Attention-deficit/Hyperactivity Disorder and Integrative Approaches

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A Brief History of Medicine

"I have an earache."

2000 B.C. "Here, eat this root."
1000 A.D. "That root is heathen, say a prayer."
1850 A.D. "That prayer is superstition, drink this potion."
1940 A.D "That potion is snake oil, swallow this pill."
1985 A.D. "That pill is ineffective, take this antibiotic."
2000 A.D. "That antibiotic is artificial, here, take this root."
—Anonymous

Increasing numbers of Americans are turning to complementary and alternative medical therapies (CAM) for themselves and their children. A host of explanations for this increase has been surveyed and researched. A recent study reported 54% of parents using CAM therapies for their children, but only 11% ever discussing them with their pediatricians. The most important attraction of CAM therapies for parents is the belief that they are "a more natural therapy" and that they have greater control over treatments. Dissatisfaction with the process or the results of conventional care was noted in a small but increasing number within the population studied.[1] Concerns regarding side effects and long-term use of medications are also factors fueling this quest, particularly in the case of children diagnosed with attention-deficit/hyperactivity disorder (ADHD).

Is this trend toward holistic care a "fad" or just a rebalancing of the medical pendulum, as it equilibrates itself with a new dynamic tension? We see the increasing use of naturopathy, homeopathy, acupuncture, botanical medicine, chiropractic, and mind-body medicine. Often what we discover as "new" is just the resurfacing

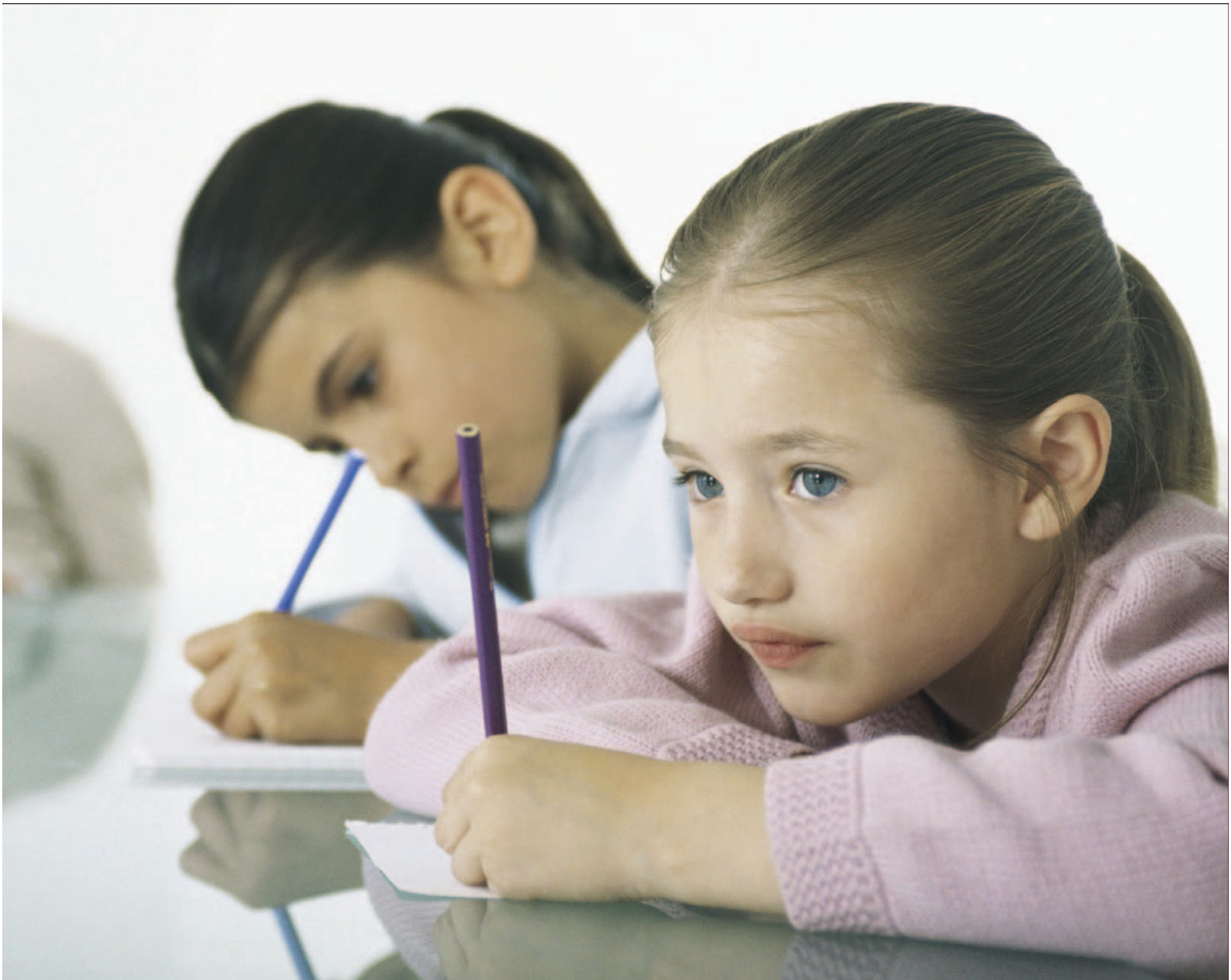
of old truths in a different time and context. The process of integrating the conventional with the traditional, the synthetic with the "natural," the part with the whole, and the old with the new is an ongoing challenge for us, as we play our part in the history of medicine.

