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Management of Self-Injurious Behaviors in Children with Neurodevelopmental Disorders—A Pharmacotherapy Overview

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Abstract

Neurodevelopmental disorders (NDDs), a group of disorders affecting approximately 1% to 2% of the general population, are caused by changes in brain development that result in behavioral and cognitive alterations, sensory and motor changes, and speech and language deficits. Neurodevelopmental disorders encompass a heterogeneous group of disorders including, but not limited to, Smith-Magenis Syndrome, Lesch-Nyhan Disease, Cri du Chat Syndrome, Prader-Willi Syndrome, Pervasive Developmental Disorders, Fragile X Syndrome, Rett Syndrome, Cornelia de Lange Syndrome, and Down Syndrome. Self-injurious behaviors are common in children with NDDs; depending on the specific NDDs, the incidence of self-injurious behaviors is nearly 100%. The management of self-injurious behaviors in this population is complex, and little high-quality data exist to guide a consistent approach to therapy. However, managing self-injurious behaviors is of the utmost importance for the child as well as the family and caregivers. Behavior therapies must be implemented as first-line therapy. If behavioral interventions alone fail, pharmacotherapy becomes an essential part of management plans. The limited available evidence for the use of common pharmacologic agents, such as second-generation antipsychotics, and less common agents, such as clonidine, n-acetylcysteine, riluzole, naltrexone, and topical anesthetics is

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reviewed. Additional data from well-designed studies in children with NDDs are needed to gain a better understanding of this common and troublesome problem, including efficacy and safety implications associated with pharmacotherapy. Until then, clinicians must rely on the limited available data, clinical expertise, and ongoing, systematic monitoring when managing self-injurious behaviors in children with NDDs.

Keywords

Self-injurious behaviors; neurodevelopmental disorders; pharmacotherapy; children; pediatrics

Self-injurious behaviors (SIBs) are non-normative behaviors performed with the intent of physical self-harm but without the intent to die.[1] Self-injurious behaviors include self-directed repetitive actions such as biting, hitting, head and limb banging, face slapping, hair pulling, and eye poking, which can result in severe injury and represent a troubling problem for patients and caregivers alike.[2,3] SIBs can occur in two groups of individuals: (i) those with psychopathologic conditions such as depression, borderline personality disorder, and eating disorders, which typically involve nonsuicidal self-injury such as cutting, and (ii) those with neurodevelopmental disorders (NDDs), which involve the behaviors described above.[1] This review focuses on SIBs specific to children with NDDs.

NDDs, defined as disorders caused by changes in early brain development resulting in behavioral and cognitive alterations, changes in sensory and motor systems, and speech and language deficits, affect roughly 1% to 2% of the population.[4-8] The prevalence and expression of SIBs in children with NDDs is variable. A comprehensive discussion of all NDDs is outside the scope of this review; however, a brief description of select childhood-related NDDs and associated SIBs is included for completeness (Table 1).[1,2,9-28]

Several risk factors have been identified for the development of SIBs in children with NDDs including severity of disease, language deficits, deficiencies in daily living skills, concomitant overactivity and impulsivity, sensory and motor impairments, repetitive behaviors, sleep disturbance, and, most significantly, the degree of intellectual disability.[1-3,29] Other contributing factors may include comorbid medical conditions such as urinary incontinence, pain, constipation, headache, menstruation, and depression.[15,30] SIBs may be observed as early as 6 months of age in children with NDDs, gaining full expression by the age of 5 years, and may persist life-long.[4-8] The impact of SIBs on the patient as well as caregivers is profound, with SIBs commonly reported as one of the most negative influences on quality of life.[7,8] Clinical, social, financial, and emotional burdens are high.[31] Patients, caregivers, and clinicians, alike, are regularly desperate for relief and solutions.

The underlying etiology and pathophysiology of SIBs in children with NDDs are poorly understood and may vary between NDDs. Several theories have been purported, though a direct link to SIBs has not been conclusively elucidated. One theory involves the concept of environmental impoverishment.[2] Children with NDDs often have impaired communication, which leads to socialization deficits and a lack of stimulation from the environment. The resulting social and environmental isolation promotes the expression of SIBs, perhaps as a means of communication, attention seeking, and social reinforcement.[1-3] SIBs may occur as

a means of escaping nonpreferred activities (i.e., negative reinforcement), to gain access to attention and/or preferred activities (i.e., positive reinforcement), or for its own consequences (i.e., automatic reinforcement); attention and escape are the most commonly identified functions of SIBs.[32] Other theories include physical discomfort and illness, state of over-arousal which is exacerbated by environmental stimuli, sensory reinforcement, disruption in the pain-endogenous opioid system, and alterations in neurotransmitters such as dopamine, serotonin, gamma-aminobutyric acid (GABA), and glutamate.[33-35]

The management of SIBs is complex, and the optimal approach to therapies (nonpharmacologic and pharmacologic) is not well-defined. Little high-quality evidence exists to guide a consistent therapeutic approach. The majority of knowledge pertaining to the management of SIBs comes from data in individuals with autism spectrum disorder (ASD), rather than other specific NDDs. Additionally, available assessment measures and objective scales to evaluate SIBs commonly evaluate problem behaviors (e.g., aggression, irritability, tantrums, and SIBs) in aggregate rather than SIBs specifically, although each type of behavior has distinct features that may require different treatment approaches.[8,16] Despite these clinical challenges, SIB management is necessary due to the severity and impact of SIBs on the quality of life, and pharmacotherapy often becomes a necessary part of the treatment plan.

This article provides an overview of pharmacologic approaches available in the management of SIBs associated with NDDs. Relevant information was identified through PubMed via a structured literature search using relevant search terms (Supplementary Table 1). Given the scarcity of research on the pharmacologic management of SIBs and the heterogeneity of study designs, the intent was not to perform a systematic review or meta-analysis. Rather, a narrative summary of available evidence supporting select therapies is presented. A review of studies reporting outcomes for both irritability as well as SIBs are included due to the difficulty in teasing out reported outcomes specific to SIBs alone. When possible, specific theories pertaining to each presented pharmacologic agent as well as disease-specific information is included.

General Approach to the Assessment, Evaluation, and Management of SIB in Children with NDDs

General knowledge of commonly used assessments and objective evaluation tools is important for managing patients with SIBs, as it allows for interpretation of the literature, application to practice, choice of therapy, and determinations of therapeutic response. Applied behavior analysis (ABA) is a systematic approach to behavior intervention.[36] Functional behavioral assessment (FBA), the most common application of ABA to the assessment of SIBs, helps determine physical and social environmental causes of specific behaviors as well as frequency, duration, and contributing comorbidities and identification of a function-based behavioral treatment.[30,37,38] FBAs include procedures such as interviews, informal observations, or functional analyses of SIBs.[38,39] Objective tools most commonly used in the evaluation of irritability and SIBs include the Clinical Global Impressions Scale (CGI) and the irritability subscale of the Aberrant Behavior Checklist (ABC-I). The CGI

refers to two physician-rated, 7-point scales used to quantify overall symptom severity (CGI-S) and clinical improvement from baseline (CGI-I).[40] In ABC-I assessments, parents or teachers rate irritability based on 15 items using a 4-point scale, which evaluates aggression, tantrums, unstable mood, and self-injury.[40,41] An updated version of the global ABC scale, referred to as the ABC-C, is also available, and is intended to be more applicable to home and school settings.[42] These objective tools are cited as outcomes in several of the studies referenced in this review.

