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PEDIATRIC CLINICS
OF NORTH AMERICA

Pediatr Clin N Am 54 (2007) 983–1006

Complementary and Alternative Medical Therapies for Attention-Deficit/Hyperactivity Disorder and Autism

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This article addresses the common use of complementary and alternative medicine (CAM) therapies used for the treatment of attention-deficit/hyperactivity disorder (ADHD) and autism in children and adolescents. The article first discusses the prevalence and standard treatment of ADHD and summarizes the current evidence on CAM therapies for the treatment of ADHD. The treatments for ADHD include nutritional interventions, biofeedback, herbal and natural products, vitamins and minerals, homeopathy, massage and yoga, the beneficial impact of playing in green spaces, and the detriment of neurotoxicants. The article then describes the prevalence and likely causes of autism and the CAM approaches to working with children who have autism. CAM therapies for autism include addressing metabolic disorders; gastrointestinal (GI) problems, including dysbiosis, "leaky gut," food sensitivities, and autoimmunity; heavy metal toxicities; and providing nutritional interventions and supplements with potential benefit for children who have autism.

Prevalence of attention-deficit/hyperactivity disorder and standard treatment

ADHD is estimated to affect 3% to 12% of school-aged children [1,2]. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*,

This work was supported by Grant No. AT000929 from the National Center for Complementary and Alternative Medicine of the National Institutes of Health.

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0031-3955/07/$ - see front matter
doi:10.1016/j.pcl.2007.09.006 *pediatric.theclinics.com*

criteria for diagnosis of ADHD requires a minimum of six of nine inattentive or hyperactive/impulsive symptoms for a minimum of 6 months, and the symptoms must be developmentally inconsistent and cause problems in more than one location (home and school) [3]. The most common treatments offered to these children are stimulant medications, such as methylphenidate and dextroamphetamine, and slow-release stimulants, such as amphetamine-dextroamphetamine and methylphenidate extended-release tablets [4]. The stimulant medications have a 30-year history of efficacy and safety in children and adolescents who have ADHD [4]. Up to 30% of patients on stimulant medications, however, may experience side effects, such as decreased appetite, insomnia, and abdominal pain, with as many as 10.9% of children experiencing a serious adverse event [4]. Stimulants are classified as schedule 2 controlled substances, which limits the prescription to a 30-day supply. Many physicians consider this burdensome [5]. Nonstimulant treatment options for ADHD include atomoxetine, and, in some cases, bupropion and clonidine are used as second-line treatment options. Only atomoxetine is approved by the Food and Drug Administration to treat ADHD in children, however. Even these nonstimulant medications have potential side effects, including increased heart rate, increased diastolic blood pressure, decreased appetite, vomiting, nausea, fatigue, liver toxicity, insomnia, or increased risk for suicidal ideation and seizures [6–9].

In the United States, an estimated 2.5 million children take stimulants [10]. Despite the evidence of efficacy for the stimulant treatments, many parents seek alternatives to stimulant medication for their children because of their concern about giving their child a controlled substance or because of the changes in personality some parents report when their child is on stimulant medications. Some parents worry that their child will develop drug abuse problems after using stimulants for ADHD, despite clear evidence to the contrary [11]. Parents and the medical and lay communities often express concern about the number of children prescribed these controlled substances and question the possibility of misdiagnosis or over-diagnosis of ADHD [12]. Further studies are needed to better understand the long-term effects of stimulant medications on the developing brain and the neuronal imprinting effects of these medications [13].

Pathophysiology of attention-deficit/hyperactivity disorder

Research is ongoing to determine the cause of ADHD, including studies on genetic risk factors, environmental risk factors, and structural and physiologic alterations in brain function [2]. Twin studies have estimated the heritability of ADHD to be 0.76 [2]. Dopamine receptors are the focus of genetic study, and the dopamine D4 receptor, which is found in the frontal-subcortical networks, functions poorly in individuals who have ADHD [14]. Dopamine and norepinephrine neural pathways are believed the likely site of pathophysiologic dysfunction of ADHD because animals that have

dysregulation of these pathways exhibit symptoms similar to ADHD [2,15]. Stimulants block the reuptake of norepinephrine and dopamine by their transporters and enhance the release of these neurotransmitters, and some inhibit monoamine oxidase [15]. Imaging studies have noted differences in the activity of the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, dorsal anterior cingulate cortex, and striatum (caudate and putamen) [16]. The dorsal anterior cingulated cortex plays an important role in attention motor control and reward-based decision making, and the striatum is the location of the dopamine transporter and dopaminergic abnormalities [16,17]. More recent reviews of the neurophysiology of ADHD conclude that there unlikely is a single dysfunction underlying this disorder, and that it is more likely that the various forms of ADHD are the result of a combination of risk factors, including genetic, biologic, environmental, and psychosocial [2,18].

Complementary and alternative medicine therapies for attention-deficit/hyperactivity disorder

The frequency of CAM use in children who have ADHD ranges between 12% and 64%, with the lower estimates likely the result of a narrow definition of CAM [12,19–21]. One report documents that nutritional changes were the most common CAM therapy used by children who had ADHD [12]. When parents of children and adolescents who had ADHD were surveyed in community mental health centers, a 19.6% lifetime prevalence of herbal therapy use was found and a 15% prevalence of herbal therapy use was found in the year preceding the survey [22]. A majority (83%) of caregivers noted that the herbal therapy was the main source of drug treatment when it was used [22]. The parents of children who had ADHD referred for care at a tertiary outpatient clinic at a children's hospital were more likely to indicate CAM use if they rated natural therapy or "control over treatment" as important in making therapeutic decisions [21]. A search on the Internet for ADHD treatment provides hundreds of links to over-the-counter products and treatments that are a "definitive cure" for ADHD. The majority of these products and treatments have little if any research documenting their safety let alone their efficacy. The remainder of this article highlights the CAM evidence available on natural treatments of ADHD.

