Clinical Roundup

Selected Treatment Options for Autism

Omega-3, Vitamin D_3, and Melatonin

I generally routinely recommend omega-3 fatty acids (1 or more g), vitamin D_3 (2000–5000 international units), a good multinutrient, probiotics, and digestive enzymes if there are gastrointestinal (GI) issues, and melatonin (2–9 mg) if there is sleep difficulty. Of the dose ranges indicated here, the lower dose is for children and the higher dose is for larger adolescents and adults. Is the combination of these three most likely to work? That is the "million-dollar question." I and my colleagues have been conducting a study at four sites that do that kind of combination treatment. A very large number of patients will be needed for combination treatments to truly show any kind of believable effectiveness.

For omega-3, evidence from studies continues to be either equivocal or positive. Omega-3, long-chain fatty-acid supplementation is reasonable to consider because omega-3 fatty acids are essential for brain development,[1] being part of optimal neuronal membranes and being a substrate for the production of eicosanoids (e.g., prostaglandins) necessary for cell communication and immune regulation. In addition, low levels of omega-3 fatty acids have been reported in children with autism spectrum disorder (ASD).[2–4]

The two omega-3 fatty acids of interest are eicosapentaenoic acid and docosahexaenoic acid. Based on data from other disorders, these fatty acids would be expected to improve mood, attention, and activity level as well as possibly reducing autism symptoms.

Vitamin D_3 is something that people continue to be interested in and seems to have a good rationale for use. There have been case series or case reports that suggest that the vitamin might be helpful. Adams at al. found that oral vitamin/mineral supplementation is beneficial for improving the nutritional and metabolic status of children with autism, including improvements in methylation, glutathione, oxidative stress, sulfation, adenosine triphosphate, the reduced form of nicotine adenine dinucleotide (NAD), and NAD phosphate.[5] This finding suggests a possible benefit derived from a comprehensive digestive enzyme supplement with meals to aid digestion of all proteins and peptides, especially for children with ASD who have GI disturbances.

My research team has has been conducting a small vitamin D_3 study with children with ASD. Because the effect size is small, studies must be conducted over a long period of time. There is not yet a study that truly shows that vitamin D_3 is indicated for ASD treatment, although Mostafa and Al-Ayadhi found that 70% of children with autism were below the 30-ng vitamin D_3 blood level, which is what most experts consider to be deficient.[6] Some say it is 20 ng. If a vitamin D_3 blood level of 30 ng were considered to be deficient, this would suggest that a lot of children with autism would need to receive supplementation.

Enzyme deficiencies in children with autism result in a reduced ability to digest protein, which affects the availability of amino acids essential for brain function. There is increasing evidence for a gut–brain connection associated with ASD, at least in some cases.

N-acetylcysteine (NAC) is an ingestible complementary and alternative treatment that has also shown great potential. NAC is a glutamatergic modulator and antioxidant that was examined in a 12-week, double-blinded, randomized placebo-controlled study in children with ASD.[7]

It has become fairly accepted in the field to think about recommending melatonin for people with developmental disabilities who have sleep problems. Rossignol and Frye published a very good review and meta-analysis of 35 melatonin studies.[8,9] These included 18 treatment studies, of which 13 were uncontrolled and five were randomized, double-blinded, placebo-controlled crossover trials. Six studies of night-time administration led to improvements in daytime behavior. Within the five randomized controlled studies, melatonin was associated with increases in sleep duration and decreases in sleep-onset latency, but night-time awakenings were unchanged. Side-effects were minimal to none.

Unfortunately, small sample sizes, variability in sleep assessments, and lack of follow-up limit the conclusiveness of these studies, but, overall, melatonin is one of the best-studied complementary and alternative treatments for ASD. Treatment with melatonin has a clear physiologic rationale; use of melatonin is sensible, easy, inexpensive, and safe.[10]

All comments, opinions, and recommendations in the Clinical Roundup are those of the authors and do not constitute those of the Journal, its Publisher, or its editorial staff.