The general approach to assessing and managing SIBs in children with NDDs should be done in concert with a multidisciplinary team and involves a stepwise approach as follows:[8]

1. Perform a comprehensive medical history and examination that assesses patient safety, level of functioning, and specific behaviors.
2. Identify, rule out, and address all contributing factors to behaviors.
3. Perform ABA and FBA.
4. Implement nonpharmacologic management and behavioral interventions.[16]
5. Initiate pharmacologic intervention.

Nonpharmacologic Management

The American Academy of Pediatrics designated the prescription of behavioral treatment based on the results of a FBA as “best practice”.[18] Results of FBA lead to function-based, patient-specific treatment programs that determine aspects of the environment warranting change in order to reduce SIBs.[43] For example, if a child engages in SIB to escape from academic demands, a function-based approach would involve delivering escape from the demand contingent on a communication request (e.g., “break please”). A nonfunction-based approach would involve time out or contingent removal of the demand when SIBs occurs. Function-based behavioral treatments are more effective than nonfunction-based interventions, resulting in decreased use of punishment-based procedures.[44] The types of nonpharmacologic approaches are a critical component of the treatment plan for SIBs. When behavioral interventions alone fail to control SIBs, pharmacologic therapies can be considered; when implemented, pharmacotherapy must be combined with the existing behavioral interventions for optimal benefit.

Pharmacologic Therapies

The majority of pharmacotherapy prescribing occurs off label, based upon a paucity of robust evidence, clinical judgement on a case-by-case basis, and with an ongoing systematic approach to monitoring and justification of therapy. As the precise pathophysiology of SIBs is yet to be defined, available pharmacotherapy primarily targets symptoms rather than the mechanism of disease.

Importantly, the available evidence for pharmacotherapies that target SIBs specifically is limited to lower levels of evidence. Well-designed studies are critically needed to better support pharmacotherapeutic decisions in practice. And, the majority of studies are

performed in patients with ASD with subsequent extrapolation and application to other NDDs. When implementing pharmacotherapy, these factors may affect clinical response, yet the risks of therapy likely still apply. Despite these limitations, the use and reliance on pharmacotherapy is common in practice.

Therefore, the choice of therapy must be determined using clinical judgement on a case-by-case basis (i.e.., interpatient variability is high) accounting for factors such as cause, type and severity of SIBs, the child's medical history and developmental age, pharmacokinetic and pharmacodynamic properties of medications, drug-drug and drug-disease interactions (e.g., sedation from multiple medications with central nervous system depression actions), and available and applicable efficacy and safety data.[45] Once initiated, pharmacotherapy must be methodically monitored for individual response and ongoing rationale for continuation of therapy. In instances where the agent does not demonstrate a clear benefit, it should be discontinued. Appropriate therapy alterations must be made based on the patient's responses to therapy over the course of ongoing development and changes in clinical status.

To help clinicians faced with making difficult clinical decisions pertaining to the implementation of pharmacotherapy, the discussion below presents select pharmacologic agents (Table 2)[12,13,33,34,40,46-67] with available supporting data in the management of SIBs in children with NDDs. The order presented does not reflect a treatment sequence; data supporting monotherapy is presented first then followed by evidence supporting dual therapy. Attempts have been made to present the highest level of evidence available for each agent. The studies selected for inclusion report SIBs-specific outcomes data. In studies that report SIBs data plus additional end points, summaries are provided for the benefit of the reader. When reviewing the data presented, readers should cautiously consider the strength of each piece of evidence when determining individual applicability. Additionally, statistical significance versus clinical significance should be considered. Numerical differences in outcome measures correlating to clinical significance are not universal nor well defined in the literature; rather, clinical significance must be considered on a case-by-case basis dependent upon symptom severity, individual response, and goals of care. Depending on the therapy, benefits may outweigh the risks of long term use or vice versa. The data presented is intended to be used by clinicians to guide individualized, patient-centered decisions.

REVIEW OF AVAILABLE DATA: MONOTHERAPY

SECOND-GENERATION ANTIPSYCHOTICS

Although there are no medications approved by the United States Food and Drug Administration (FDA) specifically for treatment of irritability and SIB secondary to NDDs, the second-generation antipsychotic (SGA) agents are commonly viewed as "first-line therapy". This is owing to the body of supporting literature and FDA approval for irritability associated with ASD in children and adolescents. Although well-designed randomized controlled trials support the use of SGAs, no head-to-head comparisons exist to prove these agents are superior to other pharmacologic interventions for the treatment of SIB. Risperidone and aripiprazole gained FDA approval for the symptomatic management (aggression, self-injury, and temper tantrums) of children and adolescents with ASD in 2006 and 2009, respectively.[68] In a recent systematic review and meta-analysis, 11 randomized

controlled trials of several pharmacologic agents used for the treatment of severe irritability and problem behaviors in children with ASD were analyzed.[16] Compared to placebo, risperidone and aripiprazole significantly improved ABC-I scores (Cohen's d for efficacy: d = 0.9 and 0.8, respectively). A review of select studies and practical points is included below.

Risperidone—In an 8-week, placebo-controlled trial, risperidone (0.25 mg/day for patients < 20 kg; 0.5 mg/day for patients ≥20 kg) was compared to placebo in 101 children and adolescents with ASD.[46] Doses were titrated to clinical response (mean dose 0.06 mg/kg/day). Scores on the ABC-I subscale were significantly reduced in the risperidone group (−56.9%) from 26.2±7.9 at baseline to 11.3±7.4 at 8 weeks compared to reductions in the placebo group scores (−14.1%) from 25.5±6.6 at baseline to 21.9±9.5 at 8 weeks, p<0.001. Adverse effects included weight gain, increased appetite, fatigue, drowsiness, dizziness, and drooling. In an open-label extension of this study, 63 patients were treated with risperidone (mean dose 0.05-0.07 mg/kg/day) for up to 4 to 6 months.[47] Sustained efficacy and acceptable tolerability were demonstrated, with increased appetite, weight gain, fatigue, and drowsiness as the most commonly reported adverse effects.

In another 8-week, placebo-controlled study, 55 children with pervasive developmental disorders (PDD) were randomized to receive risperidone 0.02 to 0.06 mg/kg/day given once or twice daily and titrated to clinical response (mean dose 0.05 mg/kg/day) or placebo.[48] Risperidone led to a significant reduction in the ABC-I subscale score, with a mean change (standard deviation (SD)) of −13.4 (1.5) compared to −7.2 (1.4) in the placebo group (6 point difference, p<0.05). Somnolence was the most frequently observed adverse effect in the risperidone group (74% vs 7% in placebo group).

Aripiprazole—In an 8-week, multicenter, randomized, double-blind, placebo-controlled trial, aripiprazole at doses of 5 mg/day, 10 mg/day, or 15 mg/day were compared to placebo in children 6 to 17 years of age (n=218) with ASD and irritability, agitation, SIBs, or combined behaviors.[51] Compared to placebo, aripiprazole at all doses resulted in significant reductions in the ABC-I subscale score with treatment differences as follows: aripiprazole 5 mg/day, −4.0 (95% CI −7.7 to −0.4, p=0.032), aripiprazole 10 mg/day, −4.8 (95% CI −8.4 to −1.3, p=0.008), aripiprazole 15 mg/day, −6.0 (95% CI −9.6 to −2.3, p=0.001). Mean clinician-rated CGI-I scores also demonstrated significant improvements across all doses compared to placebo: aripiprazole 5 mg/day, −0.7 (p=0.003), aripiprazole 10 mg/day, −0.8 (p<0.001), aripiprazole 15 mg/day −0.8 (p<0.001). The most commonly reported adverse effects with aripiprazole were sedation, extrapyramidal symptoms (EPS), and weight gain. Short duration, fixed dosing, and restriction to ASD population alone (rather than inclusion of other NDDs) limit study findings.