Nutritional interventions

Feingold diet

Much attention was given to the effect of diet on the symptoms of ADHD after Dr. Feingold [23] published his findings that 50% of his patients who had ADHD improved with the elimination of all food additives and naturally occurring salicylates. The Feingold diet eliminates nearly all processed

foods and a large proportion of fruits and vegetables, which are high in salicylates, a drastic change for most children. The extensive restriction on dietary intake required by the Feingold diet has made replicating the findings of Dr. Feingold difficult [24]. Complete control of a child's diet is difficult unless children are admitted to a clinical research center for the entire trial. The evaluation of symptoms in the contrived circumstances of a clinical research center, however, may not replicate the real world situations in which these children demonstrate their inattentive or hyperactive/impulsive symptoms. A review by Wender [25] provides an excellent summary of the origins of the Feingold diet and a summary of the clinical trials evaluating the efficacy of this dietary intervention. Although initial studies seemed to show a benefit with the diet, replication of these studies found no benefit with the Feingold diet. In the few studies that did find benefit, the blinding of the placebo intervention has been called into question because improvement was seen only when the Feingold diet was the second intervention in the crossover trials. Wender concludes that a small percentage of children who have ADHD may benefit from the Feingold diet. The expense of providing food for all participants in these trials often limits the size of the study; the largest trial included only 40 participants, decreasing the power to detect more modest effects of the dietary intervention. It is possible that a large, well-designed trial with careful controls for the intervention may find benefit for a portion of children who have ADHD symptoms. A recent double-blind, placebo-controlled study examined the effects of artificial food coloring and additives (AFCAs) on hyperactive behavior in 3- to 4-year-old and 8- to 9-year-old children from the general population [26]. All children had AFCAs removed from their diet for the 6-week trial and then consumed one of the matched study drinks containing either one of two mixes of AFCAs or placebo in random order during weeks 2, 4, and 6. The investigators reported increased global hyperactivity in the 3 to 4 year olds and the 8 to 9 year olds after consuming the AFCAs [26].

Food sensitivities

Food sensitivities are a speculated cause of ADHD symptoms and several laboratories offer serum tests for specific antibodies to a variety of foods. The specificity of these laboratory measures is not good enough to rely solely on the results [27]. Two clinical trials have examined the effect of multiple eliminations from the diet (foods, dyes, and preservatives) in an open-label manner followed by a double-blind, placebo-controlled challenge of the eliminated items [28,29]. In both trials, those who improved during the elimination phase demonstrated a greater frequency of reaction to some of the eliminated item challenges than to the placebo challenges. Only those children who responded favorably to the elimination were challenged in a double-blind manor, which would bias toward detecting a beneficial effect. The results of these studies are promising, yet clinicians need to

keep in mind the importance of challenging the eliminated foods, rather than just restricting a child's diet. Families could work with a child's teacher to evaluate the child's behavior in a blinded manner when the foods are being challenged to decrease the expectancy effect of the challenge situation.

Sugar avoidance

Many parents note a change in their child's behavior when they reduce the amount of sugar in the child's diet. Wolraich and colleagues [30] conducted a complex 9-week intervention, supplying all food for participants, to examine the effect of three different diets: high sucrose, high aspartame, and saccharin sweetener diet. No differences in behavioral or cognitive measures were found among children believed to be sensitive to sugar by their parents while on the different diets, yet these children were not diagnosed with ADHD. None of the diets, however, eliminated other sources of sugar, such as fruit or unsweetened fruit juices. A revealing study by Hoover and Milich [31] found that parental expectation of aggravation resulting from sugar ingestion may play a significant role in the perceptions of parents. In this trial, half of the mothers were told their child received a large dose of sugar and half of the mothers were told that their child received a placebo. In reality, all of the children believed to be sugar sensitive by their parents received an aspartame sweetened snack. Mothers who were told their child received a large amount of sugar rated their child's behavior as more hyperactive and were more critical of their child than the mothers who were told their child had a low sugar snack. An excellent review of the effects of diet on ADHD concludes that clinical trials do not support a link between sucrose consumption and hyperactivity [32]. No studies have examined the link between hyperactivity and the glycemic index of the diet, which may be a better measure of the amount of simple sugars consumed in the diet. Dr. David Ludwig of Boston's Children Hospital states, ''A child eats a breakfast that has no fat, no protein, and a high glycemic index—let's say a bagel with fat-free cream cheese. His blood sugar goes up, but pretty soon it crashes, which triggers the release of stress hormones like adrenaline. What you're left with, at around 10 AM, is a kid with low blood sugar and lots of adrenaline circulating in his bloodstream. He's jittery and fidgety and not paying attention. That's going to look an awful lot like ADHD to his teacher'' [33]. Although the results of clinical trials do not consistently demonstrate a negative effect of high sugar diets on behavior, recommending moderate consumption of sugar intake seems most appropriate given the growing epidemics of obesity and diabetes.