"Teach thy tongue to say I do not know and thou shalt progress" — Moses Maimonides (1135-1204)

Pediatric healthcare providers should understand the paradigm shifts and theories behind the CAM therapies that are currently being sought out for children diagnosed as having ADHD. A review of both the conventional and alternative theories and treatments of ADHD will be discussed. A focus on some of the evidence-based studies that explore the hypothesis and rationale of the CAM modalities is reviewed, with acknowledgement of the fact that what is considered "alternative" at one time may become integrated into the mainstream as evidence and experience support the outcomes. A call for more research involving CAM therapies for children with the symptom complex of hyperactivity, impulsivity, and inattention is warranted. Concerns by the medical community regarding the use of unproven and possibly harmful alternatives to the conventional "proven" ones also need to be addressed with an awareness of the relative risks of either modality.

Traditional medicine carries with it the validity inherent in the longevity and diversity of its use. We often see similar approaches and herbs being used in various complex medical systems such as Chinese medicine, Ayurvedic, Hikmat, and Native American medicine.

A current definition of complementary therapies is "those that are used in conjunction with mainstream, conventional medical therapies." Alternative medicine often refers to those ap-



proaches that are not taught in medical school and not covered by insurance. This definition is very fluid and changing as more medical institutions are offering courses in CAM and developing departments of Integrative Medicine. Also, more third-party payers are reimbursing for CAM services or have providers on their panels.

"Integrative Medicine is a healing oriented medicine that takes account of the whole person (body, mind, and spirit), including all aspects of lifestyle. It emphasizes the therapeutic relationship and makes use of all appropriate therapies, both conventional and alternative." The Program in Integrative Medicine, University of Arizona

WHAT DO WE KNOW ABOUT ADHD?

ADHD is a neurodevelopmental disorder characterized by impulsivity, distractibility, and hyperactivity that manifests in early childhood. The symptoms affect cognitive, academic, behavioral, emotional, and social functioning. It is a common disorder of childhood, with reported prevalence rates varying from 2% and 16%, depending on diagnostic criteria and population studied.[2] The prevalence of ADHD in school-aged children in the United States is 8% to 10% across all socioeconomic levels.[3] The male to female ratio is 4:1 for the predominantly hyperactive type, and 2:1 for the predominantly inattentive type. It may be underidentified in girls.