Other Second-Generation Antipsychotics—Limited robust data exist to support the use of other SGAs specifically for SIBs in children with NDDs. However, ziprasidone, olanzapine, and paliperidone, have been evaluated in case series, retrospective analyses, open-label, and small controlled studies for the management of other problem behaviors (e.g., irritability) in children with ASD.[17,69-73]

Ziprasidone has demonstrated moderate treatment response for irritability and aggression in children with ASD, however compared to risperidone and aripiprazole the evidence for effective management of behaviors is weaker.[17,69] Ziprasidone was well tolerated (e.g, weight neutral) in studies, but carries an agent-specific risk for QTc interval prolongation, limiting its use in certain populations (e.g., patients with Rett Syndrome) or patients concomitantly receiving medications that are QTc prolonging.

Olanzapine for aggression, disruptive or destructive behavior, and SIB was first reported in adult patients (n=20) with intellectual disability.[70] A significant decrease in target behaviors (i.e., aggression, SIBs, destructive or disruptive behaviors) was observed with olanzapine (mean reduction in SIB = −7.9; $p<0.044$); however, significant weight gain during the first 6 months of treatment ($p<0.006$) was reported. In a small (n=11), 8-week, double-blind, placebo-controlled trial in children with PDD with disruptive and repetitive behaviors; olanzapine was associated with a 50% response rate on the CGI-I rating scale.[73] Side effects included sedation, increased appetite, and substantial weight gain. Given limited data and a significant risk for weight gain as well as development of dyslipidemia, olanzapine should not be selected over other available SGAs at this time in children with NDDs.

Paliperidone for the treatment of irritability associated with ASD was studied in an 8-week, open-label, prospective study of 25 adolescents and young adults.[71] Paliperidone resulted in significant improvements in irritability with 21 patients experiencing greater than 25% reduction on the ABC-I subscale score [mean (SD) score at baseline = 30.3 (6.5); mean (SD) score at end point=12.6 (9.1); $p = 0.0002$]. These 21 patients were also considered treatment responders, defined by a CGI-I score of 1 or 2 ($p < 0.0002$). Overall, paliperidone was well tolerated. Notably, a positive response to paliperidone was observed in patients with a history of nonresponse to risperidone. Additional advantages of paliperidone include lower risk for drug-drug interactions due to limited metabolism via the cytochrome P450 2D6 (CYP2D6) pathway and the ability to dose once daily. Larger, placebo-controlled trials with longer treatment durations are needed prior to widespread use of this agent.

As more knowledge is gained regarding the long-term efficacy and safety in specific NDDs, the role of these particular SGAs in practice will be further elucidated. To date, however, data is insufficient to support use of ziprasidone, olanzapine, and paliperidone over risperidone or aripiprazole particularly for SIBs specifically.

Despite the demonstrated benefits of SGAs as a class and the often “first line” role in therapy, significant adverse effects (e.g., weight gain, EPS including tardive dyskinesia and akathisia, QTc prolongation, sedation, hyperprolactinemia with subsequent osteoporosis, risk for venous thromboembolism, and metabolic abnormalities) coupled with the risk of drug-drug interactions often limit use in children with NDDs.[74-76] It is important to note the significance of EPS associated with SGAs. Tardive dyskinesia causes abnormal repetitive movements of the mouth, lips, tongue and in some cases, distal limbs, and is typically irreversible. Akathisia, defined as a subjective feeling of excessive restlessness, is treatable, but has the potential to worsen SIBs, and has been associated with increased risk of developing suicidal ideation.[77,78] Even when the SGAs are tolerated, clinical response is frequently suboptimal requiring consideration of alternate medications.

CLONIDINE

Clonidine binds to the α_2 adrenoreceptors in the central nervous systems, thereby decreasing sympathetic outflow in specific regions of the brain (e.g., prefrontal cortex).[79] A proposed theory behind SIBs is that environmental stimuli may induce a state of hyperarousal.[34] Clonidine, by decreasing sympathetic outflow through stimulation of the inhibitory pathway, inhibiting the excitatory pathway, and exerting a direct effect on pain, may be effective in minimizing this over arousal.[79] Despite frequent use in practice, data supporting clonidine specifically for SIBs is limited to two case reports. A 13-year-old female with neurologic impairments and severe SIBs (skin picking, biting, poking and gouging of knees and face) resulting in infection, was initiated on clonidine (0.05 mg/day, titrated to 0.05 mg 4 times/day).[52] After clonidine initiation, parent-reported benefits were observed in the total number of and surface area affected by SIBs. A second case report describes successful use of clonidine in a 9-year-old girl with PDD and severe, persistent SIB (pinching, scratching, rubbing of skin).[34] Initiation of clonidine at 0.025 mg/day and subsequent titration to 0.4 mg/day, was associated with a dramatic decrease in surface tissue damage, number of injuries, intensity of skin trauma, and projected risk of further physical damage. In both cases, clonidine was well tolerated with the exception of transient decreased alertness and lethargy.

The available evidence lacks strength for SIBs alone; however, clonidine is commonly used in practice in children with NDDs, particularly those who have concomitant disrupted sleep and/or hyperarousal disorders due to the potential for additive benefit.[80] Clinicians should be vigilant about using clonidine in patients receiving other central nervous system depressing agents, and those with baseline bradycardia, hypotension, or other cardiac conditions.

N-ACETYLCYSTEINE

N-acetylcysteine (NAC), an antioxidant and prodrug of cysteine, restores glutathione concentrations in the blood and brain and provides intracellular protection against reactive oxygen species. It is theorized that, in addition to antioxidant properties, NAC inhibits glutamate release through the glutamate-cysteine antiporter and decreases inflammation.[40] One theory related to the etiology of SIBs is an increase in excitatory signaling due to exaggerated glutamatergic transmission. Reducing this signaling may provide benefit in managing SIBs.

A case report of a 4-year-old boy with ASD and severe, treatment-refractory SIBs describes a decrease in face gouging after initiation of NAC (450 mg/day with upward titration to 1800 mg/day).[53] In a larger (n=29), 12-week, double-blind, randomized, placebo-controlled study, the use of NAC for behavioral disturbance in children with ASD was also successful.[40] Participants (3-12 years of age) were randomized to receive NAC (900 mg daily for 4 weeks, then titrated to 900 mg twice/day for 4 weeks, then 900 mg 3 times/day for 4 weeks, as tolerated) or placebo. Patients treated with NAC experienced significant improvements in the ABC-I subscale score from baseline to week 12 compared to placebo (mean decrease of −9.7 compared to −1.7, respectively $p<0.001$; $d=0.96$). There were no differences in adverse drug reactions, however NAC was associated with gastrointestinal complaints.