Essential fatty acids

Some of the most important fats used by the human body and brain for development and function must be supplied from the diet or supplementation

because of the inability of the human body to synthesize these fats. These polyunsaturated fatty acids are known as essential fatty acids (EFAs). EFAs include the omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and the omega-6 fatty acid, arachidonic acid. A growing body of evidence suggests that individuals who have ADHD may have low levels of these EFAs, specifically DHA and arachidonic acid [34]. The standard American diet is not abundant in dietary sources of omega-3 fats, which include flax, cold water fish, and certain nuts (brazil nuts, cashews, and walnuts). Children are at particular risk for low concentrations of these omega-3 fatty acids because of the recommendations that children not consume fish on a frequent basis because of its high mercury content.

Richardson [35] published a recent review of the effects of omega-3 fatty acids in ADHD, including information on the clinical trials performed in children who have ADHD. A few of the randomized controlled trials have examined the efficacy of EFAs for the treatment of disruptive behavioral disorders or learning disabilities rather than ADHD. Few studies have examined the effect of EFAs in children who have ADHD specifically and used a randomized controlled study design. Voigt and colleagues [36] randomized children who had ADHD to receive DHA (345 mg) or placebo and found no beneficial effect on computer or parental ratings of ADHD symptoms. All of the children enrolled in this trial had their symptoms managed effectively by stimulant medication during the trial, which makes detecting the impact of the EFAs more difficult. Parental and computer assessments of symptoms were done after a 24-hour withdrawal of medication. Stevens and colleagues [37] randomized children to a blended EFA supplement containing omega-3 and omega-6 fatty acids or an olive oil placebo. In children who were taking the EFA supplement in addition to pharmacotherapy, 2 of 16 measures showed improvement including conduct problems, as rated by parents, and attention symptoms, as rated by teachers. Sinn and Bryan [38] randomized children not on stimulant medication to a blended EFA (fish oil and evening primrose oil) with or without a multivitamin or to placebo (palm oil). In the per protocol analysis, the participants on the EFA showed improvements in the Conners' Parent Rating Scale scores over 15 weeks compared with the placebo group. This study excluded 21% of participants who dropped out before 15 weeks or did not complete the required questionnaires or take required study medicine. Exclusion of such a large portion of the participants eliminates the benefits of randomization because of differences in the patients who dropped out early (worse ADHD symptoms) and biases the results toward finding a positive effect. Other studies of a blended EFA supplement have found benefit in the treatment of dyslexia with ADHD features and developmental coordination disorder (DCD) [35]. The growing body of evidence supports the use of an EFA supplement for children who have ADHD.

Electroencephalographic biofeedback

The field of electroencephalographic (EEG) biofeedback is a growing area of research for the treatment of ADHD. This form of treatment is based on the finding that children who have ADHD demonstrate abnormal quantitative EEG findings in a pattern of underactivity in the majority of cases or hyperarousal in some patients [39]. EEG biofeedback uses a series of sessions (more than 30) over several weeks to teach patients how to alter their quantitative EEG activity to a more balanced level by rewarding children when their activity is sustained in the level desired. Monastra and colleagues [40] provide an extensive review of the theory behind EEG biofeedback, the protocols developed, and the results of case studies and controlled trials. A few controlled studies have been conducted comparing EEG biofeedback to stimulant treatment or a wait list control, and these trials demonstrate improvement in ADHD symptoms and improved quantitative EEG activity [41]. Nearly all of the controlled clinical trials of EEG biofeedback allowed the participants to self-select to EEG biofeedback treatment; thus, the findings are subject to substantial selection bias. In addition, several of the trials used an active control (stimulants), yet the studies were not powered to detect noninferiority to the stimulants, which would require a large sample size. Small sample sizes favor not detecting a difference between the active control and the EEG biofeedback intervention. To evaluate the potential benefits for EEG, future studies need to randomize participants to treatment allocation, and ideally a "placebo" form of EEG biofeedback should be used as the control to account for the nonspecific effects of multiple treatment sessions over a short time period.

Herbal and natural health products

The use of herbal treatments in children often is based on use in adults, yet little is known about the safety or appropriate dosing of these herbal treatments in children. Despite the common use of herbal treatments by children who have ADHD, only one study has examined the effect of an herbal product containing *Ginkgo biloba* and *Panax quinquefolius* (American ginseng) in pediatric patients who have ADHD [42]. Ginsengs and ginkgo are believed to have nootropic effects to improve memory and facilitate learning. The study found improvement in ADHD symptoms over the 4-week intervention, but no comparison group was studied so efficacy could not be determined. Fourteen of the 36 participants were allowed to continue on medications that were not controlling their symptoms before starting the trial and two of 36 participants experienced increased symptoms of hyperactivity or impulsivity. A sufficiently powered randomized controlled study is needed to determine the efficacy and side effects of this herbal combination.

One study has examined the effects of L-carnitine for the treatment of ADHD in a placebo-controlled crossover study and found that 50% of

the participants responded to the carnitine treatment [43]. The investigators, however, do not present baseline and follow-up data for all participants in each treatment period, making it difficult to interpret the efficacy of carnitine. L-Carnitine is a necessary component of fatty acid metabolism and ATP synthesis, although how this translates specifically into improvement in ADHD symptoms is unknown. Another randomized controlled study examined the efficacy of pycnogenol (1 mg/kg per day) for the treatment of ADHD and found improvements in teacher and parent ratings of symptom severity compared with a placebo intervention [44]. The study treatment had a short duration of 4 weeks, so future studies need to examine if the effects seen continue over a longer treatment period. The pycnogenol used in this study was a standardized extract from the bark of the French maritime pine tree (*Pinus pinaster*). The proposed mechanism of action of pycnogenol is that it increases production of nitric oxide, which regulates dopamine and norepinephrine release and intake. Dopamine and norepinephrine are the targets of standard pharmacotherapy.

