

Irritability and Problem Behavior in Autism Spectrum Disorder: A Practice Pathway for Pediatric Primary Care

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abstract

OBJECTIVE: Pediatric primary care providers (PCPs) caring for patients with autism spectrum disorder (ASD) often encounter irritability (vocal or motoric outbursts expressive of anger, frustration, or distress) and problem behavior (directed acts of aggression toward other people, self, or property). The Autism Intervention Research Network on Physical Health and Autism Speaks Autism Treatment Network charged a multidisciplinary workgroup with developing a practice pathway to assist PCPs in the evaluation and treatment of irritability and problem behavior (I/PB).

METHODS: The workgroup reviewed the literature on the evaluation and treatment of contributory factors for I/PB in ASD. The workgroup then achieved consensus on the content and sequence of each step in the pathway.

RESULTS: The practice pathway is designed to help the PCP generate individualized treatment plans based on contributing factors identified in each patient. These factors may include medical conditions, which the PCP is in a key position to address; functional communication challenges that can be addressed at school or at home; psychosocial stressors that may be ameliorated; inadvertent reinforcement of I/PB; and co-occurring psychiatric conditions that can be treated. The pathway provides guidance on psychotropic medication use, when indicated, within an individualized treatment plan. In addition to guidance on assessment, referral, and initial treatment, the pathway includes monitoring of treatment response and periodic reassessment.

CONCLUSIONS: The pediatric PCP caring for the patient with ASD is in a unique position to help generate an individualized treatment plan that targets factors contributing to I/PB and to implement this plan in collaboration with parents, schools, and other providers.



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Dr McGuire contributed to the design of the practice pathway, played a leading role in drafting the initial manuscript, and revised the manuscript; Drs Fung, Hagopian, Vasa, Mahajan, Bernal, and Coury and Ms Silberman and Ms Wolfe contributed to the design of the practice pathway and reviewed and revised the manuscript; Drs Hardan and Veenstra-VanderWeele contributed to the conceptualization and design of the practice pathway and reviewed and revised the manuscript; Dr Whitaker played a leading role in conceptualizing and designing the practice pathway, drafted portions of the initial manuscript, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social communication and interaction as well as restrictive, repetitive patterns of behavior.¹ The important role of pediatric primary care providers (PCPs) in the care of children with ASD is increasingly recognized.² The comprehensive care or medical home model for the care of ASD includes management of mental health and behavioral problems, which are far more prevalent in children with ASD³ than in those without ASD and, if not addressed, may become increasingly chronic and disabling.⁴ Two types of presenting problems in ASD can be particularly challenging: severe irritability and problem behavior. For the purposes of this article, the term irritability refers to vocal and motoric outbursts expressive of anger, frustration, and distress; these outbursts are often referred to by caregivers as “temper tantrums,” “meltdowns,” or “rages.” The term problem behavior refers to directed acts of aggression that have a high potential to or do result in harm to other people, self, or property. Irritability and problem behavior (I/PB) are considered as a single topic here because they commonly, but not invariably, co-occur in ASD⁵ and because many treatment research studies use measures that aggregate I/PB.⁶ Importantly, I/PB can jeopardize educational and recreational placements and even lead to inpatient psychiatric hospitalization⁷ or residential placement.⁸

As presented by Fung and colleagues⁹ in this issue, meta-analysis of controlled trials confirms the efficacy of 2 atypical neuroleptics, risperidone and aripiprazole, approved by the US Food and Drug Administration for the management of “severe irritability” based on clinical trials in children with ASD who have frequent I/PB that is interfering with development,

functioning, or relationships. Atypical neuroleptics have become widely used in patients with ASD¹⁰ but carry a significant risk of metabolic¹¹ and neurologic adverse events.^{9,12} These concerns mandate consideration of lower-risk interventions, even for severe I/PB, targeting other factors, such as medical problems or communication challenges that have been identified as potentially contributory to I/PB in the individual patient.

To provide guidance for the pediatric PCP, the Autism Speaks Autism Treatment Network (ATN) Psychopharmacology Committee,¹³ with input from the parent member and clinicians, charged the Irritability Workgroup with developing a practice pathway for the individualized management of I/PB in the patient with ASD. As the medical professionals whom children with ASD will probably encounter first and most frequently, pediatric PCPs need a breadth of knowledge to enable them to identify contributing factors to I/PB, decide when and how to initiate treatment, and judge when to refer to specialists. Therefore, this practice pathway can be viewed more as a comprehensive rather than an exhaustive recommendation for PCPs, who must weigh their expertise and resources when addressing the range of issues that a child with ASD and I/PB may present.

METHODS

Using an iterative process, the Irritability Workgroup met regularly (weekly to monthly as needed) to achieve consensus on definitions of irritability and problem behavior and to develop the pathway. The workgroup consisted primarily of child psychiatrists from 6 current and former ATN sites (K.M., L.K.F., R.A.V., R.M., P.B., J.V., A.Y.H., and A.W.), with additional participation from a developmental pediatrician (D.L.C.) and behavioral

psychologist (L.H.) to revise and refine the initial pathway draft. The workgroup reviewed the literature on assessment and treatment of contributory factors for I/PB in ASD and grouped them into 5 domains: co-occurring medical conditions, lack of functional communication, psychosocial stressors, maladaptive reinforcement patterns, and co-occurring psychiatric conditions. In each domain, the evidence on assessment and treatment was not, by itself, sufficient to lead to recommendations; therefore, the workgroup achieved consensus on the content and sequence of each step in the pathway, focusing on the assessment and treatment of these behaviors in ASD by pediatric PCPs. Recognizing that primary care settings and available resources may vary regionally, the pathway was developed to include points at which the PCP may want to consider referrals to specialists and collaboration with the school and community providers. The pathway also highlights situations in which the workgroup agreed that use of atypical neuroleptics is clinically indicated. The workgroup paid close attention to operationalizing the monitoring of treatment and reassessment intervals.

