boredom is a commonly observed contributing factor to behavioral escalations. Instructional strategies that focus on addressing skill deficits that commonly contribute to challenging behavior, such as a lack of communication, play, and independent life skills, would be beneficial **[Boxes 2 and 3]**. There is strong evidence of the relationship between challenging behavior and poor communication skills.[61,62] Even when an alternative, augmentative communication strategy is in place, further clarification is warranted to determine its effectiveness.

There are two broad categories of consequence-based interventions. First, reinforcement-based interventions encourage desirable behavior by providing attention, access, escape, and rewards for more appropriate replacement behaviors or physically incompatible behaviors (e.g., hands on lap versus hitting others). In such scenarios, it is imperative that the replacement behavior is rewarded more quickly and consistently than the challenging behavior (e.g., if the child asks for a break during a challenging activity, they are given a break immediately versus engaging in aggressive behavior). Second, extinction-based interventions include planned ignoring or withdrawal of a reinforcer following the challenging behavior (e.g., a parent/caregiver selectively ignores repetitive questioning if the function of the behavior is thought to be social attention).[59]

## Medications for irritability and aggression

Numerous medication trials that have examined potential agents for treating irritability and aggression in autism spectrum disorder have been published, including recent meta-analyses and a systematic review.[11,63,64] We review commonly used medications, which can be considered alongside general prescribing principles **[Box 4]**. Recommendations for pharmacologic management of acute agitation in children and youth have been published in BC but are beyond the scope of this article.[65]

**BOX 4. General prescribing principles.**

1. Obtain informed consent.
2. Identify specific target(s) of treatment (e.g., irritability, aggression, anxiety, mood).
3. Use an objective measure/tool to monitor treatment (e.g., Likert scale, rating scale).
4. Start medications at a low dose; use the lowest effective dose.
5. Make one change at a time, and consider a wider context during which changes are made (e.g., environmental triggers or significant life transitions happening at the same time, which may contribute to behavioral escalations).
6. Discontinue treatments that are ineffective.
7. Monitor closely for side effects, using guidelines where applicable (e.g., Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children).
8. Avoid polypharmacy as much as possible.
9. Consider treatment discontinuation or reduction in dose after 6–12 months.

**Risperidone and aripiprazole.** The efficacy of risperidone in improving irritability has been demonstrated in several short-term, randomized, placebo-controlled trials.[38,39,66-68] Intermediate-term follow-up studies have suggested sustained gains with ongoing risperidone treatment over a 6-month period and an increased risk of relapse when switched to placebo under blinded conditions.[69,70] Longer-term data under blinded conditions are lacking, although a naturalistic follow-up study with a mean follow-up of 21 months suggested there were sustained benefits.[71] A meta-analysis showed a large effect size (d = 0.9) and a number needed to treat of two patients for risperidone with typical doses (1–2 mg/day) over the short term (4–8 weeks).[11]

The efficacy of aripiprazole has also been demonstrated in randomized controlled trials, and a subsequent meta-analysis demonstrated improvements in Aberrant Behavior Checklist – Irritability Subscale (ABC-I) scores compared with placebo.[72-74] A maintenance study performed on patients 6 to 17 years of age who had autism spectrum disorder and responded to aripiprazole treatment over 16 weeks failed to show statistically significant differences in time to relapse for placebo or aripiprazole, although a post hoc analysis suggested a number needed to treat of six patients to prevent one relapse.[75]

A double-blind randomized trial that compared risperidone and aripiprazole over 8 weeks in 59 children and adolescents with autism spectrum disorder indicated that both interventions resulted in significant improvements in the primary outcome measure of change in ABC-I scores, and safety and efficacy were not significantly different among treatment arms.[76] A further trial in 2019 that compared risperidone and aripiprazole demonstrated improvement in ABC-I subscale scores, with statistically significant improvement greatest in the risperidone compared with the aripiprazole group at 3 and 6 weeks.[77]

Adverse effects with risperidone included somnolence, increased appetite, weight gain, hyperprolactinemia, and enuresis.[38,39,69-71] Only one study evaluated metabolic parameters beyond weight: increases in insulin levels and insulin resistance were associated with risperidone treatment in the short term, although at 6 months, an open-label follow-up study showed no change in these parameters but an increase in triglycerides.[68,70] Variable rates of extrapyramidal side effects are reported (mostly akathisia), with rates as high as 16%.[68]

