A Compounding Pharmacist's Role in Managing Pharmacologic Therapies for Pediatric Patients With Autism Spectrum Disorder

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At the end of this activity, pharmacists and technicians should be better able to:

1. Describe the prevalence and DSM-5 criteria for Autism Spectrum Disorder (ASD).
2. Discuss the two commercially available medications with Food and Drug Administration-approved indications for ASD.
3. Explain the important role compounding plays in the ASD patient and what options are available to improve patient symptoms.
4. Evaluate patient cases and determine appropriate treatment options for patients diagnosed with ASD.

Any medications or treatment methods suggested in this CE activity should not be used by the practitioner without evaluation of their patient's condition(s) and possible contraindication(s) or danger(s) of use of any specific medication. This article contains a discussion of off-label uses that will be identified as such by the author.

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AUTISM SPECTRUM DISORDER IN THE PEDIATRIC POPULATION

Autism spectrum disorder (ASD) is a group of developmental disorders characterized by marked socialization, communication, and behavioral challenges. Over the past few decades, the rate of reported ASD in the United States has increased tremendously; The Centers for Disease Control and Prevention estimates that 1 in 68 children has an been identified with an ASD. While ASD occurs in all racial, ethnic, and socioeconomic groups, current epidemiological data suggest that prevalence is highest among non-Hispanic white male children. Currently, no cure exists for ASD; however, intervention has been demonstrated to have more benefit when it is started in children ages 5 and under compared to older children. Pharmacists and pharmacy technicians can assist patients and/or caregivers in a variety of ways to help manage ASD.

While there is no definitive cause for ASD, abnormalities in brain structure and function have been observed, and researchers are investigating links between hereditary, genetic, environmental, and medical theories. No one gene has yet been identified as causing ASD; there is a possibility that a cluster of genes may interfere with brain development and lead to ASD. Evidence for a genetic basis has been demonstrated through twin studies. If one identical twin has ASD, there is an 80-90 percent likelihood that the other twin also has ASD. Additionally, parents who have a child with ASD have a 2-18 percent chance of having a second child who will develop the disorder. Researchers are exploring environmental factors, such as parental age and complications during birth and pregnancy, and their effect on certain genes as potential links to ASD development. Recently, epidemiology studies reported a potential increased ASD risk for a person with a variant MET receptor tyrosine kinase gene who is exposed to high levels of air pollution as well.

Over the last six decades, several editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), the manual used by clinicians to diagnose and classify mental disorders, were published by the American Psychiatric

Table 1: DSM-5 Criteria for ASD

Criteria for ASD Diagnosis (must meet A, B, C, and D)

A: Deficits in social interaction (all of the following)	B: Impairments in communication (≥ 2 of the following)	C: Age	D: Overall
• Lack of social-emotional reciprocity • Deficits in nonverbal communicative behaviors • Failure to develop and maintain peer relationships appropriate to developmental level	• Stereotyped or repetitive speech, movements, or use of objects • Excessive adherence to routines or rituals • Highly restricted, fixated interests • Hyper- or hypo-reactivity to sensory input	• Symptoms must be present in early childhood (but may not fully manifest until social demands exceed limited capacities)	• Symptoms together limit and impair everyday functioning

Source: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision. Reference 7

Table 2: DSM-5 Severity Levels for ASD

Severity Levels for ASD

1: Requiring support	2: Requiring substantial support	3: Requiring very substantial support
• Without support, deficits in social communication skills cause noticeable impairments • Rituals and repetitive behaviors cause interference with functioning in ≥ 1 contexts	• Marked deficits in verbal and nonverbal social communication skills are apparent even with support • Rituals, repetitive behaviors, and preoccupations cause interference with functioning in a variety of contexts	• Severe deficits in verbal and nonverbal social communication skills cause impairments in functioning • Rituals, repetitive behaviors, and preoccupations markedly interfere with functioning in all spheres

Source: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision. Reference 7

Association (APA). The most recent edition (DSM 5) was published in May 2013 and includes significant updates to ASD. Under the previous edition (DSM-IV), patients could be diagnosed with one of the following pervasive developmental disorders (PDDs): autistic disorder, Asperger's disorder, Rett's disorder, childhood disintegrative disorder, or PDD not otherwise specified. Patients diagnosed with one of the PDDs listed in DSM IV should still meet the criteria for ASD in DSM 5. The current ASD criteria are presented in Table 1. Additionally, severity levels for ASD were added in DSM 5 and are summarized in Table 2.

Children with ASD tend to have communication deficits, be overly dependent on routines and repetitive patterns of behavior, and have a high sensitivity to change within their environment. Children with ASD often struggle with many other challenges as well including irritability, hyperactivity, insomnia, gastrointestinal (GI) problems, and food allergies. Patients with ASD experience symptoms on a continuum that ranges from mild to severe. Symptoms can include language difficulties, lack of eye contact, repetitive behavior, abnormal responses to people or objects, and self-injurious behavior.