At 3 points in the development of the practice pathway, members of the workgroup interviewed outside consultants with respect to each element of the pathway. First, expert advice was sought for the key domains of evaluation and initial structure of the pathway before development of the narrative. Second, a refined draft of the pathway and the initial narrative were reviewed. In the last review, a near-final draft of the pathway, narrative, and accompanying article were refined.

RESULTS

Figure 1 is a visual presentation of the practice pathway. Table 1

**Irritability and Problem Behaviors (I/PB) in Autism Spectrum Disorder:
A Practice Pathway for Pediatric Psychiatry**

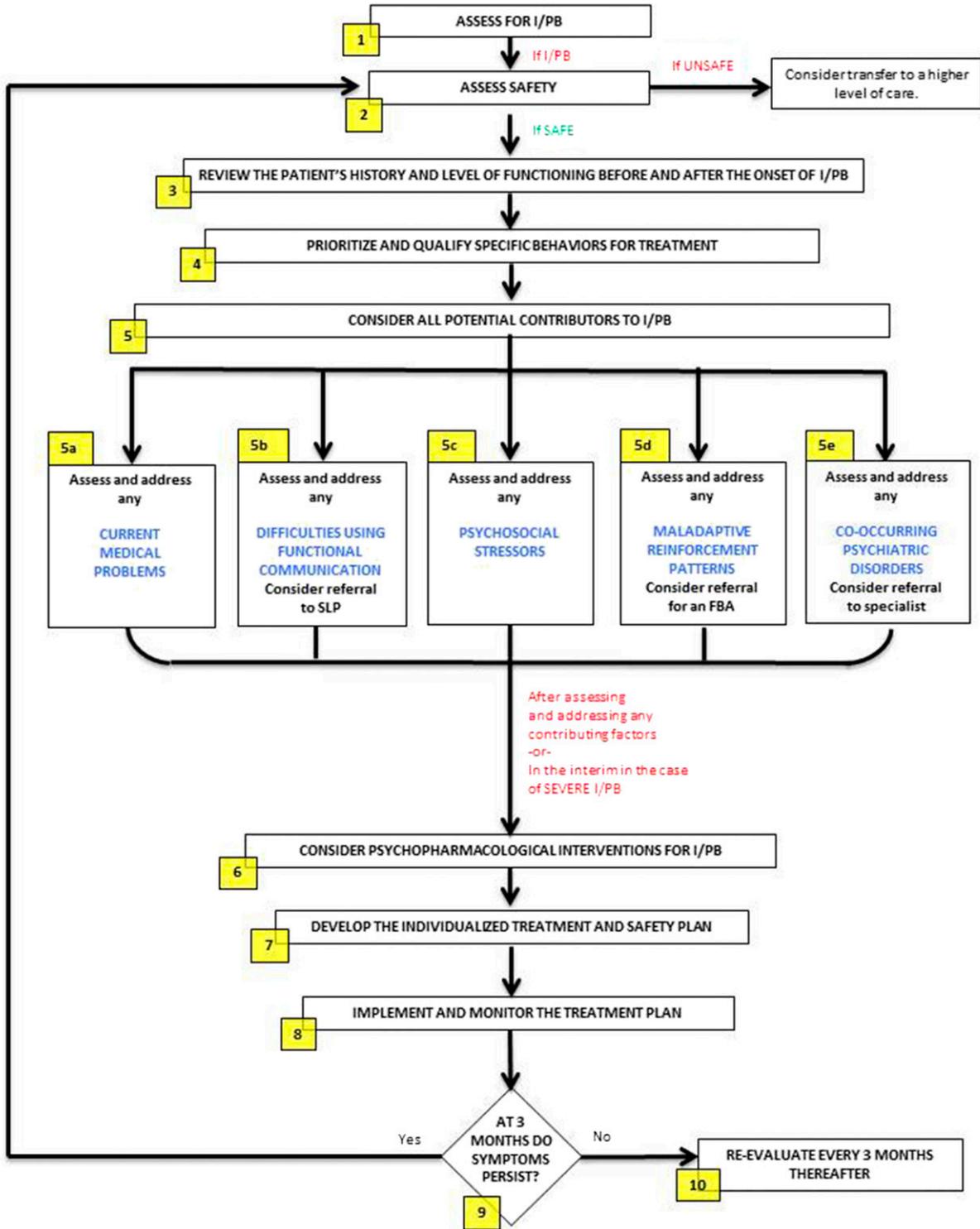


FIGURE 1
I/PB in ASD: A practice pathway for pediatric psychiatry.