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Methyl Vitamin B_{12}, *MTHFR* Pathway, and Pharmaceuticals

It is extremely crucial to do an assessment of what therapies a child is receiving and what that child's struggles are, and to ensure that the therapy and the therapist are the best fit for that child's individual struggle. On the biologic side, my job as a physician is to remove physical obstacles to effective treatment, whether these are gastroenterologic, neurologic, or nutritional. I tend to use, as my foundational baseline for every child, omega-3 fatty acids. When applied as initial target therapies, I have definitely seen that high doses of omega-3 fatty acids can truly help unlock children's nervous-system function, as preliminary evidence has suggested with respect to hyperactivity.[1]

I do absolutely endorse much of the research of Jill James and colleagues at the Arkansas Children's Hospital Research Institute, at the University of Arkansas for Medical Sciences. Much of her research entails studying oxidative stress methylation capacity; examining nervous-system function and detoxification for children with autism; exploring redox parameters; and examining increased oxidative-stress parameters and the value of treating these with methyl vitaminB$_{12}$, methylated folate, and some of the cofactors.[2,3] Much of my own work validates or reinforces some of that research. For some children, this might be methyl vitamin B_{12} injections; for other children it might be amino-acid support or oral formulas that contain the methylated B vitamins and their cofactors.

Children and their families should definitely be redirected toward a good, healthy solid diet that increases fruits and vegetables. The brain cannot be treated without treating the gut and the child's diet. For some children, eliminating gluten and casein really helps; for other children, it really does not help.[4] I have found that 100% of these children respond negatively to artificial colors and sweeteners and high-fructose corn syrup. When those things are eliminated, one does see better nervous-system regulation, although I think this is true for neurotypical children as well.

With respect to epigenetics, I turn again to Jill James and colleagues, who are truly doing some great research on the *MTHFR* pathway and implications, as well as the end result when you do support that pathway.[5] Every once in a while, I will run the *MTHFR* gene or I'll have the family do extensive epigenetic testing. Sometimes, this approach also raises many questions that are not necessarily answerable from an evidence-based perspective. I am not quite sure that I have seen the clinical results that would make testing the entire epigenetic panel a firm recommendation. I think this will come.

Pharmaceuticals are appropriate when a child is not functional enough to benefit from speech therapy or occupational therapy. For instance, when a child is so incredibly dysregulated, therapy is ineffective. If a child cannot participate for even 10 seconds of joint attention and engagement with a therapist, then this is a major stopping place for that child's development.

Some children will need a low dose of Risperdal® (rispiridone), or a low dose of Prozac® (fluoxetine) to address dysregulation, aggression, or anxiety.[6,7] One of my favorite nonstimulant attention-deficit disorder medications is Intuniv® (guanfacine), a low dose of which can relieve some of the child's extremely sensory-driven hyperactivity.[8] If a pharmaceutical can bring children to where therapy starts to work, then they are gaining skills and may not need the medication forever. However, medication can be a "life raft." If a child needs that life raft, I have got to give it to him or her, or I'm not doing my job.

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The "Toxic Kettle"

My approach is truly integrative and involves many types of modalities, from dietary modifications to nutritional supplementation to detoxification modalities. The approach can include medications when children's conditions are severe—as many of the children I see have severe impairments. Dietary modifications include avoiding refined carbohydrates, artificial additives, and allergenic foods. In addition, specialized diets can be used, including a gluten-free/casein-free diet or a specific carbohydrate diet when indicated.

Nutritional modalities may include vitamins, minerals, herbs, fatty acids, or various types of neutraceuticals; and, when necessary, treatment may include pharmaceuticals, such as antifungals and antivirals. Clinical and behavioral modalities include occupational therapy, physical therapy, speech therapy, and various behavioral therapies.

Autism is a classic example of understanding the importance of genetic susceptibilities coupled with environmental factors and insults.[1] This helps to explain why obviously not every child is affected; there may be children exposed to the same environmental triggers or insults who do not develop autism. In addition, these factors probably explain why we are seeing an increasing number of children who are affected, going from 1 in 2500 to 1 in 68 children right now.[2,3] It is hoped that the genetic- and environmental-research communities are accepting the fact that research needs to be directed to examining the importance of both factors when studying the outcomes in these children.