Adverse effects of aripiprazole include sedation, weight gain, vomiting, increased appetite, akathisia, nasopharyngitis, and

upper respiratory tract infections.[40,72,73,75,78] Changes in QTc interval appear to be minimal, and prolactin levels appear to be either unchanged or possibly reduced with treatment.[72,73,79] Results on changes to metabolic parameters in the longer term are inconclusive.[40,75,77] Extrapyramidal side effects are reported at rates of 14% to 23%.[40,72,73,75]

The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children has published guidelines and practice recommendations for monitoring antipsychotic use in children.[80] They include suggested physical examination procedures and laboratory testing as part of routine monitoring, which we generally advocate to be completed in this population and coordinated opportunistically with other procedures (e.g., dental examinations) that require sedation, if necessary.

**Other antipsychotics.** The use of other antipsychotics for managing irritability and aggression in autism spectrum disorder has also been explored. A randomized controlled trial (n = 150) of the atypical antipsychotic lurasidone failed to show a significant difference compared with placebo in the short-term treatment of irritability in children with autism spectrum disorder.[81] A small pilot randomized controlled trial examined the use of olanzapine in 11 children and adolescents with autism spectrum disorder over 8 weeks and showed statistically significant improvement over placebo on the Clinical Global Impression – Improvement scale but not on other irritability or aggression scales, and patients in the olanzapine treatment group demonstrated significant weight gain.[82] Another randomized controlled trial compared risperidone with haloperidol in 30 children and adolescents with autism spectrum disorder over 12 weeks; both interventions demonstrated a significant reduction in Aberrant Behavior Checklist (ABC) total scores (subscales not reported), risperidone showed numerically greater reductions than haloperidol, and haloperidol showed a significant increase in extrapyramidal side effects.[83] Although several published case reports, case series, and open-label trials have examined the use of other typical and atypical antipsychotics in this patient population, to our knowledge, no other randomized controlled trials have been published.

**Anticonvulsants.** Two randomized controlled trials examined the use of sodium valproate for treating irritability and aggression in autism spectrum disorder but showed inconsistent results. One study compared the use of sodium valproate with placebo over 9 weeks in 30 children and adolescents (6 to 20 years of age) with any pervasive developmental disorder who were selected for aggression; there was no statistically significant improvement compared with placebo in primary (ABC-I) outcomes.[84] The other study examined the use of valproate over 12 weeks in 27 children and adolescents (5 to 17 years of age) with autism spectrum disorder who were selected for irritability and aggression; there were significant improvements of a moderate effect size on ABC-I scores, with 63% of the valproate patients deemed responders compared with 9% in the placebo group.[85]

A small randomized controlled trial in 28 children with autism spectrum disorder that examined the use of lamotrigine for a wide range of symptoms showed no significant effects on any of the outcome measures, including ABC score.[86] Another small randomized controlled trial in 20 patients with autism spectrum disorder that examined the use of levetiracetam for behavioral problems showed no significant effects on outcome measures.[87]

**Novel approaches and augmentation studies.** A small randomized controlled trial of clonidine and two randomized controlled trials of the glutamatergic agent N-acetylcysteine in children demonstrated a modest reduction in ABC-I scores compared with placebo.[37,88,89] Several other small randomized controlled trials that examined alternative agents such as buspirone for the management of irritability associated with autism spectrum disorder have been published; however, methodological challenges limit interpretation, which is beyond the scope of this article.[90] There have also been case reports that have suggested possible efficacy of clozapine and naltrexone in treating the most severe aggression in the population of patients with autism spectrum disorder who are refractory to other medications.[91,92]

## Conclusions

The presentation of irritability and aggression in individuals with autism spectrum disorder is common and warrants a multimodal, systematic, and comprehensive approach in delineating the drivers for such behaviors. It is important to recognize that the drivers can be multifactorial, which warrants addressing them in a stepwise manner or in parallel. We present our algorithm with a focus on psychiatric comorbidities, as well as a review of recent literature to guide decision making and management in this population. ■