TABLE 1 I/PB in ASD: Detailed Practice Pathway for Pediatric Primary Care

Step	Details																																																					
1 <input type="checkbox"/>	<p>Assess for I/PB.</p> <p>Has this patient <i>recently</i> shown:</p> <table border="0"> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Tantrums, meltdowns, rages?</td> <td>No <input type="checkbox"/></td> <td>Yes <input type="checkbox"/></td> <td></td> <td>If yes, how much of a problem?</td> <td>None <input type="checkbox"/></td> <td>Mild–Moderate <input type="checkbox"/></td> <td>Severe <input type="checkbox"/></td> <td>Safety risk?</td> </tr> <tr> <td>Property destruction?</td> <td>No <input type="checkbox"/></td> <td>Yes <input type="checkbox"/></td> <td></td> <td></td> <td>None <input type="checkbox"/></td> <td>Mild–Moderate <input type="checkbox"/></td> <td>Severe <input type="checkbox"/></td> <td>No <input type="checkbox"/></td> </tr> <tr> <td>Aggression to others?</td> <td>No <input type="checkbox"/></td> <td>Yes <input type="checkbox"/></td> <td></td> <td></td> <td>None <input type="checkbox"/></td> <td>Mild–Moderate <input type="checkbox"/></td> <td>Severe <input type="checkbox"/></td> <td>Yes <input type="checkbox"/></td> </tr> <tr> <td>Self-injury?</td> <td>No <input type="checkbox"/></td> <td>Yes <input type="checkbox"/></td> <td></td> <td></td> <td>None <input type="checkbox"/></td> <td>Mild–Moderate <input type="checkbox"/></td> <td>Severe <input type="checkbox"/></td> <td>No <input type="checkbox"/></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>Yes <input type="checkbox"/></td> </tr> </table>									Tantrums, meltdowns, rages?	No <input type="checkbox"/>	Yes <input type="checkbox"/>		If yes, how much of a problem?	None <input type="checkbox"/>	Mild–Moderate <input type="checkbox"/>	Severe <input type="checkbox"/>	Safety risk?	Property destruction?	No <input type="checkbox"/>	Yes <input type="checkbox"/>			None <input type="checkbox"/>	Mild–Moderate <input type="checkbox"/>	Severe <input type="checkbox"/>	No <input type="checkbox"/>	Aggression to others?	No <input type="checkbox"/>	Yes <input type="checkbox"/>			None <input type="checkbox"/>	Mild–Moderate <input type="checkbox"/>	Severe <input type="checkbox"/>	Yes <input type="checkbox"/>	Self-injury?	No <input type="checkbox"/>	Yes <input type="checkbox"/>			None <input type="checkbox"/>	Mild–Moderate <input type="checkbox"/>	Severe <input type="checkbox"/>	No <input type="checkbox"/>									Yes <input type="checkbox"/>
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2 <input type="checkbox"/>	<p>Assess safety.</p> <p>Has patient <i>ever</i> been aggressive to others or engaged in self-injurious behavior? No <input type="checkbox"/> Yes <input type="checkbox"/></p> <p>Has patient <i>ever</i> caused tissue damage to self or others? No <input type="checkbox"/> Yes <input type="checkbox"/></p> <p><i>If yes, accidental?</i> No <input type="checkbox"/> Yes <input type="checkbox"/></p> <p>Is patient at imminent risk of injuring self or others at home or in other settings? No <input type="checkbox"/> Yes <input type="checkbox"/></p> <p><i>If yes, is the family in crisis (unable to cope with managing the patient’s behavior)?</i> No <input type="checkbox"/> Yes <input type="checkbox"/></p> <p>Enlist home-based crisis services and consider partial or inpatient hospitalization.</p> <p>Is patient at risk <i>now</i> of hurting self or others in the office? No <input type="checkbox"/> Yes <input type="checkbox"/></p> <p><i>If yes, and if the patient has a history of I/PB and safety concerns outweigh risk of another escalation, consider safe escort to an emergency department. Notify the emergency department in advance of special needs.</i></p> <p>If safety permits, proceed with the practice pathway.</p>																																																					
3 <input type="checkbox"/>	<p>Review the patient’s history and level of functioning before and after the onset of I/PB.</p> <p>History</p> <p>Medical: Genetic disorder, preterm birth, epilepsy, brain injury, typical stooling pattern, chronic medical problems, as well as all medications and supplements taken</p> <p>Take lifetime history of all medication and, for psychotropic medications, obtain dosages, duration of treatment, and blood levels (when applicable)</p> <p>Developmental: Global delay or intellectual disability, specific learning disability, developmental age and adaptive functioning versus chronological age, toilet training, motor problems, sensory deficits and sensitivities</p> <p>Communication: Means of communication (verbal, sign or modified sign, communication tools), indicators of pain, means of learning new information, ability for functional communication</p> <p>Psychiatric: Previously diagnosed psychiatric disorder (eg, anxiety disorders including obsessive–compulsive disorder, ADHD, mood and psychotic disorders), treatments, activity level, preoccupations, special interests, stereotypies, transition problems, social reciprocity, typical responses of care providers to I/PB</p> <p>Current context</p> <p>Settings: Home (family home, group home in community, group home institutional, hospital), school (mainstream no accommodations, mainstream with accommodations, mainstream with resource, full inclusion, partial inclusion, self-contained special education, home instruction, early intervention at home, center)</p> <p>Caretaker characteristics: Two parents, single parent, foster, adoptive; primary language, ethnicity, recently immigrated psychiatric history, number of children in home, number of adults in home, case manager</p> <p>Functioning before and after onset of I/PB</p> <p>Loss of skills: Does the patient no longer exhibit skills used on a regular basis before onset of I/PB? No <input type="checkbox"/> Yes <input type="checkbox"/></p> <p>Interference with self-care and functioning at home <input type="checkbox"/> learning and participation at school or program <input type="checkbox"/> travel in public or out in the community <input type="checkbox"/> acceptance by peers <input type="checkbox"/> family and caregiver relationships</p>																																																					
4 <input type="checkbox"/>	<p>Prioritize for assessment and treatment on the basis of safety, severity, and impact on daily life</p> <p><input type="checkbox"/> Qualify I/PB target behaviors: acute or chronic, frequency and severity, episodic or continuous, discrepancy in behaviors across settings (eg, influenced by environment, caretaker, and task).</p> <p><input type="checkbox"/> Specifically assess for property damage or injury to self or others.</p> <p><input type="checkbox"/> Know how incidents have been handled and what has happened as a result.</p>																																																					
5 <input type="checkbox"/>	<p>Consider all potential contributors to I/PB.</p>																																																					
5a <input type="checkbox"/>	<p>Assess and address any current medical problems.</p> <p><input type="checkbox"/> Conduct a medical review of systems.</p> <p><input type="checkbox"/> Treat any pain, seizures, sleep, GI, ear/nose/throat, dental problems, or other medical conditions. Monitor I/PB after medical treatment is applied to determine whether problems may have been secondary to a medical condition.</p> <p><input type="checkbox"/> Consider the possibility of medications being responsible for I/PB.</p> <p><input type="checkbox"/> When a medication is suspected, consider stopping, decreasing, or switching to another agent in discussion with the prescribing provider or consulting with a colleague experienced in psychopharmacology in developmental disabilities, particularly when a patient is taking multiple medications.</p>																																																					
5b <input type="checkbox"/>	<p>Assess and address difficulties using functional communication: Evaluate the level of patient’s functional communication skills and whether I/PB may be related to difficulties communicating. <i>If yes:</i></p> <p><input type="checkbox"/> Make appropriate referrals for a speech and language evaluation to ensure incorporation of an adequate and functional communication system consistently across settings.</p> <p><input type="checkbox"/> Make appropriate referrals to psychologist or behavior analyst to include a communication component in a behavior treatment plan.</p>																																																					