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SIDEBAR 1.

Alternative Treatments for Attention-deficit/ Hyperactivity Disorder

- Diet
- Omega-3 (DHA/EPA)
- Probiotics
- Vitamins
- Botanicals
- Aromatherapy
- Mind-body medicine
- Neurofeedback
- Massage/chiropractic manipulation
- Yoga, meditation, and music therapy
- Homeopathy
- Lifestyle

There is increasing scientific awareness that ADHD is a heterogeneous disorder that continues from childhood and adolescence into adulthood and in many cases carries a high risk of co-morbidities, such as mood disorders and learning disabilities.[4] Morphologic and metabolic differences in the brains of people with symptoms of ADHD have been suggested by studies using magnetic resonance imaging (MRI), positron emission tomography (PET) scans, and EEGs.

ADHD is often described as a "hypodopaminergic disorder" or a disorder of self-regulation, often called an "executive function dysfunction." The most accepted hypothesis is that the cognitive and behavioral symptoms of ADHD are the result of diminished function of polysynaptic dopaminergic circuits of the pre-frontal executive centers of the brain cortex, which are responsible for impulse control and sustained attention.[5] Decreased activity of dopamine has been associated with increased risk for addiction, as the D2 receptor has been implicated in the reward mechanisms in the brain.[6]

The etiology of ADHD is unknown, although evidence from family studies of ADHD suggests a genetic basis for some forms of this disorder.[7] Studies have identified differences in the genes encoding for both the D2 and D4 dopamine receptors in people with ADHD. Other genetic polymorphisms have been associated with increased activity of the pre-synaptic dopamine transporter, which would cause increased uptake of dopamine.[8] This supports the hypothesis of a "hypodopaminergic state" or relative dopamine insensitivity in the affected areas of the brain. An imbalance in dopamine and norepinephrine in the pre-frontal cortex with increased stimulatory activity of norepinephrine and decreased inhibitory activity of dopamine contributes to the pathogenesis of the symptom complex of ADHD. Atypical functioning of the fronto-striatal complex and reduced local activation of the basal ganglia and right anterior frontal lobe have also been studied in association with ADHD. The stimulant medications inhibit the reuptake of dopamine at the pre-synaptic level, thereby increasing dopamine at the synaptic terminals as well as causing some striatal stimulation.[9]

Other genetic factors that contribute to the symptom complex of ADHD may be the inherited tendencies toward allergic states, immune dysfunction, and various genetic polymorphisms that result in an altered capacity to detoxify heavy metals and xenobiotics.

Exposure to environmental toxins possibly associated with the development of ADHD in some cases may begin at or even before conception. Maternal tobacco and other drug use have also been associated with an increased risk of ADHD. In one study up to 25% of all behavioral disorders in children were associated with smoking in pregnancy.[10] Children with fetal alcohol syndrome may have cognitive and behavioral features consistent with the diagnosis of ADHD. The Centers for Disease Control and Prevention estimated that about 2% of American children younger than 6 years met the criteria for lead toxicity at levels that have

been associated with cognitive deficits and behavioral disturbances (> 10 µg/dL). Low-level lead intoxication has been associated with hyperactivity, impulsivity, and addictive behavior.[11] Pilot studies of chelation therapy with calcium EDTA in children with moderate elevations in blood lead levels have demonstrated improvement in ADHD behaviors .[12]

The role of genetics and the environment with the particular interactions and conditions that may be underlying the manifestation of the symptom complex of ADHD is revisited. Some of the varied hypotheses and paradigm shifts current in the "alternative approaches" for the management of ADHD are discussed as listed in Sidebar 1 (see page 510).

DIET: DOES FOOD AFFECT MOOD?

"Let food be thy medicine, and medicine be thy food" — Hippocrates (460-377 BC)

Foods and herbs long have been used as medicine in traditional healing practices. Elimination diets as well as specialized ones involving both detoxifying and strengthening potions of botanicals and minerals are common in the varied ancient tool bag of remedies.