**Competing interests**
None declared.

**References**

1. Ministry of Children and Family Development. Autism Funding Program service rate: British Columbia. Vancouver, BC: University of British Columbia, 2020. Accessed 3 September 2022. https://elearning.ubccpd.ca/enrol/index.php?id=389 [login required].
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Text revision: DSM-5-TR. 5th ed. Washington, DC: American Psychiatric Association; 2022.
3. Kanne SM, Mazurek MO. Aggression in children and adolescents with ASD: Prevalence and risk factors. J Autism Dev Disord 2011;41:926-937.
4. Hill AP, Zuckerman KE, Hagen AD, et al. Aggressive behavior problems in children with autism spectrum disorders: Prevalence and correlates in a large clinical sample. Res Autism Spectr Disord 2014;8:1121-1133.
5. Stringaris A. Irritability in children and adolescents: A challenge for DSM-5. Eur Child Adolesc Psychiatry 2011;20:61-66.
6. Fitzpatrick SE, Srivorakiat L, Wink LK, et al. Aggression in autism spectrum disorder: Presentation and treatment options. Neuropsychiatr Dis Treat 2016;12:1525-1538.
7. Food and Drug Administration. Prescribing information: Risperdal. Revised 22 August 2007. Accessed 31 August 2022. www.accessdata.fda.gov/