PHARMACOLOGIC THERAPIES FOR PEDIATRIC PATIENTS WITH ASD

Children can be a challenging patient population to correctly dose, as their bodily and organ functions undergo continuous development. These physiologic changes affect drug absorption, distribution, metabolism, and excretion; thus, obtaining a child's current height and weight are important pieces of information for every pharmacist and technician. Weight-based dosing calculations may prevent underestimation or overestimation of dosages for medications. This is of distinct importance when compounding therapies for pediatric patients with ASD.

FDA-Approved Medications Indicated for ASD

There are two FDA-approved medications, aripiprazole and risperidone (Table 3), that are indicated for ASD. Within a clinical trial setting, both medications have demonstrated effectiveness in alleviating behavioral symptoms, such as irritability. These medications require titration. Initial dose for aripiprazole is 2 mg per day titrated weekly, and risperidone should be started at 0.25 mg per day (if more than 20 kg, start at 0.5 mg per day) and titrated biweekly. The therapeutic dose for these medications varies from patient to patient; however, acceptable dose ranges are 5 mg/day to 15 mg/day given in a single dose for aripiprazole, and 0.5 mg/day to 3 mg/day given in either a single or divided dose for risperidone.

Four double-blind, randomized, placebo-controlled trials were conducted in children with ASD; two trials studied aripiprazole and two trials studied risperidone. After eight weeks of treatment, children in the aripiprazole and risperidone treatment groups demonstrated a statistically greater improvement on the Irritability subscale of the Aberrant Behavior Checklist (ABC) when compared to children in the placebo groups (Table 4). The ABC Irritability subscale contains 15 items that rate symptoms such as "injures self," "aggressive to other children and adults," "irritable," "temper outbursts," "depressed mood," "mood changes," and "yells or screams inappropriately" on a scale ranging from 0 (not at all a problem) to 3 (severe problem). The total possible score on the ABC Irritability subscale is 0 to 45. A score ≥18 is considered by clinicians to be 1.3 to 1.5 standard deviations above the population mean. Discontinuation rates due to adverse events were slightly higher in the aripiprazole treatment groups compared to the placebo groups. While discontinuation rates due to adverse events were equal for risperidone treatment groups and placebo groups, a greater number of patients taking risperidone reported adverse events, including increased appetite, fatigue, constipation, drooling, tremors, rhinitis, and weight gain.

While the exact mechanisms of action remain unknown, aripiprazole is a partial agonist of both dopamine D_2 (D_2) receptors and serotonin $5HT_{1A}$ ($5HT_{1A}$) receptors and an antagonist of serotonin $5HT_{2A}$ ($5HT_{2A}$) receptors; risperidone is

Table 3: Dosing Information for FDA-Approved Medications Indicated for ASD

Medication	Indication	Initial Dose	Titration	Target Dose	Dose Range	Frequency
Aripiprazole	Irritability associated with autistic disorder	2 mg/day	Up to 5 mg/day after 1 week	5 mg/day to 10 mg/day	5 mg/day to 15 mg/day	Single dose given QD
Risperidone	Irritability associated with autistic disorder	0.25 mg/day (<20 kg) 0.5 mg/day (≥20 kg)	0.25-0.5 mg at ≥ 2 week	0.5 mg/day (< 20 kg) 1 mg/day (≥ 20 kg)	0.5 mg/day to 3 mg/day	Single dose or equally divided dose given BID

Table 4: Efficacy of FDA-Approved Medications in Pediatric Patients With ASD

Study Medication/ Randomization	Study Design	Change in Primary Outcome Measure: Irritability[a]	*P*-value	Discontinuation Rate Due to Adverse Events (%)
Aripiprazole Studies				
98 subjects randomized to placebo or aripiprazole	8-week double-blind, randomized, placebo-controlled, flexible dose study	Placebo: -5 5 mg QD to 15 mg QD: -12.9	< 0.001 (all doses)	Placebo: 5.9 5 mg QD to 15 mg QD: 10.6
218 subjects randomized to placebo or aripiprazole	8-week double-blind, randomized, placebo-controlled study	Placebo: -8.4 5 mg QD: -12.4 10 mg QD: -13.2 15 mg QD: -14.4	< 0.05 (all doses)	Placebo: 7.7 5 mg QD: 9.4 10 mg QD: 13.6 15 mg QD: 7.4
Risperidone Studies				
101 subjects randomized to placebo or risperidone	8-week, double-blind, randomized, placebo-controlled, flexible dose study	Placebo: -3.6 0.5 mg QD to 3.5 mg QD: 14.9	< 0.001 (all doses)	Placebo[b]: 0 0.5 mg QD to 3.5 mg QD[b]: 0
80 subjects randomized to placebo or risperidone	8-week, double-blind, randomized, placebo-controlled, flexible dose study	Placebo: -6.5 0.01 mg/kg/day to 0.06 mg/kg/day: 12.1	< 0.001 (all doses)	Placebo[c]: 2.5 0.01 mg/kg/day to 0.06 mg/kg/day[c]: 2.4

a. Score obtained using the Irritability subscale of the Aberrant Behavior Checklist.
b. No subjects discontinued from the study due to AEs; however, several AEs were more common in the risperidone treatment group including increased appetite, fatigue, constipation, drooling, tremors, and weight gain.
c. Two subjects discontinued from the study due to AEs; however, several AEs were more common in the risperidone treatment group including somnolence, upper respiratory tract infection, rhinitis, and increased appetite.