Massage and yoga

A small controlled trial to study the effect of yoga enrolled children who had ADHD whose symptoms were stable on medication. The investigators reported improvement in ADHD symptoms in the yoga group on some of the measures of Conners' Parent Rating Scale, but the limited sample size made between group comparisons underpowered to detect an effect [45]. In another study, when adolescents who had ADHD were randomized to massage therapy or relaxation treatment, the adolescents in the massage group were rated by their teachers to have decreased symptoms of hyperactivity, anxiety, and inattention but the difference was not statistically better than the improvement seen in the relaxation group [46]. The lack of difference between the groups may be the result of potential benefit from the relaxation treatment or a result of the small sample size enrolled in the study. The positive trend in the findings do support further research into the efficacy of yoga and massage for ADHD symptoms.

Vitamins and minerals

Several individual vitamins and minerals are proposed as possible treatments for ADHD, yet there are few randomized controlled trials evaluating the efficacy of these treatments. Zinc reduced symptoms of hyperactivity, impulsivity, and socialization difficulties in children and adolescents who had ADHD, but it did not improve symptoms of inattention [47]. This study used a high dosage of zinc for a period of 12 weeks and more than 50% of both groups dropped out of the study. Even though benefit was seen from zinc treatment, full therapeutic response was seen in only 29% of the zinc

group versus 20% of the placebo group. Replication of these findings in another study with better retention is needed. Another study examined the effects of zinc with and without methylphenidate in a randomized controlled trial. The investigators found an improvement in parent and teacher ratings of ADHD symptoms for both groups, but those on zinc and methylphenidate had greater improvement than those on methylphenidate alone [48]. Konofal and colleagues [49] reported that children who have ADHD have lower serum ferritin levels than children who do not have ADHD symptoms and that the severity of symptoms correlates with low ferritin levels. In an open-label study, iron supplementation was found to improve symptoms of ADHD in nonanemic children, yet no controlled studies have evaluated its efficacy [50]. One small study examined the effectiveness of megavitamin therapy in a controlled trial and concluded no benefit was detected, and increased disruptive behavior and elevated serum transaminase levels were seen in the group on the megavitamin treatment [51]. If using doses of vitamins or minerals higher than the recommended daily allowance, it is important to monitor serum or cell membrane levels of these nutrients and liver enzymes to prevent toxicity.

Homeopathy

Homeopathy is a medical practice based on the belief that "like treats like" and that the energetics of a small amount of a substance can have healing effects on individuals. At least three randomized controlled trials have evaluated the efficacy of homeopathy for the treatment of ADHD with mixed results [52]. Strauss [53] reported improvements on the Conners' Parent Symptom Questionnaire for children treated with homeopathy for 2 months, although no data on the other outcomes examined were provided, making the overall effect of homeopathy difficult to interpret. The second study enrolled patients who responded to a homeopathic treatment and randomized them into a crossover discontinuation study [54]. It found improvement of ADHD symptoms on the Conners' Global Index, but the lack of a washout period before randomization resulted in all patients worsening in the first treatment period regardless of group assignment. In the final trial, all participants experienced the same interaction with the homeopath, who was allowed to change the remedy and potency used over the 18-week trial [55]. Participants were randomized to receive the active homeopathic remedy prescribed by the homeopath or a placebo homeopathic remedy. Both groups improved over the course of the trial, but no differences were detected in the magnitude of improvement between the placebo and active homeopathy groups. These findings led the investigators to conclude that the effectiveness of homeopathy may be the result of the nonspecific effects of the interaction with the homeopath and not the actual remedy given, and future research should explore this possibility. Homeopathy offers potential as a possibly

effective treatment option for ADHD, but it is unclear if this efficacy is the result of the interaction with the homeopath or the actual homeopathic remedy.

Environmental issues

Several investigators have discussed the symptoms of ADHD as a physical and mental manifestation of nature deficit disorder [56,57]. In his book, *Last Child in the Woods: Saving our Children from Nature-Deficit Disorder*, Louv [56] provides anecdotal evidence of how the loss of green spaces and creative play outdoors is correlated with the increase in childhood mental health disorders, including ADHD. Kuo has started evaluating this theory with rigorously designed research studies. In a national online survey of parents of children who have ADHD, Kuo and Taylor [57] reported improvement in ADHD symptoms with green outdoor play compared with indoor and "built outdoor" play. This cross-sectional survey provides some evidence of the benefit of green spaces for ADHD; only two of the 339 reasons parents gave as to why the activity might reduce symptoms related to being in an outdoor setting decreases the likelihood that the results are biased. The investigators suggest rigorously designed randomized controlled trials to differing play experiences to determine the effects on ADHD as rated by a blinded evaluator. Many parents have always known that a connection to nature is beneficial to children; we are now on the cusp of having documented efficacy of the beneficial effect of nature for children who have ADHD.

The environment contains a variety of chemicals and toxins, many of which are linked to neurodevelopmental disorders. The toxic effects of mercury and lead are well known, and the symptoms of these toxicities resemble the symptoms of ADHD and even autism [58,59]. The effects of heavy metals, pesticides, polychlorinated biphenyls, and polybrominated diphenyl ethers on the human brain are just being elucidated [59]. Environmental advocates and researchers are pushing for more research into the effect of even low doses of these chemicals on the developing brain in utero and during childhood [59]. The elucidation of the effects of these chemicals is more difficult when taking into consideration the large number of exposures individuals have to the thousands of chemicals in the environment and the unique susceptibility of individuals from genomics [59]. The health implications of neurotoxicants are of concern in the development of ADHD but many are concerned that these compounds may be the cause of autism (heavy metal toxicity in autism is discussed later).