drugsatfda_docs/label/2007/020272s46s47,20588s36s37,21444s20s21lbl.pdf.
8. Food and Drug Administration. Prescribing information: Abilify. Revised 19 November 2007. Accessed 31 August 2022. www.accessdata.fda.gov/drugsatfda_docs/label/2009/021436s027lbl.pdf.
9. Alessi-Severini S, Biscontri RG, Collins DM, et al. Ten years of antipsychotic prescribing to children: A Canadian population-based study. Can J Psychiatry 2012;57:52-58.
10. McGuire K, Fung LK, Hagopian L, et al. Irritability and problem behavior in autism spectrum disorder: A practice pathway for pediatric primary care. Pediatrics 2016;137(Suppl 2):S136-S148.
11. Fung LK, Mahajan R, Nozzolillo A, et al. Pharmacologic treatment of severe irritability and problem behaviors in autism: A systematic review and meta-analysis. Pediatrics 2016;137(Suppl 2):S124-S135.
12. Guinchat V, Cravero C, Diaz L, et al. Acute behavioral crises in psychiatric inpatients with autism spectrum disorder (ASD): Recognition of concomitant medical or non-ASD psychiatric conditions predicts enhanced improvement. Res Dev Disabil 2015;38:242-255.
13. Hyman SL, Levy SE, Myers SM, et al. Identification, evaluation, and management of children with autism spectrum disorder. Pediatrics 2020;145:e20193447.
14. Mannion A, Leader G. Gastrointestinal symptoms in autism spectrum disorder: A literature review. Rev J Autism Dev Disord 2014;1:11-17.
15. Buie T, Fuchs GJ III, Furuta GT, et al. Recommendations for evaluation and treatment of common gastrointestinal problems in children with ASDs. Pediatrics 2010;125(Suppl 1):S19-S29.
16. Robinson SJ. Childhood epilepsy and autism spectrum disorders: Psychiatric problems, phenotypic expression, and anticonvulsants. Neuropsychol Rev 2012;22:271-279.
17. Eddy CM, Rickards HE, Cavanna AE. Behavioral adverse effects of antiepileptic drugs in epilepsy. J Clin Psychopharmacol 2012;32:362-375.
18. Mazurek MO, Sohl K. Sleep and behavioral problems in children with autism spectrum disorder. J Autism Dev Disord 2016;46:1906-1915.
19. Mazurek MO, Kanne SM, Wodka EL. Physical aggression in children and adolescents with autism spectrum disorders. Res Autism Spectr Disord 2013;7:455-465.
20. Williams Buckley A, Hirtz D, Oskoui M, et al. Practice guideline: Treatment for insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2020;94:392-404.
21. Autism Treatment Network and Autism Intervention Research Network on Physical Health. ATN/AIR-P strategies to improve sleep in children with autism. Autism Speaks, 2022. Updated 8 March 2022. Accessed 3 August 2022. www.autismspeaks.org/tool-kit/atnair-p-strategies-improve-sleep-children-autism.
22. Rossignol DA, Frye RE. Melatonin in autism spectrum disorders: A systematic review and meta-analysis. Dev Med Child Neurol 2011;53:783-792.
23. Ming X, Gordon E, Kang N, Wagner GC. Use of clonidine in children with autism spectrum disorders. Brain Dev 2008;30:454-460.
24. Relia S, Ekambaram V. Pharmacological approach to sleep disturbances in autism spectrum disorders with psychiatric comorbidities: A literature review. Med Sci 2018;6:95.
25. Blake JJ, Lund EM, Zhou Q, et al. National prevalence rates of bully victimization among students with disabilities in the United States. Sch Psychol Q 2012;27:210-222.
26. Brown-Lavoie SM, Viecili MA, Weiss JA. Sexual knowledge and victimization in adults with autism spectrum disorders. J Autism Dev Disord 2014;44:2185-2196.
27. McClintock K, Hall S, Oliver C. Risk markers associated with challenging behaviours in people with intellectual disabilities: A meta-analytic study. J Intellect Disabil Res 2003;47:405-416.
28. Reiss S, Levitan GW, Szyszko J. Emotional disturbance and mental retardation: Diagnostic overshadowing. Am J Ment Defic 1982:86:567-574.
29. Pringsheim T, Lam D, Patten SB. The pharmacoepidemiology of antipsychotic medications for Canadian children and adolescents: 2005–2009. J Child Adolesc Psychopharmacol 2011;21:537-543.