TABLE 1 Continued

Step	Details
5c	<p>Assess and address any psychosocial stressors.</p> <ul style="list-style-type: none"> <input type="checkbox"/> Physical or sexual abuse. <i>If yes:</i> Consider specialist referral, contacting child protective services. <input type="checkbox"/> Bully victimization. <i>If yes:</i> Consider 504 accommodations in school to avoid exposure. <input type="checkbox"/> Parental stress. <i>If yes:</i> Consider referrals for financial or psychological assistance. <input type="checkbox"/> Poor match between the patient and his or her psychosocial context <input type="checkbox"/> Classroom or program characteristics. <i>If yes:</i> <input type="checkbox"/> Request classroom program change. <input type="checkbox"/> Family characteristics. <i>If yes:</i> <input type="checkbox"/> Consider parent training or other referrals.
5d	<p>Assess and address any maladaptive reinforcement patterns.</p> <ul style="list-style-type: none"> <input type="checkbox"/> Are there triggers for I/PB? Do caregivers react in a manner that may inadvertently reinforce I/PB? <i>If yes:</i> <input type="checkbox"/> Advise caregivers on how to respond to I/PB accordingly. If problems persist or are severe: <input type="checkbox"/> Make appropriate referrals to a psychologist or behavior analyst with specialization in functional behavioral assessment and treatment of I/PB.
5e	<p>Assess and address any co-occurring psychiatric disorders.</p> <ul style="list-style-type: none"> <input type="checkbox"/> Screen for co-occurring psychiatric disorders (in ASD most commonly anxiety, ADHD, obsessive–compulsive, mood and psychotic disorders). <input type="checkbox"/> For any screen-positive disorders (or others suspected), conduct or refer for more detailed diagnostic assessment. <input type="checkbox"/> As indicated, treat or refer for treatment of any co-occurring disorders with medications. <input type="checkbox"/> Cognitive–behavioral therapy conducted by a mental health provider with necessary expertise.
6	<p>Consider psychopharmacologic interventions for I/PB.</p> <ul style="list-style-type: none"> <input type="checkbox"/> When there is no current risk to safety or loss of educational placement, consider N-acetylcysteine and clonidine. <input type="checkbox"/> Under the following circumstances, consider risperidone or aripiprazole: <ul style="list-style-type: none"> <input type="checkbox"/> Safety is an issue. <input type="checkbox"/> Change in an otherwise satisfactory education or school placement will be necessary without treatment. <input type="checkbox"/> Other indicated interventions have resulted in no or incomplete improvement of behavior that continues to interfere with daily function. <input type="checkbox"/> I/PB is judged to be unrelated to medical conditions, communication difficulties, psychosocial stressors, or maladaptive reinforcement patterns or <input type="checkbox"/> Lower-risk interventions cannot be implemented.
7	<p>Develop the individualized treatment and safety plan: Coordinate an individualized treatment plan for patient based on information gathered from steps 5a–5e, taking preferences of care providers and feasibility of implementation into account.</p>
8	<p>Implement and monitor the treatment plan: After beginning to implement treatment plan, monitor with regular visits based on the severity and frequency of the I/PB behavior.</p> <ul style="list-style-type: none"> <input type="checkbox"/> Clear and measureable treatment goals should be established. <input type="checkbox"/> Carefully track response to intervention as determined by report of caregivers, direct observation, and objective rating scales, such as the ABC or longitudinal behavioral data from the school or home setting. <input type="checkbox"/> Expect improvements within 4–8 wk.
9	<p>At 3 mo do symptom(s) persist? <i>If yes:</i> Restart assessment and revise treatment plan.</p>
10	<p>Reevaluate every 3 mo thereafter.</p> <ul style="list-style-type: none"> <input type="checkbox"/> Enrich positive behavioral support plan and address quality of life goals. <input type="checkbox"/> After a 12-mo symptom-free period, consider tapering or discontinuing any medications used for the treatment of I/PB behavior. <input type="checkbox"/> Positive behavioral supports, communication aides, and psychosocial supports should be left in place.

provides more detail on each step of the pathway, and the narrative provides a summary of the literature and clinical rationale for each step. Supplemental Table 2 provides information about measures potentially useful in primary care. The pathway assumes that the diagnosis of ASD is not in question and that the child is ≥ 3 years old. The Autism Speaks Challenging Behaviors Tool Kit can be helpful in discussing I/PB with a family for the first time (<https://www.autismspeaks.org/family-services/tool-kits/challenging-behaviors-tool-kit>).