Autism

Autism is a neurodevelopmental disorder characterized by deficits in social interaction, language development, and a restricted or stereotypical pattern of interests and activities. Formerly a rare condition well out of the public eye, the prevalence of autism has increased more than tenfold in the past 20 years,

from an estimated prevalence of approximately 5 to 6 per 10,000 children to 65 per 10,000 in more recent studies [60]. There is no scientific agreement as to the cause of this rapid increase in prevalence, often referred to as an ''epidemic'' in the media. The three most likely possibilities are (1) there is a true increase in the prevalence of the disorder; (2) there is increased case-finding resulting from increased awareness of the disorder on the part of the public and medical and other professionals; and (3) there has been a loosening of the definition of autism so that more children are being diagnosed.

To complicate matter, other diagnostic categories, such as autism spectrum disorder, pervasive developmental disorder, and Asperger's syndrome have been added to the mix, including children who have some features of autism but do not meet the full criteria. The Brick Township study separated autism from autism spectrum disorder and Asperger's syndrome, however, and still recorded a prevalence of 40 per 10,000 of autism itself [61]. A recent study in Minnesota, in which autism is separated out from these other categories, gives a striking picture of the rapidity of the increase in the prevalence of this disorder [62].

Regressive autism

Regressive autism refers to children who have normal development until the age of 1 to 2 years, after which there is a loss of language, social interaction, and other developmental milestones. It is this type of autism that has caused the widespread public concern over the influence of the measles, mumps, and rubella vaccine and mercury-containing vaccines on the development of autism. The available studies indicate, however, that regressive autism accounts for only 30% of autism, although there is surprisingly sparse research on this question.

Etiology

Currently it is believed that autism is a genetically based disorder requiring an environmental trigger to manifest. This is supported by the 90% concordance rate in identical twins as opposed to the 30% concordance rate in fraternal twins [63]. There are many gene loci associated with autism, but no single gene or group of genes has been linked definitively to this disorder [64]. There is little scientific research concerning which environmental factors may trigger the expression of this disease. Many patients and physicians interested in alternative treatment of autism, however, are concerned about the role of mercury, immunizations, and other environmental toxins in triggering the development of autism.

Complementary and alternative medical therapies for autism

CAM therapies are used with great frequency in the treatment of autism. A study in 2006 showed that overall, an astonishing 74% of families of

children who had autism spectrum disorder were using some type of CAM therapy. Although these included the full spectrum of CAM therapies, the highest frequency of use (more than 54% of families) involved what were termed, ''biologically based'' therapies, including modified diets, vitamins and minerals, and other nutritional supplements [65]. Several other studies have demonstrated similarly high frequency of use, from 30% in a regional referral center to 92% in two primary care practices [66–68]. This reflects the high acceptance, among families and many physicians, of what is commonly referred to as a ''biomedical'' approach to autism. The basis of this approach is that autism is a genetics-based syndrome triggered by certain fetal, neonatal, and early childhood stimuli, and that this syndrome is associated with a variety of nutritional, GI, metabolic, and autoimmune abnormalities that can be corrected partially or fully. Most of the remainder of this article is devoted to a discussion of this approach.

The gastrointestinal system

One of the most common problems seen in children who have autism is a variety of GI symptoms and clear GI pathology. The incidence of GI problems in autism varies by study but seems to be approximately 30% to 40% of children. Symptomatically, the most common reports are of chronic constipation or diarrhea and chronic abdominal pain.

GI pathology is common and widespread. One study of children who had autism and GI symptoms showed that 69.4% of subjects had reflux esophagitis, 42% had chronic gastritis, and 67% had chronic duodenitis [69]. Many of these children are nonverbal and cannot express GI discomfort; thus, these children may react to pain by exhibiting behaviors not obviously referable to the GI system, such as self-stimulation or temper tantrums.

There are several studies demonstrating definite pathology of the small and large bowels. Torrente and colleagues [70] performed biopsies of 25 children who had autism and found duodenitis in almost all of the children. He described increased lymphocytic proliferation in the epithelium and lamina propria. Horvath and colleagues [69] also documented significant dissacharidase deficiencies in a population of children who had autism and GI symptoms.

Dysbiosis

Dysbiosis, or abnormalities of GI microflora, also is believed a common problem. Rosseneu [71] analyzed 80 children who had autism and GI symptoms and found that 61% had growth of abnormal aerobic gram-negative, endotoxin-producing bacteria. These aerobic gram-negative bacteria are producers of endotoxin, which could cause ongoing bowel damage. Fifty-five percent had overgrowth of *Staphylococcus aureus* and 95% had overgrowth of pathogenic *Escherichia coli*. There were no abnormal amounts of yeast noted in this study. In a fascinating pilot study, 11 of these children

were treated with a nonabsorbable antibiotic and not only did the abnormal flora disappear but also GI symptoms and autistic behaviors decreased significantly. This study did not have a control group, and after 2 months the abnormal bacteria returned to pretreatment levels. In another study, vancomycin treatment of children who had regressive autism and diarrhea resulted in decreased autistic behaviors as measured by blinded observers [72].