Table 5: FDA-Approved Medications Indicated for ASD

Medication	Mechanism of Action	Drug Interactions	Adverse Effects
Aripiprazole	Partial D_2 and $5HT_{1A}$ agonist; $5HT_{2A}$ antagonist	• Strong CYP3A4 (ketoconazole) or CYP2D6 inhibitors (fluoxetine) increase plasma drug concentrations	Sedation, fatigue, vomiting, somnolence, tremor, pyrexia, drooling, extrapyramidal symptoms, weight gain
Risperidone	D_2 and $5HT_{2A}$ antagonist	• Carbamazepine and other enzyme inducers decrease plasma drug concentrations • CYP2D6 inhibitors (fluoxetine) increase plasma drug concentrations	Fatigue, increased appetite, sedation, nasopharyngitis, vomiting, weight gain, drooling, constipation, dry mouth

D = dopamine; 5HT = serotonin.

an antagonist of both D_2 and $5HT_{2A}$ receptors. Aripiprazole and risperidone blood levels are affected by inducers and inhibitors of Cytochrome P450 (CYP) 2D6 and 3A4. Since these patients may be very sensitive to changes in blood levels, it is very important for the pharmacist to flag interactions and discuss monitoring or drug selection with the prescriber and patient or caregiver. Patients taking aripiprazole or risperidone can experience drug-related adverse events, including sedation, fatigue, vomiting, and weight gain (Table 5). Prescribing information for aripiprazole includes the boxed warning "Children, adolescents, and young adults taking antidepressants for major depressive disorder and other psychiatric disorders are at increased risk of suicidal thinking and behavior." Pharmacists who dispense aripiprazole must also dispense a medication guide for the drug. Pediatric patients taking these medications should be closely monitored.

MEDICATIONS COMMONLY PRESCRIBED FOR OFF-LABEL USE IN PEDIATRIC PATIENTS WITH ASD

Many pharmacotherapies are prescribed for off-label use in pediatric patients with ASD. Unfortunately, it is often not possible to tell which medication will be the most effective or what the most effective therapeutic dose might be for a particular patient. Table 6 highlights several medications that are frequently prescribed off-label for children with ASD. The medications aim to improve behavioral symptoms, decrease GI problems, or alleviate sleep disorders. Information on dosage forms that can be used when compounding these medications can be found in Table 9.

Improvements in behavioral disturbances have been reported in pediatric patients with ASD from the use of pharmacological therapies that target and inhibit glutamatergic transmission. Glutamate is the main excitatory neurotransmitter in the brain, and its potential link to ASD is currently being investigated. Studies of off-label use of N-methyl-D-aspartate (NMDA) receptor antagonists, amantadine and memantine, indicate decreases can be achieved in hyperactivity, irritability, agitation, and stereotyped behaviors by patients taking these therapies. In clinical trials, amantadine has been studied at doses of 2.5 mg/kg/day to 5 mg/kg/day, while memantine has been studied at 2.5 mg/day to 30 mg/day.

A number of studies have reported clinical improvements in behavior with low doses (0.5 mg/kg/day to 2 mg/kg/day) of naltrexone, an opioid receptor antagonist. Naltrexone predominately demonstrated efficacy in decreasing self-injurious behavior. During self-injury, researchers believe beta-endorphin is released which binds to opioid receptors. In addition, naltrexone may have beneficial effects on hyperactivity, irritability, agitation, and stereotyped behaviors as well. Additional studies are needed to determine efficacy and prescribing guidelines.

The neurotransmitter serotonin has specific functions within the central nervous system and is known to regulate many physiological activities. Off-label use of low-dose fluoxetine, a selective serotonin reuptake inhibitor (SSRI), has demonstrated efficacy with respect to repetitive behavior, overall improvement in behavior issues, and possibly language acquisition in children with ASD. Increased repetitive behavior has been linked to altered serotonin homeostasis for many years. While additional studies are needed for a new indication, SSRIs and tricyclic antidepressants are mainstays of drug therapy for obsessive-compulsive disorder. Although the complex system is not fully understood, one hypothesized theory is that altered serotonin levels during early stages of development may lead to behavioral and cellular changes observed in some children with ASD.