Step 1. Assess for I/PB

Because I/PB is so prevalent in patients with ASD, inquire routinely

as to whether any I/PB has occurred recently or since the last visit (Table 1). Accord more weight to caregiver descriptions than to office observations because the medical office is a nonroutine setting that may elicit atypical reactions from the patient (eg, unusual withdrawal or agitation). If office staff are aware that I/PB is among the reasons prompting the visit, scheduling the patient’s appointment so as to minimize waiting time and sending relevant forms to the caregiver to complete in advance can be helpful.

For clinical purposes, I/PB may be considered severe when it occurs more frequently in the patient than in peers in the same setting, regularly

interferes with learning, functioning, and relationships, or poses a risk to safety. I/PB may be regarded as mild to moderate when it occurs more frequently than in peers but only intermittently disrupts learning, functioning, and relationships and does not pose a safety risk. Even when only mild to moderate, I/PB must still be assessed and addressed to prevent the I/PB from becoming more entrenched, difficult to treat, and potentially unsafe.

Step 2. Assess Safety

Based on caregiver and school or program reports, assess whether the patient is at imminent risk of doing harm to self or others. If so, this acute situation warrants immediate

intervention. With knowledge of the family and patient, the PCP is in a unique position to assess whether the family is in crisis, which happens when the demands of the behavior exceed their present ability to cope.¹⁴ In some states, crisis services for patients with developmental disabilities or mental health conditions can be called on to provide acute interventions (eg, in-home behavioral management or respite) to support the patient and family in the community while admission to more intensive services (eg, partial or inpatient hospitalization) is being considered, preferably to a program or unit that has staff trained to serve this population.

Severe I/PB that is sometimes exhibited in the office setting often reflects a fear reaction and impulse to flee or to fight. Whenever possible, avoid physical restraint, avoid excessive talking that may overwhelm the patient's verbal abilities, use visuals or concrete language, and direct the patient to a dimly lit, quiet, safe space, if available. Consider escort to an emergency department only if the patient does not calm down and has a history of I/PB and if the need for safety outweighs the risk of escalation in the emergency department. If possible, notify the emergency department in advance so that staff can prepare for the patient's special needs.

Step 3. Review the Patient's History and Level of Functioning Before and After the Onset of I/PB

Review the patient's developmental, medical, and psychiatric history, as well as caretaker and home environment characteristics.^{2,15,16} Information on the patient's typical level of functioning (eg, adaptive skills, academic performance) before onset of I/PB, and functioning since the onset of I/PB, is needed to interpret

the significance of I/PB, to set attainable goals, and to monitor response.¹⁶ The comparison of current functioning with that before the onset of I/PB can be a good indicator of the possible impact on learning and maintenance of previously acquired skills.

Step 4. Prioritize and Qualify Specific Behaviors for Treatment

In the case of >1 problem behavior (eg, aggression and property destruction), prioritize for treatment based on the threat to safety and severity, as defined in Step 1. Aggression toward other people or self-injurious behaviors require priority. Frequent tantrums can also seriously affect child and caregiver well-being and may also represent precursor behaviors to aggression that represent a more realistic starting point for treatment.

All available sources should be used to obtain a detailed history of the specific behaviors that will be addressed and monitored during treatment. For each behavior, establish when it began, whether the onset was sudden or insidious, as well as where and when the concerning behaviors happen most frequently. Inquire as to how caregivers in different settings typically respond to the behavior and how the patient behaves if caregivers do not provide their typical response. Obtain details about whether the behavior is episodic or continuous, its frequency and typical duration, and what, if anything, seems to trigger the behavior. These parameters will form the basis of monitoring response to treatment, regardless of modality.

Step 5. Consider All Potential Contributors to I/PB

Step 5a. Assess and Address Any Current Medical Problems

A contribution of medical conditions to I/PB should be strongly considered if the behaviors are new in onset or the child has a past

history of medical problems.¹⁷ Focus on current signs and symptoms and review all current and recently discontinued medications and supplements. A complete, rather than a targeted, review of systems may be necessary, especially when the child is nonverbal. The physical examination should be thorough because children with ASD may be unable to localize symptoms or describe them in words.^{16,18} Children with ASD commonly experience all of the usual childhood illnesses and problems, although they may present differently in a child who cannot describe symptoms. Recent reviews describe behaviors indicative of gastrointestinal (GI) dysfunction¹⁹ and dental orofacial pain²⁰ in children with ASD. A recent case series suggests that addressing concomitant painful or distressing medical conditions in patients with ASD and acute or severe I/PB predicts enhanced response to treatment.²¹

Sleep Problems: Sleep problems occur more frequently in patients with ASD than in typically developing patients and are strongly associated with daytime I/PB, among other problems.²² Although more research is needed, many clinicians have anecdotal experience with improvement in I/PB after treatment of sleep problems.²² Promotion of sleep hygiene in children with sleep problems should be prioritized.²³ The ATN has a useful packet to help parents improve their child's sleep habits (<https://www.autismspeaks.org/science/resources-programs/autism-treatment-network/tools-you-can-use/sleep-tool-kit>). A recent systematic review and meta-analysis of melatonin treatment in ASD found significant improvements in sleep duration and sleep onset latency but not in nighttime awakening.²⁴ Nighttime awakening may be a sign of a variety of conditions,

including primary sleep disorder (eg, parasomnias, circadian rhythm sleep–wake disorders), co-occurring medical conditions (seizures, sleep apnea, gastroesophageal reflux), or psychiatric disorder (particularly mood disorders). These conditions may need specialist evaluation and treatment of their own sake.