An overgrowth of yeast is widely believed part of dysbiosis and responsible for many GI and behavioral symptoms of autism, and many children are treated with antifungal agents as part of their ''bowel detoxification'' protocol. The evidence for this yeast overgrowth is limited. As discussed previously, Rosseneu's study failed to identify any yeast among the abnormal bacteria, and there have been no good controlled studies evaluating yeast overgrowth in autism. Some research shows the presence of urine organic acids suggestive of yeast overgrowth in children who have autism, but the significance of these byproducts is unclear. There is widespread use of antifungals, such as nystatin, fluconazole, and ketoconazole, with much anecdotal evidence of positive results but no controlled studies.

''Leaky gut''

Another GI abnormality commonly attributed to children who have autism is called the ''leaky gut'' phenomena, related to a theorized increased intestinal permeability. In a study by D'Eufemia and colleagues [73], examination of 21 autistic children who had no known intestinal disorders confirmed increased intestinal permeability in 43%, as opposed to zero controls. Horvath and Perman [74] examined 25 children who had autism and GI symptoms using lactulose/mannitol testing and found 76% had altered intestinal permeability.

Food sensitivities/allergies

Food sensitivities or allergies also are believed to play an important role in the pathophysiology of autism. The evidence for this is indirect but suggestive. In one study, 36 children who had autism were compared with healthy controls and had significantly higher levels of IgA, IgG, and IgM antigen-specific antibodies for specific food proteins, such as lactoglobulin, casein, and β-lactoglobulin, than did controls [75]. Also, a study by Jyonouchi and colleagues [76] showed that children who had autism had higher intestinal levels of inflammatory ctytokines directed against specific dietary proteins than did controls.

Some researchers believe that gluten and casein that pass through a leaky gut barrier can form gluteomorphins and caseomorphins, which then have important central nervous system effects; however, the research in this area is inconsistent. These putative food protein sensitivities do not show up as immediate hypersensitivity on standard skin testing or IgE radioallergosorbent testing, leading to the question of whether or not children who

have autism have true food allergies or food sensitivities that are not IgE mediated.

Autoimmunity

There are several studies that suggest that autoimmune abnormalities are common in children who have autism. Some of these can be linked directly to the central nervous system. Connolly and colleagues [77] examined the sera of children who had autism for antibrain antibodies. IgG antibrain antibodies were present in the sera of 27% of children and only 2% of controls. IgM antibodies were present in 36% of the sera of autistic children and in 0% of controls. Singh and colleagues [78] evaluated the prevalence of antibodies to various brain structures in 68 autistic children and 30 controls. Of the autistic children, 49% had serum antibodies to the caudate nucleus as opposed to 0% of controls. Antibodies to the cerebral cortex and cerebellum were 18% and 9%, respectively, again with 0% of controls having these antibodies. Most recently, Cabanlit and colleagues [79] described a significantly increased incidence of brain-specific (thalamic and hypothalamic) autoantibodies in the plasma of children who had autism compared with controls. It is not clear if these antibodies cause neurologic problems or merely are a byproduct of central nervous system damage caused by other factors (eg, viral infections).

Metabolic disorders

There are several studies that demonstrate some abnormalities in the metabolic functioning of children who have autism with defects in areas such as glutathione synthesis, sulfation deficits, and folate metabolism. For instance, a study in the *American Journal of Clinical Nutrition* demonstrated that relative to the control children, the children who had autism had significantly lower baseline plasma concentrations of methionine, S-adenosyl methionine (SAM), homocysteine, cystathionine, cysteine, and total glutathione and significantly higher concentrations of S-adenosyl homocysteine (SAH), adenosine, and oxidized glutathione [80]. This metabolic profile is consistent with impaired capacity for methylation (significantly lower ratio of SAM to SAH) and increased oxidative stress. In another study, activities of erythrocyte superoxide dismutase and erythrocyte and plasma glutathione peroxidase in autistic children were significantly lower than in children who did not have autism [81]. These results indicate that autistic children have low levels of activity of blood antioxidant enzyme systems.

A review article by McGinnis [82] documents several positive markers of oxidative stress in children who have autism. Among other factors, he cites indirect markers for greater oxidative stress, such as (1) lower endogenous antioxidant enzymes and glulathione; (2) lower antioxidant nutrients; (3) higher organic toxins and heavy metals; (4) higher xanthine oxidase and cytokines; and (5) higher production of nitric oxide, a toxic free radical.

Heavy metal toxicity

It is a widespread belief among many clinicians and families involved in the alternative treatment of autism that increased body levels of heavy metals, especially mercury, are an important part of the pathophysiology of autism. A study in Texas showed that there was a direct correlation between the incidence of autism and the amount of mercury expelled from industrial pollution [83]. For each 1000 pounds of environmentally released mercury, there was a 43% increase in the rate of special education services and a 61% increase in the rate of autism. This is a correlation only and does not prove causation but nevertheless is concerning, especially as environmental mercury pollution continues to rise.

The concern about mercury is linked to the assumption that the thimerosal contained in (later withdrawn from) infant immunizations is a major factor in the rise in autism prevalence. Because children who have autism likely are not exposed to more mercury or other heavy metals than other children, it is postulated that these children have impaired abilities to detoxify or excrete mercury and other heavy metals. This is believed the result of various methylation, sulfation, and antioxidant deficiencies (discussed previously).