30. Mahajan R, Bernal MP, Panzer R, et al. Clinical practice pathways for evaluation and medication choice for attention-deficit/hyperactivity disorder symptoms in autism spectrum disorders. Pediatrics 2012;130(Suppl 2):S125-S138.
31. Antshel KM, Zhang-James Y, Wagner KE, et al. An update on the comorbidity of ADHD and ASD: A focus on clinical management. Expert Rev Neurother 2016;16:279-293.
32. 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;43:2435-2441.
33. Arnold LE, Aman MG, Cook AM, et al. Atomoxetine for hyperactivity in autism spectrum disorders: Placebo-controlled crossover pilot trial. J Am Acad Child Adolesc Psychiatry 2006;45:1196-1205.
34. Harfterkamp M, van de Loo-Neus G, Minderaa RB, 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;51:733-741.
35. Allen, LV, Jr. Atomoxetine 4 mg/mL oral solution/suspension. Int J Pharm Compd 2021:25:321.
36. Scahill L, McCracken JT, King BH, et al. Extended-release guanfacine for hyperactivity in children with autism spectrum disorder. Am J Psychiatry 2015;172:1197-1206.
37. Jaselskis CA, Cook EH Jr, Fletcher KE, Leventhal BL. Clonidine treatment of hyperactive and impulsive children with autistic disorder. J Clin Psychopharmacol 1992;12:322-327.
38. McCracken JT, McGough J, Shah B, et al. Risperidone in children with autism and serious behavioral problems. N Engl J Med 2002;347:314-321.
39. Shea S, Turgay A, Carroll A, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. Pediatrics 2004;114:e634-e641.
40. Marcus RN, Owen R, Manos G, et al. Safety and tolerability of aripiprazole for irritability in pediatric patients with autistic disorder: A 52-week, open-label, multicenter study. J Clin Psychiatry 2011;72:1270-1276.
41. Vasa RA, Mazurek MO, Mahajan R, et al. Assessment and treatment of anxiety in youth with autism spectrum disorders. Pediatrics 2016;137(Suppl 2):S115-S123.
42. Ung D, Selles R, Small BJ, Storch EA. A systematic review and meta-analysis of cognitive-behavioral therapy for anxiety in youth with high-functioning autism spectrum disorders. Child Psychiatry Hum Dev 2015;46:533-547.
43. Perihan C, Burke M, Bowman-Perrott L, et al. Effects of cognitive behavioral therapy for reducing anxiety in children with high functioning ASD: A systematic review and meta-analysis. J Autism Dev Disord 2020;50:1958-1972.
44. Zuckerbrot RA, Cheung A, Jensen PS, et al. Guidelines for adolescent depression in primary care (GLAD-PC): Part I. Practice preparation, identification, assessment, and initial management. Pediatrics 2018;141:e20174081.
45. Stewart ME, Barnard L, Pearson J, et al. Presentation of depression in autism and Asperger syndrome: A review. Autism 2006;10:103-116.
46. Pezzimenti F, Han GT, Vasa RA, Gotham K. Depression in youth with autism spectrum disorder. Child Adolesc Psychiatr Clin N Am 2019;28:397-409.
47. Menezes M, Harkins C, Robinson MF, Mazurek MO. Treatment of depression in individuals with autism spectrum disorder: A systematic review. Res Autism Spectr Disord 2020;78:101639.
48. Krebs G, Heyman I. Obsessive-compulsive disorder in children and adolescents. Arch Dis Child 2015;100:495-499.
49. Scahill L, Challa SA. Repetitive behavior in children with autism spectrum disorder: Similarities and differences with obsessive compulsive disorder. In: Psychiatric symptoms and comorbidities in autism spectrum disorder. Mazzone L, Vitiello B, editors. Cham, Switzerland: Springer International Publishing/Springer Nature; 2016. pp. 39-50.
50. Russell AJ, Jassi A, Fullana MA, et al. Cognitive behavior therapy for comorbid obsessive-compulsive disorder in high-functioning autism spectrum disorders: A randomized controlled trial. Depress Anxiety 2013;30:697-708.
51. Reddihough DS, Marraffa C, Mouti A, et al. Effect of fluoxetine on obsessive-compulsive behaviors in children and adolescents with autism