There is increasing research showing a link between the gastrointestinal system (GI), often called the "second brain," and behavior.[13] Much conflicting data have been published regarding the effects of sugars, food additives, colors, and preservatives in children with ADHD. Impaired catecholamine control of sugar was found in children with ADHD and may be associated with worsening of behavior following a sucrose challenge.[14] It may be controversial that sucrose as a single agent contributes to ADHD. However, recent studies repeatedly have shown improvement in both school performance and behavior in children who changed their diet from "junk foods" high in artificial flavors, preservatives, and sucrose to more nutrient-dense foods.[15]

ESSENTIAL FATTY ACIDS: FROM WOMB TO TOMB

Essential fatty acids, particularly docosahexaenoic acid (DHA), play a critical role during pregnancy and infant development, adult life, and old age. It has been postulated that the imbalance of essential fatty acids (EFA) in the brain plays a role in ADHD, because EFAs are "essential for normal neuronal structure and function, maintenance of membrane fluidity, impulse transmission, receptor sensitivity, and maintenance of adequate neurotransmitter pool.[16] In fact, dopamine-producing nerve endings are highly fluid and are composed of approximately 80% DHA.

IS THERE A SPECTRUM OF DISORDERS ASSOCIATED WITH DEFICIENCY/ IMBALANCE OF OMEGA-3?

There is increasing evidence that abnormalities of fatty acid and membrane phospholipid metabolism play a part in neurodevelopmental and psychiatric disorders. A positive response to treatment with a daily dose of 9 g of omega-3 in people diagnosed with bipolar disorder was suggested.[17] Beneficial improvements were reported in small studies involving treatment with omega-3 in ADHD, dyslexia, developmental coordination disorder, depression, and autistic spectrum disorders.[18]

Some studies found that children with ADHD have a measurable reduction in tissue levels of omega-3 fatty acids when compared with age-matched controls.[19] A greater number of behavior problems assessed by the Conners' Rating Scale, temper tantrums, and sleep problems were reported in subjects with lower total omega-3 fatty acid concentrations.[20] The comorbidity of learning disabilities is seen in children with ADHD. It was shown that children who have difficulties such as dyslexia have lower levels of omega-3 fatty acids than controls.[21] Other studies showed the severity of these clinical signs of fatty acid deficiency to be strongly correlated with the severity of dyslexic signs and symptoms, not only in the visual domain, but also with respect to auditory, linguistic, and motor problems.[22]

Some studies have suggested that children who were formula fed have an increased risk of having ADHD symptoms compared with those who were breast fed.

Some studies have suggested that children who were formula fed have an increased risk of having ADHD symptoms compared with those who were breast fed.[23] Breast-fed children and those who had received milk with added polyunsaturated fatty acids appear to be better at solving problems and learning language, compared with children receiving milk that does not contain polyunsaturated fatty acids.[24] The World Health Organization (WHO) made the recommendation in 1995 that baby formulas provide 40 mg of DHA per kg of infant body weight. In the United States, DHA has been added to many infant formulas since 2002. Nutritionists recommend 2 to 3 servings of fish a week, or 100 mg a day, to maintain DHA levels.

Children with ADHD were reported to have an increased oxidation of omega-3 as well as an impaired ability to synthesize DHA from vegetable precursors found in a regular diet.[19,25] The omega-3 to omega-6 ratio should be between 1:1 or 1:6 for maintaining membrane and receptor sensitivity. It is also hypothesized that an increase in omega-6 in the diet adds to the imbalance of the membrane ratio of omega-3 and omega-6. In addition, diets high in trans-fats are associated with impaired fetal and childhood brain development, and they are known to block the enzymatic conversion of the vegetable derived omega-3 and omega-6 fatty acids into the critical long chain fatty acids of DHA.[26]