Because cholinergic receptor abnormalities are thought to potentially contribute to the neuropathology of ASD, a few studies of acetylcholinesterase inhibitors prescribed off-label including donepezil, galantamine, and rivastigmine have been done in pediatric patients with ASD. Studies with donepezil in doses ranging from 1.25 mg/day to 5 mg/day have reported improvements in irritability, hyperactivity, and language skills in some patients. Similar improvements in behavior and language as well as social skills were seen with galantamine at doses of 4 mg/day to 24 mg/day. A small, open-label study of rivastigmine (doses ranging from 0.8 mg/day to 1.6 mg/day) demonstrated significant improvements in expressive speech and overall behavior. These studies suggest increasing synaptic acetylcholine could be of benefit to children with ASD and additional studies are needed to establish efficacy.

Nystatin and fluconazole are both antifungal therapies commonly used to inhibit the overgrowth of yeast organisms, specifically *Candida albicans*. While clinical trials are needed, it is generally acknowledged that abnormal levels of bacteria in the gut can cause yeast overgrowth. Clinical trials are needed to establish efficacy and guidelines for prescribing and monitoring antifungal therapy. Despite lack of data, antifungal medications are often prescribed.

Oxytocin, a hormone associated with emotional bonding, trust, and many biological processes, functions as a neurotransmitter and has been found to stimulate brain areas linked to social control in children and adults with and without ASD. Researchers hypothesize that these brain regions could be enhanced or influenced by pharmacotherapy. Recent experimental studies suggest oxytocin improves emotion recognition and social cognition in young patients

Table 6: Medications Commonly Prescribed for Off-Label Use in Pediatric Patients With ASD			
Medication	**Mechanism of Action**	**Clinical Potential**	**Adverse Effects**
Amantadine	NMDA receptor antagonist	Behavioral disturbances (irritability, hyperactivity)	Generally well-tolerated; possibly nausea, dizziness, insomnia
Memantine	NMDA receptor antagonist	Behavioral disturbances (irritability, stereotyped behavior, hyperactivity)	Generally well-tolerated; possibly diarrhea, dizziness, headache
Naltrexone	Opioid receptor antagonist	Behavioral disturbances (self-injurious behavior)	Transient sedation
Fluoxetine	SSRI	Behavioral disturbances (repetitive behaviors); language acquisition	Initial loss of appetite, vivid dreams, suicidal behavior or thinking
Donepezil	Acetylcholinesterase inhibitor	Behavioral disturbances (irritability, hyperactivity); language	Mood lability
Galantamine	Acetylcholinesterase inhibitor	Behavioral disturbances (irritability, hyperactivity); language; social skills	Possibly headache
Rivastigmine	Acetylcholinesterase inhibitor	Overall behavior; language	Nausea, diarrhea
Nystatin	Antifungal	Yeast overgrowth	Oral irritation, upset stomach
Fluconazole	Antifungal	Yeast overgrowth	Upset stomach, headache
Oxytocin	Hormone	Social behavior	Loss of appetite, upset stomach
Melatonin	Hormone (Dietary supplement)	Insomnia	Rare
Glutathione	Antioxidant	Behavioral disturbances (glutathione redox ratio)	Generally well-tolerated
Methylcobalamin	(Vitamin)	Behavioral disturbances (glutathione redox ratio)	Hyperactivity, insomnia

NMDA = N-methyl-D-aspartate; SSRI = selective serotonin reuptake inhibitor.

with ASD; thus, oxytocin could potentially help children who struggle to empathize and make social connections with other people. Further studies are needed to establish efficacy and prescribing guidelines.

FREQUENTLY COMPOUNDED VITAMINS, MINERALS, AND OTHER DIETARY SUPPLEMENTS FOR PEDIATRIC PATIENTS WITH ASD

More than half of all children diagnosed with ASD experience some form of sleep disorder. A low melatonin level is more often found in children with ASD than children without ASD and is thought to partially cause the high rate of sleep disturbances. Pediatric insomnia is defined as "repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite age-appropriate time and opportunity for sleep and results in daytime functional impairment for the child and/or family." Insufficient sleep can lead to chronic sleep deprivation. This can worsen a child's ASD symptoms and decrease daily function of both the patient and the caregiver. Increasing melatonin levels within the body by supplementation has demonstrated efficacy in improving sleep disturbances in pediatric patients with ASD and is commonly used to manage insomnia. While an optimal dose has not been established because

melatonin is regulated as a dietary supplement rather than a drug, a low dose (studies have used 1 mg to 3 mg) should be used initially and then the dosage assessed based on a particular patient's response.

Studies attempting to assess the prevalence of gastrointestinal conditions in pediatric patients with ASD have reported figures ranging from 10-90 percent; coexisting GI issues can impair or prevent the delivery of vital nutrients to the body. Micronutrient supplementation may be necessary and can be a successful way to boost nutrients lacking in a patient's diet, and can potentially be beneficial in improving symptoms associated with ASD. Dietary limitations, lactose intolerance, food allergies, and a particular child's preference for certain colors, tastes, and textures all contribute to a higher rate of nutritional deficiencies in children with ASD than children without ASD. Several studies have reported GI issues, such as esophagitis, chronic constipation, diarrhea, and gaseousness, are more common as well.