Limitations to these data include small sample size, short duration, lack of long-term safety information and studied populations that were limited to the ASD population. Further, no standardized dosing regimen for NAC has been established for this indication. NAC may be advantageous in select patients, particularly those who have failed other therapies or those receiving polypharmacy, given its minimal drug-drug interactions and relative safety profile. NAC is primarily available as over-the-counter supplements, although one prescription product (i.e., Cetylev™) is available. The prescription product is not approved for use specifically for SIB and may not be readily available in all pharmacies. The over-the-counter supplements are not regulated by the FDA; therefore caution should be exercised when selecting these products, and insurance coverage may pose a challenge.[81,82]

RILUZOLE

Riluzole is a glutamate-modulating agent that exerts its effect via inhibition of glutamate release and enhanced reuptake at the presynaptic nerve terminal.[57] Originally approved for amytrophic lateral sclerosis in 1995, riluzole has demonstrated clinical benefit in psychiatric disorders and may be a promising treatment option in the management of SIBs. Riluzole has been proposed to exhibit noncompetitive blockade of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors, which play a critical role in fast excitatory synapse transmission, information processing, and behavioral plasticity.[57] Neuroprotective properties may also be attributable to inactivation of voltage-gated sodium channels and increased production of neurotrophic factors.

Early data from a 2011 case series demonstrate efficacy in three individuals (15, 18, and 20 years of age) with ASD and moderate-to-severe intellectual disability with SIBs and/or repetitive movements.[33] Riluzole was initiated at 50 mg/day in combination with the patients' other psychotropic medications and was titrated after 1 week to 50 mg twice/day for 4 weeks and then 100 mg twice/day thereafter. Each patient experienced a combination of improvements in behaviors on the CGI-S and CGI-I scales (e.g., decreased repetitive behaviors, aggression, and SIBs). Riluzole was well-tolerated with the only notable side effect being anemia in one patient. Although this was a small case series, results support rationale for further research regarding the use of riluzole for the management of SIBs.

There are currently more than 50 ongoing clinical trials assessing the efficacy of riluzole noted on clinicaltrials.gov for indications such as depression, Fragile X Syndrome, Obsessive Compulsive Disorder, ataxia, pediatric bipolar disorder, irritability in ASD, Tourette syndrome, and other similar disorders. As riluzole makes its way into practice, clinicians should be aware of essential monitoring parameters and potential drug interactions. Specifically, liver aminotransferases should be measured at baseline and every 3 months during therapy, and potential for drug interactions with CYP1A2 inducers and inhibitors should be carefully managed.

AMANTADINE

Amantadine is a noncompetitive *N*-Methyl-D-aspartic acid (NMDA)-receptor antagonist with possible neuroprotective and anti-inflammatory properties.[58] In a double-blind, placebo controlled study, 39 patients (5-19 years of age) with autistic disorder received amantadine

2.5 mg/kg/day (increased to 5 mg/kg/day after 1 week) or placebo for 4 weeks.[59] No significant difference in parent-recorded ABC-I ratings (p=0.178) were observed between amantadine and placebo, however CGI ratings were better in the treatment group with 53% of patients experiencing improvement compared to only 25% improvement in the placebo group, p=0.076: the estimated treatment difference in favor of amantadine was 27.6 percentage points (95% CI, 57% to −1.8%). p=0.076). Amantadine was well tolerated. Although the results were not statistically significant, a 28% difference in the number of patients who experienced improvement on the CGI scale in the amantadine group compared to placebo suggests potential for clinically meaningful benefits in refractory cases. Results are limited by short study period (4 weeks), extrapolation of results from ASD population, and behaviors evaluated that are not specifically SIBs. Based on this single report, amantadine appears to have limited effect on irritability, however further research is warranted.

MIRTAZAPINE

The involvement of serotonin has been implicated in SIBs due to its established role in impulsivity and aggression as well as its connection with depression and suicide.[1] Due to its effect on the serotonin system, mirtazapine has been hypothesized to decrease symptoms such as aggression, irritability, and SIBs in patients with ASD.

The efficacy of mirtazapine (7.5-45 mg/day; mean 30 mg/day) in ASD was assessed in a 4-week, naturalistic, open-label study of 26 patients with PDD.[60] On the CGI-S and CGI-I scales, 34.6% and 30.8% of participants, respectively, were considered responders ("much improved" or "very much improved") to mirtazapine. Significant improvements were observed on the CGI-S scale ($p<0.04$) and the CGI-I assessment of sleep ($p<0.002$); however, no statistically significant differences were seen from baseline to end point for ABC-I (baseline = 19.12 ± 9.14; end point = 15.85 ± 9.14; $p < 0.08$). Importantly, although 11 patients had decreased irritability, reduction in SIBs was not specifically noted for any of the participants. Adverse effects associated with mirtazapine were mild and transient, but included increased appetite, irritability, and sedation.

Based on this study, mirtazapine appears to have moderate efficacy in treating select behaviors associated with ASD; however, evidence is insufficient to support its use for management of SIBs alone. Mirtazapine has other efficacy benefits that may make it an appropriate choice in certain patients, such as for children with concomitant refractory insomnia, irritability, anxiety, or depression. Mirtazapine is associated with drowsiness, weight gain, elevated cholesterol, and anticholinergic effects, as well as drug-drug interactions due to its metabolism via CYP1A2.

PHARMACOTHERAPY AFFECTING ENDOGENOUS OPIOID SYSTEM AND PAIN PATHWAYS

It has been proposed that individuals who engage in SIBs may experience pain differently than those who do not.[83] One theory proposes that individuals with NDDs have a reduction in pain sensitivity.[1,2] An opposing theory suggests an increased expression of pain. Although the exact relationship between pain and SIB remains unclear, the endogenous opioid system

may be involved.[2] As a result, pharmacotherapy that targets pain processing and opioid binding has been evaluated.

Naltrexone—Naltrexone is a pure opioid antagonist that exhibits high affinity for μ-opioid binding sites. Its role in the treatment of SIBs evolved from the theory that SIBs stimulate release of endogenous endorphins, which may drive some of the observed repetitive behavioral patterns.[63] Naltrexone was of great interest in the late 1980s and early 1990s.[61] However, available literature demonstrates conflicting efficacy results and is limited to case reports, small case series, and small controlled studies, with few studies specific to children.

A double-blind, placebo-controlled crossover study examined the efficacy and safety of naltrexone (50 mg/day) in 33 adult patients with NDDs and SIBs.[62] On the total ABC and CGI-S scales, naltrexone did not demonstrate benefit compared to placebo. The authors do not report irritability subscale scores, but state that a separate analysis performed on items specific for SIB in the ABC questionnaire also failed to show response. Observed side effects included fatigue, nausea, and sedation. These results are consistent with previously described placebo-controlled studies of naltrexone in patients with SIB and ASD.[63] In contrast, in a double-blind, placebo-controlled, crossover study of six male patients (15-31 years old) with SIBs and mental disability, naltrexone 50 mg/day (0.6-1.5 mg/kg for 3 weeks) resulted in significant reductions in the frequency of SIBs in two patients, and a trend towards benefit in a third.[84] Similarly, in a single-subject (12-year-old female with ASD), double-blind controlled analysis, naltrexone resulted in a zero rate of SIBs for 22 months.[61] The evidence regarding the use of naltrexone for treatment of SIBs is minimal and conflicting at best, and clinical use today has largely fallen out of favor. At present, naltrexone should be reserved for those patients who are refractory to other treatment options.