Toxins range from heavy metals, such as mercury and lead[4,5]; to chemicals, such as plasticizers, including bisphenol A and phthalates; and pesticides, including organochlorine and organophosphate pesticides.[6] While many of the studies are designed to investigate a single toxicant's toxicity levels, children are being exposed to increasing amounts of toxins in combination. Newer paradigms would suggest that we really need to look at combinations of toxicants. We are not really seeing single exposures. This is much more a problem of chronic, low-dose multiple exposures, rather than acute high-dose single exposures.

I use a picture of what I call the immune or toxic threshold "kettle" to help patients understand the effects of genetic and environmental influences on the immune system. When the kettle "overflows," the patient can have immune imbalances and/or biochemical imbalances, then clinical imbalances, and eventually syndromes and disorders. There can be an underlying genetic predisposition, as well as contributing factors, such as allergies, hormone imbalances, or metabolic imbalances. There can also be all kinds of infections, from viruses, to fungi, to bacteria; psychologic stresses; and toxicants.

All of these are "layers" in this kettle. The lower down one is in the kettle, the more reserve one has to resist these exposures and these insults, and thus not overflow.[7] Living in the world as it is, it is impossible to avoid all these exposures, but reducing them as much as possible can reduce the level of toxic/inflammatory load well below the threshold that leads to problems.

If one has a child who is so aggressive that he or she is putting siblings in danger, a clinician is going to try to get to the bottom of that. However, it takes time for some of these investigations to "bear fruit," and for some of the nutritional and dietary modifications to work. If a child is self-injurious or truly aggressive, that child may need a medication to control those behaviors for his or her own safety as well as the safety of others. However, I do not believe in behavioral medications as the sole treatment modality. Although medications may be necessary to control behavior while I am looking for the underlying causes, my goal is to correct those causes by natural means if possible and avoid chronic use of medications.

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The Gastrointestinal Tract and Adult ASD

According to the Centers for Disease Control and Prevention, rates of autism spectrum disorders (ASDs) in 8-year-old children in the United States are 1 in 68.[1] Although autism is com-

monly known as a behavioral disorder, there is significant evidence that it is multifactorial and that people with autism often have concurrent neurologic, gastrointestinal (GI), immunologic, and/or detoxification impairments and oxidative stress.[2,3]

It is important to be sure to include the parent's medical history and the child's birth and feeding history as well as the child's immunization history and environmental exposures. A review of all systems on one's intake form for children with autism should also be performed.

I believe most practitioners acknowledge the role of the GI tract in health and disease. Abnormalities—such as impaired integrity of the intestinal wall, poor carbohydrate digestion, fat malabsorption, and dysbiosis—are all common in children with autism.[4,5] Common clinical signs of GI dysfunction include gastroesophageal reflux disease, diarrhea, constipation, flatulence, vomiting, and a distended abdomen.

The clinician must also look for extraintestinal signs of GI impairment, including behavioral or sleep disturbances, toe walking, dermatitis, posturing (bending over a structure to relieve abdominal pressure), sensory sensitivity, and/or self-injurious behavior. Children with autism have higher rates of celiac disease and gluten sensitivity, with consequent nutritional deficiencies from malabsorption.[6,7] Diagnosing and resolving these nutritional deficiencies (and underlying causes) are imperative to reestablishing health.

I advise including a diet diary or nutrition review with the initial evaluation of a patient. Where does the family shop? Does the family buy fresh or prepackaged foods? Does the child crave any particular foods? Often what he or she craves is symptomatic to underlying pathology. Almost all children with autism improve with a whole-foods (gluten-free/casein-free) or specific carbohydrate/gaps diet.