A compounding pharmacy can be extremely helpful when nutritional therapy is required for a patient. Most vitamin and mineral combinations need to be tailored specifically for the individual patient due to requirements for specific vitamin salt forms or dosages above or below commercially available dosages. Compounding pharmacies can provide combinations of vitamins, minerals, and supplements in dosage forms that will comply with each patient's taste preferences and dietary restrictions as well. Several nutrients commonly requested to be compounded for pediatric patients with ASD are listed in Table 7.

Commonly used dosage forms for nutritional therapy include suspensions, popsicles, troches, and effervescent powders that can be added to water. More details on dosage forms are included in Table 9. However, compounding pharmacists need to adjust dosage forms based on the compatibility of the particular vitamins or minerals a patient requires. For example, folic acid is only stable in water at a high pH, but most other B vitamins are acidic and may not be stable for long periods of time in an aqueous environment. Dosage forms such as troches or effervescent powders which are added to water and immediately consumed would be more appropriate to use than oral suspensions. For further information on calculating doses, please see "The Art, Science, and Technology of Pharmaceutical Compounding," Third Edition.

While vitamins and minerals are commonly prescribed to children with ASD as adjunct therapy, the number of robust scientific studies on their effectiveness in alleviating symptoms of ASD has been limited. Existing studies and current thinking on several common vitamin/mineral therapies are highlighted as follows.

There is increasing evidence that deficiencies in omega-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), contribute to neurodevelopmental disorders. DHA is critical for early brain development, while EPA is involved in later development. These omega-3 fatty acids are essential for cell membrane structure and function and contribute to the regulation of cell signaling. Studies have found that children with ASD tend to have lower levels of omega-3 fatty acids than the general population. Conclusions from two small clinical trials have suggested improvements in language, learning skills, and social abilities can be achieved in children with ASD with omega-3 fatty acid supplementation; however, larger controlled trials are still needed. Furthermore, omega-3 fatty acids play a role in inflammation suppression. Since many children with ASD experience gut inflammation, it has been proposed that omega-3 fatty acid supplementation could help decrease GI symptoms as well.

Emerging data in ASD research suggest an imbalance between oxidative systems and anti-oxidative stress systems in children diagnosed with ASD. Multiple studies have demonstrated that children with ASD have impaired methylation processes (decreased S-adenosylmethionine, the primary methyl donor for most cellular methyltransferase reactions including the methylation of deoxyribonucleic acid, ribonucleic acid, and proteins) and increased oxidative stress (measured by calculating oxidized to reduced glutathione ratios) compared to neurotypical children. When antioxidant defense mechanisms fail to counterbalance reactive oxygen species generated from endogenous oxidative metabolism or prooxidant environmental exposures, oxidative stress can occur. At this time, it is not clear what possible genetic or environmental factors might initiate oxidative stress and abnormal metabolic profiles in children with ASD; however, supplements have been shown to improve methylation capacity. When children with ASD were given methylcobalamin (the active form of B12), folinic acid, and trimethylglycine combination therapy, significant benefits in methylation, (reduced) glutathione, and markers of oxidative stress were measured.

Glutathione is an antioxidant involved in neuroprotection against oxidative stress; therefore, therapies that increase the reduced form of glutathione are thought to enhance the anti-oxidative stress system. Another trial in pediatric patients with ASD reported that administration of subcutaneous methylcobalamin and folinic acid led to an improvement in the oxidized to reduced glutathione ratio as well. For further information on the biochemical basis behind

Table 7: Frequently Compounded Vitamins, Minerals, and Supplements for Pediatric Patients With ASD		
Vitamins	**Minerals**	**Supplements**
• Vitamin A • Vitamin C • Vitamin D • Vitamin E • Methylcobalamin • Pyridoxal 5 phosphate • Pantothenate • Riboflavin • Folinic acid	• Magnesium glycinate or aspartate • Zinc citrate or gluconate • Calcium glycinate	• 5 methyl tetrahydrofolate • Curcumin • Dimethylglycine • Glutathione • Omega 3 fatty acids • Probiotics (occasional) • Silymarin • Trimethylglycine

Source: Nutritional Supplement Use for Autistic Spectrum Disorder, Text Revision.

these clinical observations, please see recently published article "Efficacy of methylcobalamin and folinic acid treatment on glutathione redox status in children with autism" in the *American Journal of Clinical Nutrition*. Researchers hypothesize that decreasing the imbalance between the oxidative and anti-oxidative stress systems may result in improved clinical outcomes for children with ASD.