Topical Anesthetics—Topical anesthetics inhibit ion influx required for conduction of impulses by stabilizing the neuronal membrane. The ability to block skin sensation may be useful in SIBs which are hypothesized to persist due to automatic reinforcement, defined as direct stimulation independent of environmental effects.[64] This theory was tested by applying 1 g of eutectic Marcaine lidocaine analgesic (EMLA) to the cheeks of a 12-year-old male with ASD, severe intellectual disability, and SIBs, refractory to other therapies.[64] The study was conducted over a 3-day period. Efficacy was measured by comparing the number of SIBs per minute after no application of anesthetic and after application of anesthetic. Application of anesthetic decreased the frequency of face slapping by 43% on day 1, 45% on day 2, and 26% on day 3. Despite observed benefit, generalizability of the results is limited by single-subject, unblinded, observational study design and short treatment duration. Although topical anesthetic is generally well tolerated, a potential for systemic absorption and subsequent safety concerns may be present. Incorporation of topical agents into the treatment plan for patients with SIBs is not routinely recommended and is restricted to select cases where SIBs is limited to a distinct and small topical area and risk for systemic absorption is minimal (e.g., an older patient with good skin integrity, no open wounds, and isolated face slapping).

ANTIEPILEPTICS AND MOOD STABILIZERS

Topiramate—Although the precise mechanism by which topiramate reduces SIBs is unknown, modulation of GABA and glutamate activity likely plays a role.[65] Topiramate has been reported to be effective in an 8-week open-label trial of three adults with Prader-Willi Syndrome (PWS) as evidenced by improvement in SIBs (skin picking) in all patients following initiation of topiramate (starting dose: 25 mg/day; maintenance dose: 150–200 mg/day).[12] Similarly, an 8-week open-label study of eight adults with PWS demonstrated clinically significant improvement in SIB in seven individuals following the initiation of topiramate (initial dose: 25 mg/day; maintenance dose: 125-200 mg/day).[13] Scores on the self-injury and self-restraint checklist decreased from 2.12 at baseline to 1.25 after treatment with topiramate ($p<0.01$). These small open-label studies in adults suggest that topiramate could be an effective agent for the management of SIBs in patients with PWS, but requires extrapolation from the adult population to pediatric practice.

Other Antiepileptics—The use of antiepileptics as mood stabilizers, specifically valproate, oxcarbazepine, levetiracetam, and lamotrigine, have been studied in the setting of behavioral problems associated with ASD. Most available evidence with this class does not specifically evaluate SIBs, but rather focuses on assessing hyperactivity, impulsivity, aggression, and mood instability.[85-87] However, the efficacy of divalproex for the treatment of irritability in ASD was analyzed in a 12-week, randomized, double-blind, placebo-controlled trial of 27 children (5-17 years old).[66] For patients receiving divalproex, improvement was seen in both ABC-I and CGI. Responders were defined as those who had CGI-I ratings of 1 or 2, indicating a substantial reduction in symptoms (divalproex = 62.5% responders; placebo = 9% responders). Mean change in ABC-I scores from baseline to end of treatment were −7.5 for divalproex and −2.6 for placebo ($p=0.048$). Divalproex was well tolerated overall; although, one patient experienced a paradoxical increase in irritability related to insomnia, and another had clinically significant weight gain (> 7% starting weight). An in-depth discussion of the agents in this class is not included here. The reader is referred to a comprehensive review of mood stabilizers in children and adolescents with ASD for further detail.[85]

Antiepileptics as mood stabilizers may play a role in the general management of children with NDDs, and theoretically a secondary benefit of decreasing irritability and possibly SIBs may be observed. However, data is lacking to support the use of these agents for SIBs alone.

REVIEW OF AVAILABLE DATA: DUAL THERAPY

Risperidone Plus NAC

Two double-blind, randomized, placebo-controlled trials of NAC in combination with risperidone demonstrated benefit in the treatment of ASD.[54,55] The efficacy and safety of NAC (1200 mg/day in two divided doses) compared to placebo as augmentation of risperidone for treating irritability associated with ASD in 40 children with ASD (3.5-16 years of age) for 8 weeks was assessed.[54] Those receiving NAC experienced significant reductions in ABC-I subscale scores from baseline [mean (SD) baseline score 13.2 (5.3) versus 9.7 (4.1) after treatment] compared to placebo [mean (SD) baseline score 16.7 (7.8)

to 15.1 (7.8) after treatment; p=0.035]. Adverse effects were uncommon; however, the NAC group experienced constipation, increased appetite, fatigue, nervousness, and daytime drowsiness. In another study, 50 patients (4-12 years of age) were randomized to receive risperidone plus NAC (600 to 900 mg/day in three divided doses) or risperidone plus placebo.[55] Patients receiving NAC plus risperidone (n=20) experienced a significantly greater reduction in irritability on the ABC-I subscale (p=0.02) at week 10 compared to those who received placebo. The mean (SD) change on the ABC-I subscale from baseline to week 10 was 9.25 (4.08) for the NAC plus risperidone group versus 5.35 (3.23) in the placebo plus risperidone group. There were no significant differences in adverse effects between groups. Compared with placebo, this data indicates that NAC may provide benefit when added to risperidone.

Risperidone Plus Riluzole

In a 2013 double-blind, placebo-controlled, randomized control trial, riluzole was studied as adjunctive treatment to risperidone, compared with placebo, for the management of irritability associated with ASD in children 5 to 12 years of age (n=49).[57] Riluzole was initiated at 12.5 mg twice/day for 1 week, and then titrated to 25 mg twice/day in patients 10 to 40 kg and to 50 mg twice/day in patients greater than 40 kg for 9 weeks. Children in the riluzole group demonstrated significantly greater improvement in ABC-C irritability subscale score at week 10 compared to the placebo group (p=0.03). Mean reduction in the ABC-C irritability subscale score from baseline to post-treatment was −9.55 for children who received riluzole versus −5.85 in the placebo group. Reduced Cohen's effect size was reported to indicate practical significance, which was moderate to high by week 10 (d=0.70). Adverse effects were similar between the two groups, with the exception of increased appetite and weight in the riluzole group. Compared with placebo, when added on to risperidone, riluzole improved the ABC-C and the CGI-I in children with behavioral symptoms associated with ASD.

Risperidone Plus Amantadine

In a 10-week, randomized, double-blind, placebo-controlled trial, risperidone plus amantadine was evaluated for effect in the treatment of ASD.[58] Forty patients were randomized to receive risperidone (1-2 mg/day) plus placebo or risperidone plus amantadine (100 mg for patients < 30 kg or 150 mg for patients > 30 kg). ABC-C subscale, adverse effects checklist, and CGI-I were assessed at 5 and 10 weeks. By week 10, patients in the risperidone plus amantadine group experienced significantly greater mean reductions in the irritability subscale score from baseline compared to placebo (mean difference 3.2, 95% CI 0.48 to 6.01, p=0.022). Improvements in the CGI-I scores were also observed with 50% of patients in the amantadine group scoring as "very much improved" or "much improved" compared to 20% in the placebo group (p=0.047). There were no significant adverse effects between groups. Limitations include short observational period, small sample size, and fixed and relatively low dose of amantadine. Based on these outcomes, amantadine may have positive effect on irritability when used in combination with risperidone.

Risperidone Plus Topiramate

An 8-week, double-blind, placebo-controlled trial assessed the effect of risperidone (2 mg/day for patients < 40 kg and 3 mg/day for patients >40 kg) plus topiramate (100 mg/day for patients <30 kg and 200 mg/day for patients >30 kg) in 40 children (4-12 years old) compared with risperidone plus placebo in children with ASD.[65] On the ABC-I rating scale, a significant difference in irritability was observed for patients in the topiramate group with a mean difference of 9.05 from baseline to week 8 versus a mean difference of 1.5 in the placebo group ($p \leq 0.0001$). Somnolence and decreased appetite were observed more frequently in those receiving topiramate.