ADHD AND ALLERGY

There are known associations among allergic disorders, food allergies with recurrent otitis media, sleep problems, and ADHD. Other data also suggest that people with atopy and food allergies may have an increased requirement for EFA, the normalization of which has a beneficial effect on atopic disorders.[27] Children with ADHD also often manifest symptoms of EFA deficiency such as thirst, frequent urination, dry hair, and skin.[28] Many studies using "oligoantigenic" or allergy elimination diets have been shown to improve behavior in some children with ADHD.[29,30] Several mechanisms have been postulated involving the inflammatory mediators and neuro-peptides, which have been shown to be increased in the blood after exposure to a sensitizing food.

WHAT ARE THE PROS OF USING PROBIOTICS?

Frequent episodes of otitis media and treatment with antibiotics are common in children with ADHD. Apart from food allergy, an increase in intestinal permeability has been proposed in some children with the symptom complex of ADHD. Maintenance of normal gut flora with normal species may be important in preserving the mucosal barrier of the gut. There is some increasing evidence that supplementation with probiotic like bifidobacteria and lactobacilli can decrease the effects of food allergy.[31] More studies are needed to explore this hypothesis and the pro and cons of using probiotics in children with symptoms of ADHD.

SIDEBAR 2.

Natural Treatments

- St. John's wort *(Hypericum perforatum)*
- Glutamine
- Taurine
- Glycine
- Dimethylglycine
- Gamma-aminobutyric acid
- Dimethylaminoethanol (DMAE/deanol)
- S-adenosylmethionine (SAMe)
- Phosphatidylserine/inositol
- Tyrosine
- Tryptophan
- Gingko biloba
- Ginseng

HOW VITAL ARE VITAMINS AND MINERALS?

Inadequate nutrients during fetal life may also play a significant role in the development of the neurological system and may be of some importance in ADHD.[32] Several small studies showed blood levels of zinc,[33] magnesium,[34] iron, and the B vitamins[35] (particularly B1, thiamine), to be lower in children with ADHD than in controls. There is biological plausibility that restoring optimal levels may provide some benefit in behaviors that have been associated with deficiencies. Zinc is important as a co-factor in the metabolism of neurotransmitters, dopamine, melatonin, and fatty acids. A direct linear correlation was found in one study between zinc levels and response to treatment with amphetamines. Positive effects of supplementation with zinc sulfate (150 mg/day) were demonstrated in a large, randomized, controlled trial of hyperactive children, with significant improvement in impulsive behaviors and socialization skills compared with placebo.[36] Small studies showed low levels of magnesium in serum and red blood cells of children with ADHD, and improvement in behavior was demonstrated in 30 of 52 children with ADHD who were treated with 100 mg magnesium daily and B6 supplementation.[37] Iron is involved in the metabolism of dopamine and its regulation. A preliminary report demonstrated reduction of ADHD symptoms within a month of supplementation with iron in non-anemic children diagnosed with ADHD.[38]

There are no studies that validate the use of megavitamin doses. The two randomized controlled studies using high doses of vitamin C, niacin, and pyridoxine did not show benefit; however, they involved small numbers of participants and had only short-term follow-up.

"NATURAL REMEDIES"

"The scientists' religious feeling takes the form of a rapturous amazement at the harmony of natural law, which reveals an intelligence of such superiority that, compared with it, all the systematic thinking and acting of human beings is an utterly insignificant reflection." — Albert Einstein (1879-1955)

Botanical: Is there bounty in botanicals?

On review of the Natural Medicine Comprehensive Database, more than 25 "natural" remedies have been promoted for the treatment of ADHD. Some are mentioned in Sidebar 2. Fewer botanicals have been studied in children than in adults. This is similar to conventional medications, which generally are first researched in adults and then often used "off-label" in chil-

dren. Some small studies are emerging that have demonstrated a measurable treatment response. Larger trials are warranted.