What is the evidence that there is an increased body burden of mercury and other heavy metals in children who have autism? There is surprisingly little. One of the problems in discussing heavy metal toxicity is that there are no simple tests for determining body levels of heavy metals. Blood tests for mercury are not useful because mercury remains in the tissues and not the circulation. Hair analysis has been used, but it is not clear that these tests adequately reflect body burdens of mercury. In conventional medicine, mercury toxicity is measured by giving a dose of a chelating agent, such as ethylene diamine tetraacetic acid (EDTA) or 2,3-dimercaptosuccinic acid (DMSA), and then measuring urine mercury levels. There is no significant body of data using this procedure to compare autistic children and controls. One study compared blood and hair levels of autistic children with those of controls and found no significant differences. It did not examine, however, urine levels after chelation [84]. A study by Adams and colleagues [85] did show that children who had autism had significantly higher levels of mercury in their baby teeth than typically developing children. Bradstreet and colleagues [86] performed a retrospective analysis of 221 children and 18 controls who had been treated with three doses of DMSA. Heavy metal concentrations in the urine were analyzed showing urinary concentrations of mercury were significantly higher in 221 autistic children than in the 18 controls. Limitations of this study were that it was a retrospective study with nonrandom selection of controls and that the imbalance between the number of cases and the control group was large. Selection bias is a concern for controls and autistic children. Also it is unknown if the control group was representative of all children (the general pediatric population), because it

was such a small sample size and the way they were selected was not delineated.

In summary, although it is clear that mercury is a potent neurotoxin, especially in the developing brain, the idea that mercury exposure is a significant cause of autism is at this point largely is unproved. There is a need for a prospective study comparing postchelation urinary heavy metal levels in autistic children compared with controls. In addition, chelation therapy is recommended widely by biomedical practitioners for children who have autism, based on the assumption that removing these metals will result in improvement in autistic symptoms. There is no scientific support for this contention at this time. There are possible electrolyte imbalances that could accompany chelation therapy and, if used at all, should be done carefully under the direction of an experienced practitioner.

Nutritional deficiencies, including omega-3 fatty acids

It is a tenet of the biomedical approach that nutritional deficiencies are widespread and important in autism. It is believed these are linked mainly to poor digestion and absorption of nutrients resulting from GI problems (discussed previously) and abnormalities in the metabolic processing of nutrients. The evidence for these nutritional deficiencies, however, is uneven and rarely complete.

Vancassel and colleagues [87] evaluated levels of omega-3 fatty acids and other polyunsaturated fatty acids in the serum of children who had autism compared with controls. Children who had autism had 23% lower levels of plasma omega-3 fatty acids than did controls. Autistic children also had 20% lower levels of plasma polyunsaturated fatty acids than did controls. The reason for this is unclear. Do children who have autism have different levels of omega-3 fat intake than control children? Perhaps children who have autism have differences in how they use and metabolize these fats. More research is needed to elucidate the mechanisms responsible for these observed differences.

Integrative therapies for autism

Conventional behavioral approaches

Speech therapy is recommended almost universally to deal with the language deficits of children who have autism. Anecdotally, it is believed effective by almost all parents and most professionals. There is little solid research supporting the efficacy of speech therapy for autism. Although several studies show specific areas of language improvement, all of these involve few subjects and none have been randomized or controlled. Considering the almost universal use of speech therapy in the treatment of autism, this is an area with surprisingly inadequate research.

Intensive behavioral therapy is another therapy commonly used for children who have autism. Direct behavioral intervention by trained facilitators occurs in home and school settings from 20 to 40 hours a week. There are several specific methods, such as Lovaas, Floortime, and applied behavior analysis. Intervention is directed at increasing appropriate social and language behavior while decreasing self-stimulatory activities. Overall, there is reasonable evidence as to the effectiveness of this modality. A 2003 review in the *Canadian Journal of Psychiatry* concludes, ''delivering interventions for more than 20 hours weekly that are individualized, well planned, and target language development and other areas of skill development significantly increases children's developmental rates, especially in language, compared with no or minimal treatment'' [88].

Alternative behavioral approaches

Another modality used commonly in children who have autism is sensory integration therapy. Children who have autism have significant sensory issues. They often do not enjoy touching, can be upset by noisy environments, and exhibit other sensory difficulties. To modify these deficits, sensory integration therapy often is recommended. This usually involves a variety of sensory stimuli administered under controlled conditions. As with the therapies described previously, there is only anecdotal evidence of effectiveness. There are several small studies but any evidence of efficacy is preliminary at best.

A second alternative behavioral modality is auditory integration therapy. This is based on the idea that a hypersensitivity to certain sounds can cause behavioral and emotional difficulties in autistic children. Essentially, auditory integration therapy attempts to reprogram and ''integrate'' the auditory system by sending randomized sound frequencies through earphones worn by an autistic child. This usually is done in 20- to 30-minute sessions over a period of approximately 10 days. There are many anecdotal reports of efficacy, but studies so far are uncontrolled or limited to small numbers. A systematic review of the few controlled studies showed equivocal results and found insufficient evidence to support its use [89].

Nutrition

Dietary interventions

The most common alternative biomedical intervention used with autistic children is the gluten-free casein-free (GFCF) diet. This is based on the theory (discussed previously) that food sensitivities, especially to gluten and casein, can produce not only GI symptoms but also, in association with gut inflammation and increased gut permeability (leaky gut), can lead to many of the neurologic manifestations of autism. In general, for the GFCF diet, parents are advised to strictly avoid all foods containing gluten or casein for periods of 60 days or more.

The anecdotal evidence for the efficacy is abundant. In various support groups, chat groups, and other situations bringing together parents of children who have autism, the GFCF diet often is described as promoting significant and positive changes in GI symptoms, language, socialization, and other autistic behaviors.