Given ASD's multifactorial nature, laboratory testing for children with the condition can be complex. I am partial to ordering the urinary organic acid test, because the results include information on metabolic, nutrient, and neurotransmitter status; GI yeast and bacteria; oxidative stress; mitochondrial function; and glutathione production. If dysbiosis is present, the probiotic *Saccharomyces boulardii* has been shown to be helpful for restoring gut-flora equilibrium.[8]

Adults with ASD comprise an undiagnosed and underserved population. In May 2014, researchers at Kaiser Permanente found that adults with autism are more prone to hypertension, hyperlipidemia, obesity, diabetes, GI disturbances, epilepsy, and sleep disorders.[9] Adult patients with ASD might present to a clinician with limited eye contact, difficulties with communication, and/or anxiety, or these patients might report histories of anxiety and social difficulties.

One adult patient with Asperger's syndrome reported to me that she spends an enormous amount of energy trying to understand how people around her communicate, and how she can fit in (which, in her mind, is impossible). A recent small study validated this patient's feelings.[10] By using functional MRI to measure brain-activation patterns of adults with high-functioning autism and matched controls in various social situations, researchers found that the adults with autism lacked a "self factor" (i.e., they viewed themselves as spectators in the experience of social interactions).[10] Although this study clearly has limitations because of the small population studied, this research can help us understand and reach people further in this population who need our assistance.

When performing a physical examination on an adult with autism, I recommend being consciously aware that the patient is most likely experiencing anxiety and has sensory sensitivities. Give him or her verbal cues, and know that something as routine as a blood pressure cuff might elicit an anxiety or pain response.

In conclusion autism has a multidimensional nature. Thus, practitioners of alternative and complementary medicine are in an optimal position to help children and adults with ASD.

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Animal-Assisted Intervention in the Classroom

The inclusion of animals in therapeutic treatment is not new. Most people have anecdotal reports of the therapeutic efficacy of animals or have seen accounts of this in the news, movies, television shows, or books. What is new is the scientific study of human–animal interaction for child mental health and well-being.

There is a growing stream of research on the effects of human–animal interaction for children with autism spectrum disorder (ASD). The umbrella term animal-assisted intervention (AAI) includes both animal-assisted therapy (AAT; goal-directed, targeted treatment) and animal-assisted activities (AAA; open-ended, enrichment activities).

In one study, I and my colleagues implemented and evaluated a classroom-based AAA program for social functioning in children with ASD.[1] The AAA program consisted of 8 weeks of animal exposure in the school classroom in addition to sixteen 20-minute animal-interaction sessions. Significant improvements were identified in social functioning, including increases in social approach behaviors and social skills, and decreases in social withdrawal behaviors, from before to after the AAA program, but not during the wait-list period, when the children did not have access to an animal. More than half of the children's parents also reported that their children demonstrated an increased interest in attending school during the program.[1]

At this stage, it is unknown whether there are certain grades or ages of students for whom AAA works best. It appears to be unique in that many other enrichment activities tend to be targeted to specific ages. We found no significant differences in outcome based on age in our study group, which consisted of 64 children, ages 5–12, who were diagnosed with ASD.

The video-based behavioral data also did not show any differences in how often children of different ages interacted with the animals. This is in contrast to most toys and games, for which there are large differences in what a 5-year-old wants and what a 12-year-old wants. Instead, with the animals, children of various ages found their own preferred interaction styles with animals and appeared to enjoy this just as much (as indicated by similar rates of smiling, laughing, and engaging with the animals). We plan to follow-up on potential age differences and species preferences in our current research stream.

One key area for further investigation is why AAI works for children. The most commonly cited reason is based on social support theory. It has two components. First, it suggests that, when an animal is present, people experience social facilitation and are more likely to interact with one another. Research has shown that when an individual is with an animal, other people perceive that individual as being friendlier, happier, more approachable, and less threatening. It is possible that the presence of the animals made children feel more comfortable around one another, in addition to providing an impetus for positive interaction.

The second part of the social support theory is that animals provide direct social support to people in ways that other humans may not.[2] Animals are perceived as being nonjudgmental. They do not care if a person is having a "bad hair" day, if one is not popular, or if the teacher does not like a particular child. Animals will still be happy to see people and offer them soft, comforting contact.