Several double-blind, placebo-controlled clinical trials have been conducted on high-dose vitamin B6 and magnesium chloride treatment in pediatric patients with ASD. Vitamin B6 is required for hundreds of enzymatic reactions in the body, including the production of major neurotransmitters such as dopamine and serotonin, glutathione, and hemoglobin. It exists in six different forms: three unphosphated forms and three phosphated forms. Survey data suggest some children benefit more from unphosphated forms (pyridoxine), but all forms should be well absorbed and have similar effects. Magnesium is prescribed in conjunction with pyridoxine to prevent a possible increase in hyperactivity which can occur in some children when vitamin B6 is taken alone. Most studies indicated a clinical benefit when pyridoxine hydrochloride was given at a high dose (3.5 mg/kg to 7 mg/kg; maximum of 1,000 mg). The exact reason for the improvement observed in children with ASD is unknown; however, researchers hypothesize that children with ASD have a decreased ability to convert vitamin B6 to its active form. Furthermore, studies have suggested that children with ASD have a decreased methionine and homocysteine metabolism ability, which leads to an impairment in their cellular methylation capacity.

THE PHARMACIST'S ROLE IN COUNSELING THE PARENT AND/OR CAREGIVER

Community pharmacists are in a unique position to provide pharmacy counseling and related information to caregivers that can have a significant impact on both the child's and caregiver's quality of life. Due to their young age, children have a limited ability to understand and manage their disorder and rely on a parent and/or caregiver for their care. Several free online resources exist for ASD with information ranging from disease state information to support groups for both patients and caregivers (Table 8).

Because children with ASD often have one or more food allergies (see Figure 1), dietary restrictions are common for many patients. In addition to allergies, food sensitivities can cause issues due to abnormalities within the digestive and immune systems. For example, some children experience incomplete digestion of complex carbohydrates (disaccharides and polysaccharides) that can be found in certain fruits or vegetables. Undigested carbohydrates remaining in the intestinal tract can lead to the growth of abnormal gut flora, inflammation of the intestine wall, and GI discomfort.

Other common dietary restrictions followed by children with ASD include the avoidance of all gluten (wheat protein) and casein (milk protein). Symptoms are thought to arise when the digestive tract does not fully digest the gluten and casein peptides into single amino acids. If the partially digested gluten and casein peptides enter the bloodstream through inflammation of the gut, they can bind to opioid receptors in the brain and mimic the effects of opiate drugs. Many parents have reported reductions in their child's symptoms associated with ASD by following a gluten-free, casein-free diet. This diet can be challenging for parents as it requires the elimination of all wheat, rye, barley, oats, milk, and all milk products. While further clinical trials are needed, a growing body of evidence does suggest dietary interventions can help reduce GI issues as well as potentially alleviate ASD symptoms. Caregivers and parents often turn to pharmacists for advice in identifying foods, medications, and products that might exacerbate their child's symptoms.

Table 8: Available Resources for ASD		
Resource	**Website**	**Highlight of Resource Information**
American Academy of Pediatrics	www.aap.org	Training and webinars on ASD for health care professionals; yearly national conference for health care professionals
Autism Research Institute	www.autism.com	Educational support for families about treatment options for patients with ASD; weekly webinars on ASD for caregivers and health care professionals
Autism Society	www.autism-society.org	Information/referral service to assist families in finding local support; yearly national conference for health care professionals
Autism Speaks	www.autismspeaks.org	Advocacy Tool Kit available for individuals newly diagnosed with ASD and their families; information on autism apps recommended by community members
Elaine Gottschall, MSc	www.breakingtheviciouscycle.info/home/	Common GI issues associated with ASD; diet suggestions to alleviate GI symptoms (Specific Carbohydrate Diet)
CDC: Autism Spectrum Disorders	www.cdc.gov/ncbddd/autism/index.html	Statistics, screening, diagnosis, and treatment of ASD; scientific articles and free materials available for print or order
Medical Academy of Pediatric Special Needs	www.medmaps.org/	Comprehensive CE program and information for health care professionals on ASD; resource for parents seeking qualified doctors within their communities
National Autism Association	nationalautismassociation.org	Local chapters available to support families affected by ASD; yearly national conference for health care professionals

Pharmacists play a vital role in compounding medications for children with ASD that are free of allergens found in many commercially available products. For example, children with ASD can be sensitive to commercially available nystatin suspension because it contains methylparaben, propylparaben, sucrose, saccharin, and yellow dye. Commercially available amoxicillin suspensions and capsules may contain red dye which is another sensitivity for children with ASD. Before beginning to compound a medication, it is important to keep in mind that children with ASD tend to have strong taste, color, and textural preferences. For example, many children do not care for the peppermint taste of commercially available memantine syrup. Memantine can be compounded in to minimize this flavor (see details in Table 9). Obtaining information upfront from the caregiver about both a child's allergies and aversions can help a pharmacist decide on the most appropriate dosage form to use when compounding therapies for that particular child. This strategy can lead to improvements in medication adherence and make the overall experience as positive as possible for both the caregiver and child.