GI Dysfunction: A recent meta-analysis found a higher prevalence of GI symptoms among children with ASD compared with pediatric controls, particularly diarrhea, constipation, and abdominal pain.²⁵ A recent study documents a relationship between GI symptoms and irritability in children with high-functioning ASD.²⁶ Recommendations for the evaluation and treatment of common GI problems in the ASD population are available.¹⁹ Expert clinical consensus suggests that treating GI problems can lead to improvement in I/PB,¹⁹ but more research is needed.

Epilepsy and Epileptiform Abnormalities: A recent review²⁷ describes the complex relationship between epilepsy, epileptiform abnormalities on EEG, and behavior in ASD. Studies using rigorous diagnoses of ASD and behavioral measures are rare. A recent small case series of children with ASD and epileptiform abnormalities found no difference in I/PB between patients with and without EEG abnormalities, but those with seizures had significantly worse I/PB than their peers without seizures.²⁸ As noted by Fung et al⁹ and others,²⁹ evidence that anticonvulsants diminish I/PB is inconsistent.

Medication Side Effects: Children with ASD can be sensitive to psychoactive medications, which are sometimes responsible for I/PB.^{2,16,30} For example, first- or second-generation neuroleptics and selective serotonin reuptake inhibitors can cause akathisia, a subjectively unpleasant sense

of motor restlessness that can be abrupt or insidious, may fluctuate during the day, and typically affects the lower extremities. Several prescription medications, including stimulants, phosphodiesterase inhibitors, muscle relaxants, and a number of antiepileptic medications, can increase irritability, decrease impulse control, or adversely affect mood. Serotonin reuptake inhibitors and benzodiazepines can cause disinhibition or behavioral activation that can present as I/PB. Antihistamines and other medications with anticholinergic properties can cause confusion or frank delirium that leads to I/PB. Other over-the-counter medications, such as pseudoephedrine or dextromethorphan, and complementary and alternative medicines, may also trigger acute behavioral changes. Importantly, abrupt withdrawal of medication can also trigger I/PB.^{2,16,30}

When present, specific treatment of any medical or medication-related problems should be added to the treatment plan.

Step 5b. Assess and Address Difficulties Through Functional Communication

The patient with ASD who lacks a functional communication system may exhibit I/PB as a manifestation of frustration or as a means of communication.^{31,32} I/PB may rapidly diminish when the patient is provided with a more efficient and effective system of communicating.^{33,34} If the patient does not have consistent access to and use of an adequate communication system across settings, the treatment plan should include evaluation by a speech language pathologist, either in the school as part of the child's Individualized Education Program or in the community setting by medical referral, to identify and

facilitate appropriate expressive communication interventions.¹⁶ As indicated, specific communication strategies (Picture Exchange Communication System, sign language) or augmentative and alternative communication devices (dedicated devices and tablet apps³⁵), and literacy instruction³⁶ should be considered.

Step 5c. Assess and Address Any Psychosocial Stressors

Abuse: Children with developmental disabilities are at elevated risk of physical and sexual abuse.^{37,38} Both types of abuse are associated with problem behavior.³⁸ Based on knowledge of the patient and family, the PCP is in the best position to differentiate accidental injury from deliberately inflicted tissue damage that is due to abuse, the latter necessitating involvement of protective services. People with ASD are more vulnerable to being sexually abused or victimized.³⁹ The assessment of possible sexual abuse in the child with ASD can be complex and, absent clear-cut evidence on physical examination, involves consideration of multiple factors often necessitating the expertise of colleagues specializing in that area.⁴⁰

Bully Victimization: Elementary and middle school students with ASD are at higher risk for repeated bully victimization than children having other disabilities, which may actually be a bigger problem for higher-functioning children who are more mainstreamed at school.^{41,42} Few studies have been conducted on this topic, but 1 cross-sectional study found that victimization was associated with internalizing problems (anxiety, depression) in children with ASD.⁴³ The PCP can help identify this problem for the school and advocate for interventions to prevent bullying. Importantly, not all negative peer experiences result from bullying, and social isolation and more subtle forms of

peer rejection can also be significant stressors.

Parental Stress: A recent longitudinal study found that parental general distress related to parenting a child with special needs predicts tantrums, aggression, noncompliance, and self-injurious behavior (among other behavior problems), with only modest evidence of a bidirectional relationship.⁴⁴ Participation in psychoeducational, supportive programs⁴⁵ may reduce parental stress and improve mental health.⁴⁶ The PCP can help support parents in distress, including linking them to ASD support groups and referring them to get help for their own mental health needs.⁴⁷

Poor Match Between the Environment and the Patient: A different type of psychosocial stressor can arise when the home, school, or other environment does not provide sufficient structure or fails to meet the emotional needs of the child based on developmental age, leading to chronic frustration, manifested as I/PB.⁴⁸ An example would be the patient with ASD who is verbal and placed in a classroom with mostly nonverbal classmates, or vice versa. The PCP can be an important advocate for the patient in drawing the attention of parents and educators to this kind of mismatch and asking them to consider a different, more appropriate placement.

Step 5d. Assess and Address Any Maladaptive Reinforcement Patterns

In many cases, I/PB is occasioned by events in the environment and serves a specific reinforcing function for the patient. For example, problem behaviors may be triggered when the patient is presented with a difficult task. This behavior might then become reinforced if the care provider gives the patient a break or redirects him to a different

activity. Functional behavioral assessment of I/PB is designed to identify variables that occasion and maintain I/PB symptoms (as reviewed^{4,49-51}). The most commonly reported behavioral functions for I/PB include access to attention, access to tangible rewards, escape from tasks or demands, and apparent sensory reinforcement (inferred when these behaviors occur across situations independent of consequences). Recent reviews have found that behavioral interventions based on understanding of the function of I/PB are highly effective in producing a consistent decrease in aggressive or self-injurious behavior in ASD.^{49,51} Even without changing the response to the behavior itself, specific events and antecedents that commonly precede I/PB, such as unstructured times or transition from preferred to nonpreferred activity, can often be addressed by using environmental supports and introducing structure such as visual schedules or predictable routines. Additional detail on functional behavior analysis and treatment is provided at <http://www.kennedykrieger.org/patient-care/patient-care-programs/inpatient-programs/neurobehavioral-unit-nbu/applied-behavior-analysis>. The ATN has also developed a guide for parents on applied behavior analysis (<https://www.autismspeaks.org/science/resources-programs/autism-treatment-network/atn-air-p-applied-behavior-analysis>).