Standardized extracts of Ginkgo biloba (50 mg) and Panax quinquefolius (200 mg) in combination in an open-label trial were shown to improve both school performance and behavior, as measured by the Conners' rating scales, in 74% of 36 children with ADHD after 4 weeks of a twice-daily dose.[39] A more recent randomized, double blind, placebo-controlled study using L-theanine (an amino acid found in green tea) in children with ADHD also showed significant improvement in symptoms. L-theanine may improve central dopaminergic activity, stabilize mood, increase concentration, reduce anxiety, and improve quality of sleep. It has been consumed in large quantities for throughout the past 20 years in Japan and some parts of Europe.

In a small-randomized controlled trial, treatment with 1 mg/kg/day of pycnogenol (pine bark extract) for 4 weeks was linked to reduction of behaviors associated with ADHD, including in visual-motor coordination. There was a notable "relapse" in symptoms a month after stopping use.[40]

Aromatherapy: Are sweet-smelling solutions a solution?

Essential oils (EO) have been used from the time of the Egyptians and in many spiritual practices and religious traditions. According to a study by Torsons of London in 1993, EO molecules interact with receptors on nerve and other tissues similar to drugs (and hormones). When inhaled, some believe that EO directly access the limbic system. EO also act like hemoglobin molecules in the blood stream. Relaxing and neuro-stimulating properties of lavender and rosemary oils were studied in human subjects who were evaluated for mood and were given math computations before and after aromatherapy. Lavender increased relaxation and both computational speed and accuracy. Rosemary acted as a mild stimulant and increased computation speed without decreasing accuracy.[41] Valerian has been studied in children with cognitive deficits. Compared with baseline and placebo, treatment with valerian led to significant reduction in sleep latencies and nocturnal time awake, lengthened total sleep time, and improved sleep quality.[42] The treatment was most effective in children with hyperactive behavior.

Other sedative herbs used in Europe for "restlessness" include chamomile, lemon balm, and hops. Melatonin has also been used to help with the sleep difficulties seen in children with ADHD. In a randomized controlled trial, 25 children with chronic insomnia and ADHD were treated with 5 mg of melatonin and showed significant improvements in sleep latency, onset, and total sleep time as compared with controls.[43]

MIND-BODY-MEDICINE IS MANIFEST IN MULTIPLE MODALITIES BOTH OLD AND NEW'

Neurofeedback

Neurofeedback is based on theories that include the organic basis of ADHD and utilizes biofeedback to guide people to regulate their brain activity. It relies on research that has demonstrated that most people with ADHD, as compared with matched peers, have excess (theta) slow wave activity and reduced (beta) fast wave activity.[44] It provides immediate feedback to the person about brain activity in the form of a video game, as well as in some cases auditory feedback. This self-regulation of slow cortical potentials has been postulated to involve similar neuro-biologic pathways as medication.[45] Neurofeedback used with meta-cognitive strategies has shown positive results in ADHD, with decrease in use of medications. In some cases, this was comparable to the use of stimulants in decreasing the symptoms of hyperactivity, inattention, and impulsivity.[46] However, the need for weekly visits averaging 40 sessions of individualized training and lack of insurance reimbursement make this a costly treatment option.

Massage

Massage in various forms is part of many traditional healing systems. Massage therapy enhances "a sense of well being," which supports the concept of activating the "innate healing" ability of the body. It has been hypothesized that the mechanism involves release of endogenous endorphins in the body. A small study of massage as therapy in students with ADHD showed an improvement in short-term mood and long-term classroom behavior.[47] In another study of adolescents with ADHD, more "on time and on task" behaviors as well as lower hyperactivity scores were reported by teachers. The massage group rated themselves as "happier." Randomized controlled trials in premature infants and depressed adolescents have also shown beneficial results.[48] Chiropractic manipulation reportedly increases body alignment and awareness; however, there are no studies that have demonstrated beneficial effects of this therapy in children with ADHD.