Risperidone Plus Buspirone

Buspirone has been hypothesized to play a role in irritability associated with ASD by boosting serotonin levels in the brain.[67] The theory is supported clinically in one randomized, double-blind placebo-controlled trial of buspirone (10 mg/day in patients <40 kg or 20 mg/day in patients >40 kg) as an adjunct to risperidone (2 mg/day in patients <40 kg or 3 mg/day for patients >40 kg) in 40 children and adolescents with ASD. During the 8-week study duration, 81.2% of patients in the buspirone group compared to 38.9% of patients in the placebo group had a 30% or greater decline in irritability score.[67] The most common side effects observed in the buspirone group were increased appetite, drowsiness, and fatigue. Buspirone appears to be a safe and effective agent for children and adolescents with irritability in ASD. Buspirone may be considered for children with SIBs who suffer from concomitant anxiety. However, clinicians should be aware that evidence is limited to a single, small study.

Although each of these studies provides initial evidence supporting the use of risperidone in combination with other pharmacotherapy, the data is limited and additional study is warranted to more conclusively confirm findings.

OTHER THERAPIES

Several additional novel treatment strategies and therapies—albeit with less supporting evidence—have been proposed or are under current investigation. A summary of these options is provided in Table 3.[10,88-95]

DISCUSSION/CONCLUSION

Managing SIBs in children with NDDs is critical both for the child and the family and caregivers, but is often frustrating due to the refractory nature of the problem. No evidence-based guideline currently exists to guide clinicians in managing SIBs in children with NDDs. This is due to a lack of clear understanding of the underlying etiology and pathophysiology of SIBs, heterogeneity of NDDs, need to extrapolate data, and lack of robust supporting evidence specifically reported for SIBs. If SIBs are still present after resolving contributing factors and the implementation of nonpharmacologic interventions, initiation of pharmacologic management reliant on the most-up-to-date available evidence, clinical judgement on a case-by-case basis, and ongoing monitoring of treatment effects is necessary. Given the current supporting evidence and FDA approval, an SGA (i.e.,

risperidone or aripiprazole) may be considered first, accounting for drug-drug interactions as well as other patient safety parameters. If SIBs persist, individualized, patient-specific factors should be considered including, but not limited to, diagnosed NDD, types of behaviors, risk for interactions and toxicities (e.g., these therapies are frequently used in combination with other medications with central nervous system depressing actions), monotherapy versus dual therapy, and available evidence. The most conservative initial dosing is recommended with titration to the lowest effective dose. Routine and ongoing monitoring of therapeutic response and for safety is necessary. Individualized outcome measures appropriate for each patient should be identified in order to appropriately monitor and adjust pharmacotherapy and to maximize response.

The primary limitation of the presented evidence is that the majority of studies examined children with ASD rather than specific NDDs. Although it is common for ASD or ASD-like symptoms to co-occur in NDDs, the unique pathophysiology and etiologies in each heterogenous NDD may affect the degree to which a child responds to therapy. Second, the outcome measures and assessment scales used in clinical trials, such as ABC-I and CGI, provide information for a combination of behaviors and do not distinguish between unique symptoms. Many studies also rely on unstandardized subjective assessments of behavior to draw conclusions. Both of these concerns limit the ability to rigorously evaluate the treatment effects of individual medications specifically on SIBs. Finally, as emphasized throughout the review, the available evidence is weakened by small sample size, potential for bias, lack of long-term follow-up (e.g., in many cases studies limited to weeks), and restricted generalizability.

These limitations notwithstanding, this review presents the nonpharmacologic and pharmacologic management strategies for SIBs, as well as the best available supporting evidence. Still, many unanswered clinical questions exist regarding the treatment of SIBs in patients with NDDs. Opportunities for future research to advance knowledge around the management of SIBs include the need for more rigorous research studies, including prospective investigations in specific sub-populations of children with NDDs, the use of standardized symptom measurement instruments, and study durations adequate to assess important long-term outcomes; the conduct of head-to-head medication trials; and, the evaluation of novel combinations of therapies, including dual pharmacologic therapy or mixed pharmacologic and nonpharmacologic interventions. Until more data are available, clinicians must continue to rely upon the limited available evidence, clinical judgement and expertise, and carefully monitored response(s) to therapy when managing SIBs in children with NDDs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Review of Select Specific NDDs[a] Associated with Self-Injurious Behaviors[b]

NDD	Etiology	Clinical Characteristics	Prevalence	Incidence of SIBs[c]	Specific SIBs[c]
Smith-Magenis Syndrome[1,9]	Usually caused by deletions in the 17p11.2 region; a mutation in the RAI1 gene is associated with SIBs	Brachycephaly, midface hypoplasia, hoarse voice, speech delay, psychomotor and growth delay, cutaneous feature, behavior problems, hypotonia	1:15,000-1:25,000 live births	Nearly 100% of patients will have SIB	– Biting – Hitting – Picking at fingernails and toenails – Insertion of foreign objects into orifices
Lesch-Nyhan Syndrome[1,10]	Mutation in hypoxanthine-guanine phosphoribosyl-transferase 1 (HPRT[d])	Hyperuricemia, choreoathetoid movement, intellectual disability, aggression towards others	1:380,000 live births	When <1.5% HPRT enzyme is present, nearly 100% of patients will have SIB	– Lip biting – Finger biting – Head banging – Banging of arms and legs
Cri du Chat Syndrome[1]	Deletion on chromosome 5p	Cat like cry, intellectual disability, limited language development, sleep disturbances, hypersensitivity to auditory stimuli, vomiting-rumination	1:15,000-1:50,000 live births	76.8%-92%	– Head hitting – Scratching – Self-biting
Prader-Willi Syndrome[11-14]	Deletion of paternal 15q11-q13 region of chromosome 15	Hypotonia, intellectual delay, hypogonadism, dysmorphic features, short stature, obesity, behavioral and psychiatric manifestations	1:15,000 live births	70%-90%	– Skin picking – Nail biting – Hair pulling
Pervasive Developmental Disorders (ASD[e], Asperger's Disorder, Disintegrative Disorder, Pervasive Developmental Disorder not otherwise specified)[2,15-19]	Exact etiology unknown; combination of genetic, environmental, and neurobiological factors	Poor communication, social deficits, restrictive and stereotyped behaviors, hyperactivity, behavioral problems, tantrums, irritability, aggression	1:59[19] individuals (ASD)	33%-71%	– Hitting – Self-biting
Fragile X Syndrome[20-22]	A single gene mutation on the X chromosome disrupts production of the fragile × mental retardation protein, which regulates the production of proteins needed for maturation and elimination of synapses during brain development	Neurobehavioral phenotype with associated cognitive delay, aggression, impulsivity, anxiety	1:8000 females and 1: 4000 males	17%-70%	– Self-biting – Rubbing – Scratching
Rett Syndrome[23-25]	Loss-of function mutations in the X-linked MECP2 gene, which leads to abnormal brain development and function	Stunted head growth, loss of acquired verbal skills, repetitive hand movements, ataxia, intellectual disabilities, and autistic-like behaviors	Females only, 1:10,000 live births	50%	– Mouth hitting
Cornelia de Lange Syndrome[26-28]	De novo mutations in cohesion complex genes, such as the nipped-B-like-gene (*NIPBL*), which affect the protein	Multiple behavioral and developmental symptoms, abnormal limb development, growth delay, cardiac and genitourinary anomalies, myopia,	1:10,000 – 1:30,000 live births	40%	– Face hitting (most classic) – Self-biting – Skin picking

NDD	Etiology	Clinical Characteristics	Prevalence	Incidence of SIBs[c]	Specific SIBs[c]
	network that regulates separation of chromatins during cell division	hirsutism, sleep disturbance, and hearing loss			
Down Syndrome[25]	Attainment of extra copy of chromosome 21	Dysmorphic features, congenital malformations, endocrine disorders, obesity, hearing loss	1 in 700 live births	15%	– Eye poking

[a]The disorders highlighted in this table were chosen for two primary reasons: (i1) these disorders may be encountered by clinicians caring for children and youth with special healthcare needs (CSHCN) and (ii) published data exist pertaining to SIBs in these specific NDDs.