This may be one of the reasons why, in a separate study, we found that children with ASD have lower physiologic arousal in social settings when there is an animal present, compared with toys.[3] Children with ASD often show heightened anxious arousal, particularly in social situations. It is possible that the support and comfort of an animal's presence reduces anxious arousal, making children with ASD more amenable to interaction with their peers. The stress-reducing effect of animals has been demonstrated in a number of populations, including situations where people are experiencing social ostracism.

One criticism of human–animal interaction research is that the effect of an animal presence may actually be the result of the presence of a positive, attention-capturing stimulus that does not necessarily need to be an animal. To address this concern, we compared the presence of animals to another enjoyable and engaging stimulus—toys. We found that the presence of animals was related to increased positive social behaviors, above and beyond the attention control achieved with toys.[4]

The research on AAI for ASD is in its early stages. I conducted a systematic review of the empirical literature to date and found that there is preliminary proof of the concept of the potential benefits of animals for children with ASD.[5] The next step is to standardize replicable protocols and conduct larger-scale studies to evaluate the effects of individual differences to determine the circumstances and individuals for whom animals may be most beneficial.

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Animal-Assisted-Interventions

There has been a surge of interest in interaction between humans and animals as a source of emotional relief and potential improvement of health. There are now many studies that indi-

cate that people who own dogs, for example, and have problems with their hearts have been shown to have increased survival time after an infarction if they have companion animals.[1,2]

This is not just because having an animal leads to an improved lifestyle, such as being outside and walking more. It is mostly because animals can increase a person's social skills and enhance opportunities for social contacts. This means that a person might have a more intense social life, a factor that has been recognized as a potential positive factor for health.

With my colleagues, I reviewed six published studies on the effects of brief interactions with dogs and the effects of introducing dogs in families with children diagnosed with autism spectrum disorder (ASD). The emphasis was on social behaviors and language use. While the six studies were encouraging, further research with better designs and using larger samples is needed to strengthen translation of such interventions to the clinical setting.[3]

In the case of children with ASD, the type of skills that I and my colleagues focus on when working with dogs in a therapeutic setting are attention time, language development, and helping a child take more time to do things. Often, these children are hyperactive. They want to reach a goal immediately. So, it is very important that they learn to wait, for example, before reaching out or obtaining something. Working together with a dog can help a child to focus, increase attention span, and reduce frustration.

There is another important aspect that we are working on—not in therapeutic sessions—but just as a basic science question: What are the characteristics that make an animal more or less preferred? We have been investigating this point recently by analyzing preferences for facial stimuli in companion animals, such as dogs or cats.

One main finding of these studies is that these species show infantile characteristics that are very salient in humans, especially for children.[4] Ethologist Konrad Lorenz had already recognized and named this this as the "baby schema," a very specific facial configuration usually found in puppies, such as a very round face, big paws, very soft skin, and big eyes.[5] The very strong preference for infantile characteristics, which allows human beings to be attracted to infants, has been selected by evolution and emerges very early during development.

Recently, we have started to standardize methodologies for exposing children with ASD to animal-assisted interventions (AAIs) through horses and equestrian rehabilitation (ER; also known as therapeutic horseback riding). AAIs with horses are recognized as among the most effective animal-assisted rehabilitative activities for children with ASD.[6,7] Although encouraging, current evidence is still based on a scarce number of studies, and their generalization is often limited by common methodological weaknesses (e.g., lack of control groups).

We have examined the efficacy of an ER program in children with ASDs, evaluating communication and cognition, as well as social and motor skills. Fifteen 6–12-year old children with ASD participated weekly in structured activities involving both riding horses and work on the ground, such as grooming. Outcomes were evaluated through standardized assessments and compared to those from a control group of 18 children not attending the program. Analyses have shown improved social functioning in the ER group and a milder effect on motor abilities. Improved executive functioning was also seen (i.e., reduced planning time in a problem-solving task). ■

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