Yoga, Meditation, and Music Therapy

Yoga, meditation, and music therapy are forms of mind-body-spirit practice. Various forms of yoga, originally from the Indian subcontinent, have gained popularity in the United States. Studies have shown the benefits of yoga for asthma, stress reduction, pain management, depression, and ADHD.[49] Both meditation and yoga practice for children are now being offered in summer camps and after-school programs. Subjective improvements in behavior were reported in a 6-week open trial of twice weekly yoga lessons for child and parent with daily practice at home.[50] A recent study of adolescent boys with ADHD using both instructional and improvisational models of music therapy reported

a significant reduction of symptoms in the classroom in teacher's assessments using the Conners'-*Diagnostic and Statistical Manual for Mental Disorders,* fourth edition (DSM-IV), sub-scales.[51]

HOMEOPATHY, THE ALCHEMY OF LESS IS MORE

Homeopathy was as developed by the German chemist Samuel Hahnemann (1755-1843) in the late 18th and early 19th century. Hahnemann identified "vibrational patterns" of disease. Homeopathy is based on the principal that a substance producing the same cluster of symptoms can treat the symptoms of a patient. The original substance is repeatedly diluted and "agitated," with the "medicinal energy" remaining in the end product. Higher dilutions are used as constitutional remedies for chronic conditions, with lower dilutions for acute symptoms. Homeopathy is taught in medical schools in Europe and Asia and therefore is not considered "alternative." Families that are acculturated to it and have experienced its benefits for other ailments have used it as the first-line treatment for ADHD. Two randomized controlled trials have demonstrated improvements in behaviors as measured by the Conners' Global Index.[52,53]

LIFESTYLE MEDICINE AS A TREATMENT OPTION?

Incorporating some of the principles of lifestyle medicine include developing routines and rhythms that help with the regulatory disturbance that is described in children with ADHD. A changing of the environment for the child versus the child for the environment is the approach. A balance of both is actually needed as children learn to internalize the structure and strategies that have been created for them externally as part of self-regulation. Using Mother Nature to heal with play in natural "green" surroundings has been studied and suggested as 'widely effective' in reducing symptoms seen in children with ADHD.[54] Establishing a sleep routine to provide adequate sleep and limiting television viewing (less than 2 hours a day as recommended by American Academy of Pediatrics) are important, because lack of sleep and overstimulation are known to be associated with symptoms of inattention and hyperactivity, irritability, and aggression in children.

SIDEBAR 3.

Multi-modal Management

1. Classroom accommodations
2. Trial of medication
3. Coaching
4. Social skills groups
5. Parenting skills training and support groups, etc., are often needed and recommended.

CONCLUSIONS

The conventional comprehensive approach for evaluating and treating children who present with symptoms of ADHD often includes assessment for associated co-morbidities of learning disabilities, anxiety, depression, motor co-ordination disorders, etc. as warranted by each individual child. A multidisciplinary evaluation is followed by a multi-modal treatment plan (see Sidebar 3), which includes a trial of medication, combined with educational accommodations and behavior management strategies. Many of the alternative approaches discussed here can be integrated into the multi-modal plan as well as used individually. Additional research into the effects of these approaches is indicated, utilizing scientifically sound clinical trial methods.

As we continue to explore and offer alternative treatment options to children with ADHD, it is important to remember the Hippocratic oath of "Primum Non Nocere" ("first do no harm") as well as the wisdom in "Vis Medicatrix" ("the healing power of nature"). A hierarchy starting from the safest and lowest potential side-effect profile to the more concerning ones should be considered and discussed carefully with parents. Although the numbers and studies are relatively few, more research as well as regulation and standardization of botanical products and supplements for use in children is needed. In keeping pace with the rising interest and use of CAM, it is imperative that pediatricians stay informed, support, and expand the research on modalities that have a viable hypothesis, a low adverse side-effect profile, and may show benefit.

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