[b]NDDs are presented in order of descending incidence of SIBs.

[c]Self-injurious behaviors

[d]Hypoxanthine-guanine phosphoribosyl-transferase 1

[e]Autism Spectrum Disorders,

Table 2.

Review of Select Pharmacotherapy[a] with Evidence[b] for Management of Problem Behaviors in Children with Neurodevelopmental Disorders

Pharmacologic Agent	Receptor Effects	Available Data	Specific Neurodvelopmental Disorders Studied	Ages of Patients Studied	Problem Behavior Types Studied	Strength of Evidence (GRADE)[c]	Dose[d]
Risperidone[46-50]	5-HT_{1A}, 5-HT_{2A}, 5-HT_{1b}, 5- HT_{1C}, 5-HT_{1D}, and D_2 receptor agonist; α_1 and α_2 adrenergic receptor agonist	Randomized, placebo-controlled trials; open-label extension trial	Pervasive Developmental Disorder, Down Syndrome; Fragile X Syndrome[49]	5-16 years	– Irritability – Aggression – SIB[e] – Temper tantrums	Irritability associated with ASD[f]: High Other Problem Behaviors in Other NDDs[g]: Very Low/Low	Initial: < 20 kg: 0.25 mg/day ≥20 kg: 0.5 mg/day Titration: 0.25 – 0.5 mg at ≥2 weeks Maintenance: < 20 kg: 0.5 mg once a day or divided in two doses ≥20 kg: 1 mg once a day or divided in two doses Maximum: 3 mg/day
Aripiprazole[51]	Partial D_2 and 5-HT_{1A} receptor agonist and 5-HT_{2A} receptor antagonist	Case series; randomized, placebo-controlled trials	ASD	6-17 years	– Irritability – Aggression – SIB – Temper tantrums	Irritability associated with ASD: High Other Problem Behaviors in Other NDDs: Very Low/Low	Initial: 2 mg once a day Titration: 5 mg increments each week Maintenance: 5-10 mg once a day Maximum: 15 mg once a day
Clonidine[34,52]	α_2 adrenoreceptor agonist; activates inhibitor neuron and reduces sympathetic outflow from the central nervous system	Case reports; open-label pilot study	Pervasive Developmental Disorder	5-13 years	– SIBs – Aggression	Very low	Initial: 0.025-0.05 mg/day (~0.002 - 0.003 mg/kg/day in younger children) Titration: 0.025 mg as

Pharmacologic Agent	Receptor Effects	Available Data	Specific Neurodvelopmental Disorders Studied	Ages of Patients Studied	Problem Behavior Types Studied	Strength of Evidence (GRADE)[c]	Dose[d]
							tolerated every 1-2 weeks to target dose of 0.005-0.01 mg/kg/day in 3-4 divided doses Maximum: 0.01 mg/kg/day Weight-based maximum (in 3-4 divided doses): 27-40.5 kg: 0.2 mg/day 40.5-45 kg: 0.3 mg/day >45 kg: 0.4 mg/day
N-Acetylcysteine[40,53-55]	Prodrug of cysteine that restores glutathione and scavenges oxidants	Case report; randomized, double-blind, placebo-controlled studies	ASD; excoriation (skin-picking) disorder (adults)[56]	4-50 years	– Irritability – SIBs – Hyperactivity	Low	Initial dose: 500 - 600 mg once or twice a day Maintenance dose: 1800-2700 mg/day in two to three divided doses
Riluzole[33,57]	Inhibits glutamate release, enhances glutamate reuptake, inactivated voltage-dependent Na^+ channels	Case series; randomized, double-blind, placebo-controlled trial	Fragile X Syndrome; ASD	5-20 years	– Aggression – Irritability – SIBs – Repetitive behaviors	Monotherapy: Very Low Dual Therapy with Risperidone: Low	**Children (5-12 years old)**: Initial: 12.5 mg twice a day Maintenance: 10-40 kg: 25 mg twice a day > 40 kg: 50 mg twice a day **Adolescents**: Initial: 50 mg once a day

Pharmacologic Agent	Receptor Effects	Available Data	Specific Neurodvelopmental Disorders Studied	Ages of Patients Studied	Problem Behavior Types Studied	Strength of Evidence (GRADE)[c]	Dose[d]
							Maintenance: 100 mg twice a day
Amantadine[58,59]	Noncompetitive NMDA receptor antagonist	Double-blind, placebo-controlled trials	ASD	4-19 years	– Hyperactivity – Irritability	Very low	Initial: 2.5 mg/kg/day Maintenance dose: 2.5 mg/kg twice a day Weight-based maximum dose: < 30 kg: 100 mg/day >30 kg: 150 mg/day
Mirtazapine[60]	Central presynaptic α_2 adrenergic antagonist; $5HT_2$ and $5HT_3$ serotonin receptor antagonist; H_1 histamine receptor and peripheral α_1 adrenergic and muscarinic antagonist	Naturalistic, open-label study	Pervasive Developmental Disorders and ASD	3.8-23.5 years	– Aggression – SIB – Irritability – Hyperactivity	Very low	Initial: 7.5 mg/day Titration: 7.5 mg every 1 - 2 weeks Maximum: 45 mg/day in divided doses
Naltrexone[61-63]	Pure opioid antagonist with high affinity for μ opioid binding sites	Case reports; small case series; small studies	Prader-Willi Syndrome	2-46 years	– SIBs – Hyperactivity	Very low	Fixed-dose: 50 mg/day Weight-based dosing: 0.5-2 mg/kg/day
Topical Anesthetics (EMLA[i])[64]	Stabilizes the neuronal membrane; inhibits ion influx, which is required for conduction of impulses	Case report	– ASD	12-year-old	– SIBs	Very low	1 gram applied to targeted site
Topiramate[12,13,65]	Blocks neuronal voltage-	Open-label trial; double-blind, placebo-controlled trial	ASD Prader-Willi Syndrome	4-38 years	– Irritability	Very low	Initial: 0.5 - 1 mg/kg/day

Pharmacologic Agent	Receptor Effects	Available Data	Specific Neurodvelopmental Disorders Studied	Ages of Patients Studied	Problem Behavior Types Studied	Strength of Evidence (GRADE)[c]	Dose[d]
	dependent sodium channels; enhances GABA[j] activity; antagonizes AMPA[k]/kainite glutamate receptors; weakly carbonic anhydrase inhibitor				– Stereotypic behavior – Hyperactivity – SIBs		Titration: 0.5 - 1 mg/kg every week Weight-based maintenance dose: < 30 kg: 100 mg/day >30 kg: 200 mg/day
Divalproex[66]	Enhances GABA action and availability; mimics GABA action at postsynaptic receptor sites	Randomized, double-blind, placebo-controlled trial	ASD	5 -17 years	– Irritability	Very low	Initial: 10 -15 mg/kg/day Weight-based dosing: Initial: < 40 kg: 125 mg once a day ≥40 kg: 250 mg once a day Titration: 5 – 10 mg/kg/day at weekly intervals; titrate to effect Doses > 250 mg should be given in divided doses
Buspirone[67]	5-HT_{1A} and 5-HT_{1B} receptor agonist and D_2 antagonist	Randomized, double-blind placebo-controlled trial	ASD	4 -17 years	– Irritability	Very low	Initial: 5 mg/day Titration: 5 mg each week Weight-based maximum: <40 kg: 10 mg/day >40 kg: 20 mg/day in

Pharmacologic Agent	Receptor Effects	Available Data	Specific Neurodvelopmental Disorders Studied	Ages of Patients Studied	Problem Behavior Types Studied	Strength of Evidence (GRADE)[c]	Dose[d]
							two divided doses

[a]Pharmacologic agents are presented in the order presented in the article text. The order in which the agents are presented does not reflect a treatment algorithm; data supporting monotherapy is presented first then followed by evidence supporting dual therapy.