PCPs can often identify what events precede and what consequences follow I/PB, based on interviews of parents or care providers.⁵² Even without a specific understanding of antecedents and consequences, PCPs can educate care providers about general and basic behavioral management techniques, including reinforcement of positive behaviors, and guidance on

how to create a well-structured, engaging environment. When necessary, referral should be made to an experienced behavior analyst or mental health expert for comprehensive functional behavior assessment in the home.¹⁶ If these behaviors occur at school, collaboration and coordination with the school are encouraged. Specifically, PCPs can inform parents and the school that a form of functional behavior assessment by the school is required by the 1997 amendments to the Individuals with Disabilities Education Act for students who exhibit problem behavior at school in the United States.⁵³ Behavioral interventions emerging from functional assessments should be added to the treatment plan. These will typically emphasize removing inadvertent reinforcement and teaching socially appropriate replacement behaviors.

Step 5e. Assess and Address Any Co-occurring Psychiatric Disorders

Co-occurring psychiatric disorders are highly prevalent in ASD. Irritability is a core or associated clinical feature of many psychiatric disorders and may be the primary presentation of such disorders in patients with ASD, particularly those who are nonverbal. Therefore, a psychiatric differential diagnosis of I/BP is in order whenever a patient presents with new onset or markedly worsened I/PB. The disorders to be considered include those known to occur at elevated rates in ASD: attention-deficit/hyperactivity disorder (ADHD), anxiety disorders, and obsessive-compulsive disorder, which typically present first in childhood, as well as episodic mood disorders (depression and mania) that typically begin in adolescence or early adulthood.⁵⁴ Importantly, although the newly described *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) diagnosis of disruptive mood dysregulation disorder¹ includes

core behaviors of severe, recurrent temper outbursts and persistent irritable mood, this diagnosis should rarely, if ever, be diagnosed in patients with ASD because the DSM-5 specifies that it does not apply when symptoms are better explained by another disorder, including ASD. As with co-occurring medical conditions, treatment of any co-occurring psychiatric disorder in the patient with ASD is indicated both because it may directly diminish I/PB and because it may enhance response to other interventions, as suggested by a recent case series of psychiatric inpatients with ASD.²¹

Assessment for co-occurring psychiatric disorders should account for the child's intellectual and communicative abilities, symptoms typical of ASD, and developmentally normative behaviors.^{16,30} Depending on local options, evaluation and treatment of other co-occurring psychiatric disorders are often referred to a mental health expert experienced in ASD, with the exception of ADHD. Most PCPs have experience managing ADHD in the general pediatric population and can refer to the ATN practice pathway for guidance regarding evaluation and choice of medications, primarily including stimulants and α -agonists, in the ASD population.⁵⁵ In other circumstances, PCPs may be called on to manage other psychiatric disorders when a referral is not immediately available, in which case they should refer to the literature regarding special considerations in the assessment and treatment of psychiatric disorders in children with ASD (see for a review^{30,56}). Unfortunately, outside of ADHD there is little evidence for treatment of co-occurring psychiatric disorders in ASD. One exception is data supporting cognitive behavioral therapy for anxiety disorders⁵⁷; however, this specialized treatment may not be broadly available and must be adapted to the individual's

capabilities. With regard to other psychiatric disorders, it is reasonable to adapt treatments with evidence in the general pediatric population.⁵⁸⁻⁶⁰ If medications are used, it is important to recognize that adverse events are likely to be more common in ASD, including activation and disinhibition from serotonin reuptake inhibitors⁶¹ and irritability from stimulants,⁶² so "start low and go slow."

Step 6. Consider Psychopharmacologic Interventions for Severe I/PB

In most cases, targeted psychopharmacologic interventions for I/PB should be considered only after any contributing factors are assessed and addressed. In the case of severe I/PB that is acutely or imminently unsafe, targeted psychopharmacologic intervention should be considered even while contributing factors are being evaluated. In a systematic review of the efficacy and safety of pharmacologic treatments for severe I/PB in children with ASD, risperidone and aripiprazole had the strongest evidence in reducing Aberrant Behavior Checklist Irritability Subscale (ABC-I) scores, but with adverse effects including somnolence or sedation, weight gain, and extrapyramidal symptoms such as tremor, dyskinesia, akathisia, and rigidity.⁹ Additional adverse effects of the neuroleptics mentioned earlier include urinary retention, constipation, insulin resistance, dyslipidemia, hyperprolactinemia, hematologic abnormalities, QTc prolongation, seizures, and neuroleptic malignant syndrome. These potential adverse effects must be monitored closely with frequent follow-up, laboratory testing, electrocardiogram, and assessment for movement disorders.⁶³ Ameis and colleagues⁶³ provided a more detailed discussion of monitoring of atypical neuroleptics in ASD.

Given the risks and benefits, atypical neuroleptics such as risperidone and aripiprazole therefore should be used to treat severe I/PB in ASD only in the following situations: safety is an issue; the behaviors interfere with current functioning to the degree that a change in school or residential placement will be necessary without treatment; other indicated interventions have resulted in no or incomplete improvement of behavior that continues to interfere with daily function; I/PB is judged to be unrelated to psychosocial stressors, communication difficulties, underlying medical or psychiatric conditions, or environmental factors; or lower-risk interventions cannot be implemented. Families sometimes struggle with the choice of whether to use medication for their child, and the ATN Medication Decision Aid can help PCPs and families work together to weigh the potential benefits and risks (<https://www.autismspeaks.org/science/resources-programs/autism-treatment-network/tools-you-can-use/medication-guide>).