What about the evidence? There are only two controlled studies concerning the efficacy of the GFCF diet in the treatment of autism, but both show positive results. In the first study, by Knivsberg and colleagues [90], 10 matched pairs of children who had autism were randomized to a GFCF diet or a placebo control for 1 full year. Behaviors then were evaluated by blinded observers using the DIPAB, a Danish instrument for measuring autistic traits. Post intervention, the diet group had a mean DIPAB rating of 5.60, significantly ($P = .001$) better than the control group rating of 11.20. Specifically, social contact increased in 10 of 15 of the treated children, whereas ritualistic behaviors in that group decreased in 8 of 11 children. In the second study, by Lucarelli and colleagues [75], autistic children were found to have decreased behavioral symptoms after 8 weeks on a dairy elimination diet. Too often in clinical practice, the GFCF diet is started in conjunction with nutritional supplements and other interventions, making it difficult to know if behavioral or other improvements can be attributed to the diet.

Supplements

There are many nutritional supplements used in the treatment of autism, including omega-3 fatty acids, probiotics, zinc, vitamin B_6, and other multivitamin and mineral supplements.

Omega-3 fatty acids

Omega-3 fatty acids are used widely in the treatment of autism. The research on this is preliminary but encouraging. In a pilot study, 18 children were given an omega-3 fatty acid supplement (with 247 mg of omega-3s and 40 mg of omega-6s) for 3 months [91]. Their language skills were measured at baseline and after the 3-month trial. There was a highly significant increase in language skills over a variety of measures. A double-blind, placebo-controlled study evaluated the effects of 1.5 mg total omega-3 fatty acids on children who have autistic disorders accompanied by severe tantrums, aggression, or self-injurious behavior [92]. It was a small study, with only 22 children, but it did show significant advantages of omega-3s over placebo.

Another study of relevance concerned the use of omega-3 fatty acids in DCD [93]. Although not part of the autistic spectrum, DCD is relevant because children who have this disorder present with some of the features of autism spectrum disorders. In this double-blind, controlled trial, 117 children were given an omega-3 fatty acid supplement or placebo for 3 months.

Treated children made startling gains in reading, spelling, and mathematic skills compared with the placebo group. For example, the average reading scores in the treatment group advanced 9.5 months in 3 months as opposed to an increase of 3.5 months in the placebo group ($P = .004$). There are no clearly accepted guidelines for the dosage or ratio of omega-3 fatty acids in autism treatment. Further research is needed.

Probiotics

Probiotics are used frequently in the biomedical treatment of autism. As discussed previously, it is speculated that children who have autism have abnormal gut flora and increased intestinal permeability. Treatment with antibiotics for presumed bowel bacterial overgrowth seems to result in only temporary changes in bowel flora, however, leading to the conclusion that ongoing use of probiotics might be necessary to ensure normal bowel flora. Despite widespread use and anecdotal reports of efficacy, there are no well-designed studies concerning the impact of probiotic treatment on the treatment of autism.

Zinc

Zinc is one of the single minerals recommended most widely for children who have autism. Its use stems from research by Dr. William Walsh [94], of the Pfeiffer Institute in Chicago, who found that copper-to-zinc ratios were increased in more than 85% of children who have autism. He also found that a dysfunction of metallothionein, a protein involved in the regulation of these and other metals, was present in 99% of 503 autistic children. This research was published by the Pfeiffer Institute only, however, and not in any peer-reviewed journals. There are no controlled studies indicating the efficacy and safety of zinc supplementation in the treatment of autism.

Metabolic interventions

There are several metabolic interventions intended to provide support based on the theory that autistic children have defects in methylation and sulfation. These include the use of methylcobolamin, folic acid derivatives (eg, folinic acid), and trimethylglycine or dimethylglycine. Based on the work by James and colleagues [80], biomedical practitioners often recommend the use of injectable subcutaneous methyl B-12 and oral supplementation of folinic acid and other methylating agents to increase language and social functioning. Although James' study did demonstrate correction of laboratory values of metabolic factors in autistic children, there are no published randomized controlled trials to date demonstrating safety and efficacy of these interventions. This is an area ripe for well-designed intervention trials, especially considering that children who have autism and their families may have an increased frequency compared with the general population of

single nucleotide polymorphisms in the methylenetetrahydrofolate reductase and other methylation genes [95].

Other complementary and alternative medical therapies

Complementary therapies, such as homeopathy, craniosacral therapy and other manipulative therapies, Reiki and other energy medicine modalities, biofeedback, and traditional Chinese medicine all are used. There are scattered anecdotal reports of efficacy, but no research evidence exists to support their use in the treatment of autism.

Summary

The repeating theme of all of the natural treatments for ADHD and autism is the large gap between high use rate and the low number of well-controlled, large, randomized trials. It is essential for researchers to include a comparison group when studying natural treatments for these conditions, which often are based on parental or teacher reports. The beneficial effects demonstrated in uncontrolled trials could be explained by the regression to the mean phenomenon in a condition with symptoms that wax and wane. Without a control group, it is impossible to determine if the improvement seen in a trial is the result of the natural course of the symptoms. Effective CAM treatments for ADHD are highly desired by parents who seek alternatives to stimulant medications. This also is true for parents of children who have autism who actively seek out any therapeutic option with potential for benefit. More well-conducted, controlled, clinical trials are needed to determine the safety and efficacy of these natural therapeutic options.

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