DOSAGE FORMS COMMONLY USED WHEN COMPOUNDING MEDICATIONS FOR PEDIATRIC PATIENTS WITH ASD

Children with ASD are often sensitive to specific tastes, textures, and allergens commonly used in commercial drug formulations; many children struggle with swallowing pills as well. Finding an appropriate dosage form for a new medication prescribed to a child with ASD can be a chal-

Figure 1: Food Allergies Commonly Found in Children With ASD

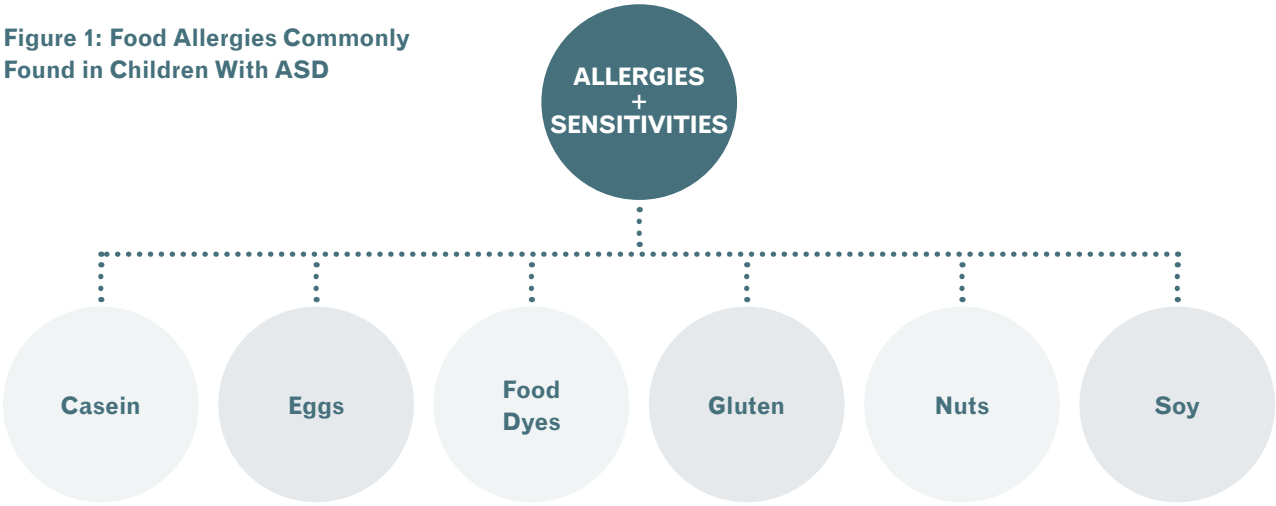

Table 9: Commonly Used Dosage Forms for Pediatric Patients With ASD

Dosage Form	Advantages of Dosage Form	Child Proofing Information	Suggested Medications for Compounding With Dosage Form
Transdermal creams	Avoid bitter flavors, first pass metabolism, and pill swallowing; reduce possible yeast overgrowth in the gut	Placed into an appropriately sized child proof foil laminate bag	Glutathione, Melatonin, Naltrexone,
Troche	Variety of flavors available; Avoid pill swallowing	Placed into an appropriately sized child proof foil laminate bag	Melatonin, Amantadine, Memantine, Nystatin, Fluconazole
Popsicles	Viewed as a "treat"; variety of flavors available; avoid pill swallowing	Placed into an appropriately sized child proof foil laminate bag	Amantadine, Memantine, Nystatin, Fluconazole, Vitamins, Minerals
Oral suspensions	Variety of flavors available; avoid pill swallowing	Child proof lid	Melatonin, Nystatin,a Vitamins, Minerals, Amino acids
Oral effervescent powder packets	Variety of flavors available; avoid pill swallowing	Placed into an appropriately sized child proof foil laminate bag	Melatonin, Fluconazole, Nystatin, Memantine, Amantadine, Vitamins, Minerals, Amino acids
Suppositories	Avoid bitter flavors, first pass metabolism, and pill swallowing	Prescription bottle with child proof lid; dispensing device used to obtain dose from bottle coupled with a child proof lid	Medications that are challenging to compound in other dosage forms (e.g., antibiotics)
Nasal sprays	Avoid first pass metabolism and pill swallowing	Placed into an appropriately sized child proof foil laminate bag	Oxytocin, Methylcobalamin
Injectables	Avoid bitter flavors, first pass metabolism, and pill swallowing	Placed into an appropriately sized child proof foil laminate bag	Methylcobalamin (subQ)

a. Commercially available but commonly compounded in sugar-free form for children with ASD.
Note: The dosage forms and suggested medications above are intended to be examples of pharmacologic therapies encountered by pharmacists and technicians working within a compounding setting.

lenge. Table 9 provides a summary of some dosage forms and medications that can be encountered by pharmacists and technicians working within a compounding setting.

Several dosage forms can be compounded in a variety of flavors including troches, popsicles, oral suspensions, and oral effervescent powder packets. Popsicles are viewed by some patients as a treat, so disguising their medication within this form can increase adherence and decrease stress associated with medication time for both the patient and the parent or caregiver. One possible drawback of a popsicle, oral solution, and effervescent powder is that the entire popsicle or liquid measured must be consumed to get the full dose of medication. Many medications can be compounded in several different dosage forms. For example, melatonin can be compounded as a transdermal cream, troche, oral suspension, or oral effervescent powder packet. If a patient has an aversion to one dosage form, it is possible to try another dosage form for many medications and improve adherence to therapy.