As noted by Fung et al,⁹ single studies of N-acetylcysteine and clonidine showed significant efficacy in reducing ABC-I scores and did not cause significant side effects in the areas assessed. Although replication of these studies is needed to confirm the findings, N-acetylcysteine and clonidine might be considered for treatment of I/PB in ASD when atypical antipsychotics are deemed inappropriate.

Step 7. Develop the Individualized Treatment and Safety Plan

The treatment plan for I/PB should address the individual needs of the patient with ASD based upon an evaluation of all potentially contributory factors. With rare exception, the treatment of potentially contributory medical

or psychiatric conditions should be a top priority because if left untreated or undertreated, these conditions may interfere with other interventions. The individualized treatment plan will also take account of factors that may limit the ideal treatment plan (eg, limited access to specialists, insurance problems, and limited family resources for implementing the plan).

As per the 2007 American Academy of Pediatrics report,² PCPs should prescribe only psychotropic medications with which they have sufficient expertise, including knowledge of indications and contraindications, dosing, potential adverse effects, drug–drug interactions, and monitoring requirements. When consultation is needed, telephone consultation services such as the Massachusetts Child Psychiatry Access Project are available in some states.⁶⁴ Primary care clinicians have found these services helpful in supporting management in the primary care setting. Before embarking on treatment, it is important to work with the family to develop an emergency plan that outlines what to do if the child's behavior suddenly deteriorates during treatment and needs immediate attention. This includes identifying behavioral interventions that may deescalate the child, administering medications, calling 911, or going to the nearest emergency department.⁶⁵ Encourage parents to review this plan with family, other caregivers, therapists, and school staff. In situations where I/PB are severe, the local police department should also be informed of the child's ASD diagnosis and behavioral risk to allow response preparation.

Step 8. Implement and Monitor the Treatment Plan

This step should occur at least monthly during office visits

and, as needed, with phone contact between visits. Carefully track response to intervention. Treatment response should be determined by caregiver report and direct observation of the behavior by teachers or other providers. Objective rating scales, such as the ABC,⁶⁶ or longitudinal behavioral data based on observations in the school or home setting can help determine effectiveness of treatment. Clear and measurable treatment goals should be established (eg, reduction in frequency of aggressive outbursts by a specific number or reduction in duration of outbursts by a specific time). If atypical neuroleptics are to be used, the guidelines for monitoring presented by Ameis and colleagues⁶³ can be useful.

Step 9. At 3 Months, Do Symptoms of I/PB Persist?

Some benefit and improvement should be expected within ~4 to 8 weeks; however, a longer time window may be necessary to track less frequent behavior. If clinically significant symptoms persist at 3 months, reassess for all contributing factors, and revise the treatment plan. If no clinically significant symptoms persist at 3 months, continue to enrich positive behavioral support plans and address quality of life goals.

Step 10. Reevaluate Every 3 Months Thereafter

After a symptom-free period of ≥ 12 months, consider gradually tapering or discontinuing any psychotropic medications used for treatment of I/PB. Importantly, it is advisable to wait for a stress-free period to do this, even if this means prolonging medication treatment past 12 months. Positive behavioral supports, communication aides, and psychosocial supports should be left in place.

DISCUSSION

The pediatric PCP is in an important position to identify and initiate treatments for I/PB in the patient with ASD independently or in collaboration with other providers. No other provider in the patient's life combines the medical expertise and first-hand knowledge of the individual patient's health and development. The practice pathway is most likely to be efficient and effective in generating a treatment plan if it is systematically followed and the specific combination of individual contributing factors is identified for each patient. Importantly, evaluation and individualized treatment of I/PB, as outlined in the practice pathway, are an iterative process that may require an extended initial visit and will probably be refined over subsequent visits.

Inasmuch as this practice pathway is necessarily broad in its scope, it is limited in its detail. The pathway draws on different aspects of treatment models proposed for people with developmental or intellectual disabilities such as the neurobehavioral model,^{67–70} which describes the tandem usage of psychiatric assessment and applied behavioral analysis for the treatment of severe problem behavior. A recent article by Minshawi et al⁷¹ provides a similar approach to the treatment of self-injurious behavior, specifically in ASD. In contrast with such detailed reviews, however, the practice pathway presented here is designed to assist PCPs with initiating and coordinating interventions in the primary care setting. Although this pathway has not yet been tested in the primary care setting, the balance of evidence and clinical consensus that informs this pathway supports the premise that careful multifactorial assessment and treatment planning maximize the efficiency and effectiveness

of treatment for I/PB while minimizing risks for the individual patient.

CONCLUSIONS

The pediatric PCP caring for the patient with ASD and I/PB is in a unique position to initiate the development of an individualized treatment plan based on the combination of contributory factors in that patient and implement the plan

in collaboration with parents, schools, and other providers.

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ABBREVIATIONS

ABC: Aberrant Behavior Checklist
ADHD: attention-deficit/hyperactivity disorder
ASD: autism spectrum disorder
ATN: Autism Treatment Network
DSM-5: *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
GI: gastrointestinal
I/PB: irritability and problem behavior
PCP: primary care provider

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Irritability and Problem Behavior in Autism Spectrum Disorder: A Practice Pathway for Pediatric Primary Care

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Irritability and Problem Behavior in Autism Spectrum Disorder: A Practice Pathway for Pediatric Primary Care

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