[b]Data in this table have been compiled and extrapolated from studies discussed in this review as well as the LexiComp and Micromedex databases. Although these dosing recommendations are meant to provide guidance on the usual dosing ranges for these understudied agents, prescribing clinicians should always consult drug information resources and/or consult with a clinical pharmacist for the most up-to-date and patient-specific dosing recommendations when initiating therapy. Clinicians are urged to prescribe the most conservative initial dose, with titration to the lowest effective dose.

[c]Evidence was graded by the manuscript authors using the GRADE system for appraising studies. (Reference: Goldet G, Howick J. Understanding GRADE: an introduction. JEBM 2013;6:50-54.)

[d]Dosing suggestions have been compiled and extrapolated from studies discussed in this review as well as the LexiComp and Micromedex databases. Although these dosing recommendations are meant to provide guidance on the usual dosing ranges for these understudied agents, prescribing clinicians should always consult drug information resources and/or consult with a clinical pharmacist for the most up-to-date and patient-specific dosing recommendations when initiating therapy. Clinicians are urged to prescribe the most conservative initial dose, with titration to the lowest effective dose.

[e]Self-injurious behaviors

[f]Autism Spectrum Disorders

[g]Neurodevelopmental Disorders

[h]*N*-Methyl-D-aspartic acid

[i]eutectic Marcaine lidocaine analgesic

[j]Gamma-Aminobutyric Acid

[k]α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

Table 3.

Review of Select Alternative Pharmacotherapy with Evidence for Management of Self-Injurious Behaviors in Children with Neurodevelopmental Disorders[ab]

Alternative Agent	Mechanism of action	Rationale for Use in Self-Injurious Behaviors	Available Data	Specific Neurodevelopmental Disorders Studied	Behaviors Targeted	Ages Studied	Suggested Dosing	Clinical Notes
Allopurinol[88]	Xanthine oxidase inhibitor; leads to decrease in uric acid	Inborn error of purine metabolism in Lesch-Nyhan syndrome leads to hyperuricemia, which has been associated with SIB[c]	Case reports, case series (adults)	Lesch-Nyhan syndrome	– SIB – Aggression	54-80 years	Initial dose: 5-10 mg/kg/day Maintenance dose: 200-300 mg/day	Specific to Lesch-Nyhan syndrome
Baclofen[89]	Gamma-aminobutyric acid analogue; crosses the blood-brain barrier and reduces excitatory stimulus in the cortex and basal ganglia	Some children with NDDs[d] might be deficient in GABA[e]	Double-blind, cross-over trial	Nonspecific	– SIB – Aggression	9-37 years	Initial: 10 mg 3 times a day (2.5 mg once daily for young, small, or fragile patients) Titration: Every 3 days to weekly Maintenance: 20-80 mg/day in divided doses (higher doses have been used with prolonged duration)	Patients may develop tolerance
Ecopipam[90]	Selective D1-dopamine receptor antagonist	Abnormal function of basal ganglia dopamine pathways has been proposed as mechanism of SIB in Lesch-Nyhan syndrome	Phase 1b, nonrandomized, dose-escalation safety study	Lesch-Nyhan syndrome	– SIB	9-52 years	Initial: 12.5 mg/day Titration: Double the dose every 2 days, as tolerated Maintenance: 200 mg/day	Experimental therapy[90] Specific to Lesch-Nyhan syndrome
Fluphenazine[91]	First-generation antipsychotic; D1-receptor antagonist	SIBs in Lesch-Nyhan syndrome may be caused by supersensitivity to dopamine[91]	Case report of two patients	Lesch-Nyhan syndrome	– SIB	20 months; 15-year-old	Initial: 0.25 mg once daily Titration: Increase by 0.25 mg each week Maintenance: 5 mg divided 1 to 2 times daily	
Loxapine[92]	Medium potency, dibenzoxazepine antipsychotic; D1, D2, D4 antagonist	Proposed to induce changes in cerebral subcortical inhibitory areas of the brain leading to suppression of aggression	Prospective, open-label trial	ASD[f]	– Irritability	13-65 years	5-15 mg/day (low-dose)	Studied as add-on therapy to various baseline medications Acts like a second-generation antipsychotic at low doses
Pioglitazone[93]	Potent, selective agonist of peroxisome proliferator-activated receptor-gamma	Crosses the blood brain barrier and may decrease inflammation in the cortex of patients with ASD	Randomized, double-blind, placebo-controlled trial (combination therapy only)	ASD	– Irritability	4-12 years	15 mg twice a day	Substrate of CYP[g]2C8 (major); CYP3A4 (minor)

Alternative Agent	Mechanism of action	Rationale for Use in Self-Injurious Behaviors	Available Data	Specific Neurodevelopmental Disorders Studied	Behaviors Targeted	Ages Studied	Suggested Dosing	Clinical Notes
								Pharmacodynamic interactions with hypoglycemic medications
Vitamin B12[94]	Co-factor of antioxidants; stimulates regeneration of methionine	Physiologic abnormalities such as oxidative stress and inflammation have been associate with symptoms of ASD	Small, pilot, randomized controlled trial; large, randomized controlled trial	ASD	– Nonspecific	3-8 years	64.5 μg/kg subcutaneously every three days	Conflicting outcomes Assess behavioral symptoms in general; primary outcome was overall improvement based on CGI
5-hydroxytryptophan[10,95]	Precursor for the synthesis of serotonin	Hypoxanthine-guanine phosphoribosyltransferase enzyme deficiency in Lesch-Nyhan syndrome leads to dysfunction of cholinergic and serotonergic systems; increase in 5-hydroxytryptophan synthesis has been proposed to stimulate receptors	Open-label trial; double-blind clinical trial of one patient	Lesch-Nyhan syndrome	– SIB	1-12 years	8 mg/kg	Specific to Lesch-Nyhan syndrome Conflicting outcomes

[a] Alternative pharmacologic agents are presented in alphabetical order.

[b] Data in this table have been compiled and extrapolated from studies discussed in this review as well as the LexiComp and Micromedex databases. Although these dosing recommendations are meant to provide guidance on the usual dosing ranges for these understudied agents, prescribing clinicians should always consult drug information resources and/or consult with a clinical pharmacist for the most up-to-date and patient-specific dosing recommendations when initiating therapy. Clinicians are urged to prescribe the most conservative initial dose, with titration to the lowest effective dose.

[c] Self-Injurious Behaviors

[d] Neurodevelopmental Disorders

[e] Gamma-Aminobutyric Acid

[f] Autism Spectrum Disorders

[g] Cytochrome P450