One class of medications that can be challenging to compound is antibiotics. Antibiotics have poor transdermal bioavailability. Suppositories are a useful dosage form for these cases. As with any medications dispensed to households with children, containment of the medication within child proof packaging is an important last step of the compounding process.

CONCLUSIONS

The revised diagnosis of ASD in DSM-5 represents a more accurate and medically useful way of diagnosing individuals with autism-related disorders. Once diagnosed, children with ASD are frequently administered a combination of prescription and nonprescription medications, vitamins, minerals, and other dietary supplements to help alleviate their symptoms. As health care professionals with high visibility within the public, community pharmacists and pharmacy technicians play a key role in educating families on ASD. The variety of dosage forms that are available for compounding pharmacologic therapies and are amenable to the unique needs of each child with ASD can help improve the functionality and overall quality of a patient's life. ■

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Editor's Note: For the list of references used in this article, please contact *America's Pharmacist* Managing Editor Chris Linville at 703-838-2680, or at chris.linville@ncpanet.org.

Continuing Education Quiz

Select the correct answer.

1. ASD patients who display mild repetitive speech and fail to maintain relationships with peers are typically diagnosed with which severity level.
a. Level 1
b. Level 2
c. Level 3

2. The risperidone target dose for a child weighing 65 pounds is 0.5 mg/day.
a. True
b. False

3. Which of the following medications are FDA approved for ASD?
a. Olanzapine
b. Sertraline
c. Fluoxetine
d. All of the above
e. None of the above

4. Low dose naltrexone is prescribed off-label on the theory that it works to decrease self-injurious behaviors by which mechanism of action?
a. 5HT antagonist
b. Opioid receptor antagonist
c. NMDA receptor antagonist
d. Acetylcholinesterase inhibitor
e. None of the above

5. Studies suggest that cholinergic enhancing treatments can be beneficial to children with ASD. Which of the following drugs would provide such an effect?
a. Nystatin
b. Fluconazole
c. Oxytocin
d. Donepezil
e. None of the above

6. Which of the following is not true about oxytocin?
a. Oxytocin is a hormone.
b. Oxytocin can be compounded as a nasal spray.
c. Oxytocin can be compounded as an oral liquid.
d. Oxytocin is used to help with socialization.

7. Vitamin B6 is required for hundreds of enzymatic reactions in the body including the production of:
a. Dopamine
b. Glutathione
c. Hemoglobin
d. All of the above

8. Methylcobalamin is preferred over cyanocobalamin for dietary supplementation in patients with Autism.
a. True
b. False

9. Compounding unique dosage forms for patients with Autism may help:
a. Eliminate allergens found in a commercially available drug
b. Reduce taste and textural issues
c. Meet specific dosage needs of the patient
d. All of the above

10. Children's compounded medication should always be dispensed in child proof packaging.
a. True
b. False

11. Melatonin can be compounded as a
a. Transdermal cream
b. Troche
c. Oral suspension
d. Effervescent powder packet
e. All of the above

12. Which class of medications can be particularly difficult to compound
a. Antifungals
b. Antibiotics
c. Vitamins and minerals
d. Acetylcholinesterase inhibitors

13. The benefits of making oral suspensions for children with autism include:
a. Many flavoring options
b. Avoiding bitter flavors
c. Avoiding pill swallowing
d. Both a and c are correct

Use the following case to answer questions 14-15.

Part 1

A 4-year-old boy enters your pharmacy with his parents and a prescription for melatonin compounded as a transdermal cream. You do not recognize them as current patients of your pharmacy, and notice the exhausted-looking parents struggling to calm the irritable and equally exhausted-looking boy. Upon speaking with the family, you learn that they have recently moved to the community. The boy was diagnosed with ASD earlier that morning by his new pediatrician and refuses to swallow pills.

14. What would you do next?
a. Tell the parents you will have the cream ready in one hour.
b. Ask the parents if their child has any allergies and particular taste, color, or texture preferences before you begin compounding the cream.
c. Let the parents know you can assist them with online resources if they would like more information about caring for a child with ASD.
d. Choices b and c

Part 2

A month later, the boy and his parents return to your pharmacy to get a refill of the melatonin cream. The parents comment that the melatonin does seem to be helping their son's insomnia; however, the process of administering the medication is very stressful for the family because their son dislikes the feeling of the cream on his skin.

15. What would you do next?
a. Tell the parents you will have the cream ready in one hour.
b. Ask the parents if their child has any particular aversions to liquids and suggest compounding the melatonin as an oral suspension instead of a cream.
c. Suggest compounding the melatonin as a suppository instead of a cream.
d. Offer to the parents for the child to take over-the-counter melatonin.