spectrum disorders: A randomized clinical trial. JAMA 2019;322:1561-1569.
52. Neil N, Sturmey P. Assessment and treatment of obsessions and compulsions in individuals with autism spectrum disorders: A systematic review. Rev J Autism Dev Disord 2014;1:62-79.
53. Bambara LM, Kern L, editors. Individualized supports for students with problem behaviors: Designing positive behavior plans. 2nd ed. New York, NY: Guilford Publications; 2021.
54. Sailor W, Dunlap G, Sugai G, Horner R, editors. Handbook of positive behavior support. New York, NY: Springer; 2009.
55. Skinner BF. The behavior of organisms: An experimental analysis. Oxford, UK: Appleton-Century-Crofts; 1938.
56. Carr JE, LeBlanc L. Functional analysis of problem behavior. In: Cognitive behaviour therapy: Applying empirically supported techniques in your practice. O'Donahue W, Fishers JE, Hayes SC, editors. Hoboken, NJ: Wiley; 2003.
57. Iwata BA, Dorsey MF, Slifer KJ, et al. Toward a functional analysis of self-injury. J Appl Behav Anal 1994;27:197-209.
58. Minshawi NF. Behavioral assessment and treatment of self-injurious behavior in autism. Child Adolesc Psychiatr Clin N Am 2008;17:875-886.
59. Minshawi NF, Hurwitz S, Morriss D, McDougle CJ. Multidisciplinary assessment and treatment of self-injurious behavior in autism spectrum disorder and intellectual disability: Integration of psychological and biological theory and approach. J Autism Dev Disord 2015; 45:1541-1568.
60. Dunlap G, Iovannone R, Wilson KJ, et al. Prevent-teach-reinforce: A standardized model of school-based behavioral intervention. J Posit Behav Interv 2010;12:9-22.
61. Boonen H, Maljaars J, Lambrechts G, et al. Behavior problems among school-aged children with autism spectrum disorder: Associations with children's communication difficulties and parenting behaviors. Res Autism Spectr Disord 2014; 8:716-725.
62. Hutchins TL, Prelock PA. Using communication to reduce challenging behaviors in individuals with autism spectrum disorders and intellectual disability. Child Adolesc Psychiatr Clin N Am 2014;23:41-55.
63. Elbe D, Lalani Z. Review of the pharmacotherapy of irritability of autism. J Can Acad Child Adolesc Psychiatry 2012;21:130-146.
64. Salazar de Pablo G, Pastor Jordá C, Vaquerizo-Serrano J, et al. Systematic review and meta-analysis: Efficacy of pharmacological interventions for irritability and emotional dysregulation in autism spectrum disorder and predictors of response. J Am Acad Child Adolesc Psychiatry 2023;62:151-168.
65. Child Health BC. Provincial least restraint guideline: Initial management of least restraint in emergent/urgent care and inpatient settings. Vancouver, BC: Child Health BC, 2022. Accessed 21 August 2022. https://childhealthbc.ca/media/226/download.
66. Nagaraj R, Singhi P, Malhi P. Risperidone in children with autism: Randomized, placebo-controlled, double-blind study. J Child Neurol 2006;21:450-455.
67. Pandina GJ, Bossie CA, Youssef E, et al. Risperidone improves behavioral symptoms in children with autism in a randomized, double-blind, placebo-controlled trial. J Autism Dev Disord 2007; 37:367-373.
68. Kent JM, Kushner S, Ning X, et al. Risperidone dosing in children and adolescents with autistic disorder: A double-blind, placebo-controlled study. J Autism Dev Disord 2013;43:1773-1783.
69. Research Units on Pediatric Psychopharmacology Autism Network. Risperidone treatment of autistic disorder: Longer-term benefits and blinded discontinuation after 6 months. Am J Psychiatry 2005; 162:1361-1369.
70. Kent JM, Hough D, Singh J, et al. An open-label extension study of the safety and efficacy of risperidone in children and adolescents with autistic disorder. J Child Adolesc Psychopharmacol 2013;23:676-686.
71. Aman M, Rettiganti M, Nagaraja HN, et al. Tolerability, safety, and benefits of risperidone in children and adolescents with autism: 21-month follow-up after 8-week placebo-controlled trial. J Child Adolesc Psychopharmacol 2015;25:482-493.
72. Marcus RN, Owen R, Kamen L, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. J Am Acad Child Adolesc Psychiatry 2009;48:1110-1119.
73. Owen R, Sikich L, Marcus RN, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. Pediatrics 2009; 124:1533-1540.
74. Hirsch LE, Pringsheim T. Aripiprazole for autism spectrum disorders (ASD). Cochrane Database Syst Rev 2016;2016:CD009043.
75. Findling RL, Mankoski R, Timko K, et al. A randomized controlled trial investigating the safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric patients with irritability associated with autistic disorder. J Clin Psychiatry 2014;75:22-30.
76. 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;45:185-192.
77. DeVane CL, Charles JM, Abramson RK, et al. Pharmacotherapy of autism spectrum disorder: Results from the randomized BAART clinical trial. Pharmacotherapy 2019;39:626-635.
78. Marcus RN, Owen R, Manos G, et al. Safety and tolerability of aripiprazole for irritability in pediatric patients with autistic disorder: A 52-week, open-label, multicenter study. J Clin Psychiatry 2011;72:1270-1276.
79. Ho JG, Caldwell RL, McDougle CJ, et al. The effects of aripiprazole on electrocardiography in children with pervasive developmental disorders. J Child Adolesc Psychopharmacol 2012;22:277-283.
80. Pringsheim T, Panagiotopoulos C, Davidson J, et al. Evidence-based recommendations for monitoring safety of second-generation antipsychotics in children and youth. Paediatr Child Health 2011;16:581-589.
81. Loebel A, Brams M, Goldman RS, et al. Lurasidone for the treatment of irritability associated with autistic disorder. J Autism Dev Disord 2016;46: 1153-1163.
82. Hollander E, Wasserman S, Swanson EN, et al. A double-blind placebo-controlled pilot study of olanzapine in childhood/adolescent pervasive developmental disorder. J Child Adolesc Psychopharmacol 2006;16:541-548.
83. Miral S, Gencer O, Inal-Emiroglu FN, et al. Risperidone versus haloperidol in children and adolescents with AD: A randomized, controlled, double-blind trial. Eur Child Adolesc Psychiatry 2008;17:1-8.
84. Hellings JA, Weckbaugh M, Nickel EJ, et al. A double-blind, placebo-controlled study of valproate for aggression in youth with pervasive developmental disorders. J Child Adolesc Psychopharmacol 2005;15:682-692.
85. Hollander E, Chaplin W, Soorya L, et al. Divalproex sodium vs. placebo for the treatment of irritability in children and adolescents with autism spectrum disorders. Neuropsychopharmacology 2010;35:990-998.
86. Belsito KM, Law PA, Kirk KS, et al. Lamotrigine therapy for autistic disorder: A randomized, double-blind, placebo-controlled trial. J Autism Dev Disord 2001;31:175-181.
87. Wasserman S, Iyengar R, Chaplin WF, et al. Levetiracetam versus placebo in childhood and adolescent autism: A double-blind placebo-controlled study. Int Clin Psychopharmacol 2006;21:363-367.
88. Hardan AY, Fung LK, Libove RA, et al. A randomized controlled pilot trial of oral N-acetylcysteine in children with autism. Biol Psychiatry 2012;71:956-961.
89. Ghanizadeh A, Moghimi-Sarani E. A randomized double blind placebo controlled clinical trial of N-acetylcysteine added to risperidone for treating autistic disorders. BMC Psychiatry 2013;13:196.
90. Ghanizadeh A, Ayoobzadehshirazi A. A randomized double-blind placebo-controlled clinical trial of adjuvant buspirone for irritability in autism. Pediatr Neurol 2015;52:77-81.
91. Rothärmel M, Szymoniak F, Pollet C, et al. Eleven years of clozapine experience in autism spectrum disorder: Efficacy and tolerance. J Clin Psychopharmacol 2018;38:577-581.
92. Elchaar GM, Maisch NM, Augusto LM, Wehring HJ. Efficacy and safety of naltrexone use in pediatric patients with autistic disorder. Ann Pharmacother 2006;40:1086-1095.