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Integrative Management of ADHD: What the Evidence Suggests

by James Lake, MD

It is important for mental health professionals to be familiar with emerging research findings about widely used complementary and alternative medicine (CAM) treatments of attention-deficit/hyperactivity disorder (ADHD) in order to provide patients with accurate information on efficacy, safety, and appropriate use.

A high percentage of children and adults who have been given a diagnosis of ADHD use alternative therapies alone or in combination with conventional pharmacological treatment.[1] More than half of parents of children with ADHD treat their children's symptoms using 1 or more CAM therapies, most commonly vitamins, dietary changes, and expressive therapies; yet only about 10% disclose use of such nonpharmacological therapies to their child's pediatrician.[2] Most nonpharmacological therapies used to treat ADHD are supported by limited evidence; however, as many as 80% of patients who use herbal preparations and other natural products regard these therapies as the primary treatment of their symptoms.[2]

Conventional treatment

Stimulant medications, including dextroamphetamine, methylphenidate, and related compounds, are the most widely used treatments of ADHD. The nonstimulant atomoxetine has less potential for abuse but also may be less effective than stimulants.[3] SSRIs and other antidepressants are used with varying degrees of success. Behavioral modification aimed at rewarding desirable behavior and extinguishing disruptive or inappropriate behavior continues to be a mainstay of conventional treatment. Psychotherapy and psychosocial support help reduce anxiety and feelings of loss of control that frequently accompany ADHD. It is estimated that ADHD is correctly diagnosed and treated in fewer than one-fifth of adults, which results in significant social and occupational morbidity.

Limitations and risks of conventional treatment

Long-term amphetamine use in childhood is associated with delays in normal development.[4] One-third of individuals of all ages who take stimulants for ADHD report significant adverse effects, including insomnia, decreased appetite, and abdominal pain.[5] Cases of stimulant-induced psychosis have also been reported.[6] Stimulants and other conventional treatments of ADHD in adults are probably only half as effective as they are in children.[4]

Adverse effects of nonstimulant drugs used to treat ADHD include hypertension, decreased appetite, nausea, fatigue, liver toxicity, insomnia, and seizures. A meta-analysis of 6 controlled trials concluded that stimulant therapy started in childhood reduces the risk of subsequent substance abuse by as much as one-half. In contrast, stimulants started in adolescence or adulthood increase the risk of future substance abuse.[7] Nonstimulant medications and extended-release stimulants are less likely to be abused.[8]

Nonconventional therapies

Dietary changes. Early studies on a highly restrictive diet that eliminates all processed foods reported promising findings in children with ADHD[9]; however, a review of controlled studies failed to support these findings.[10] The oligoantigenic diet (OAD) is a highly restrictive elimination diet in which food colorings and additives as well as dairy products, sugar, wheat, corn, citrus, eggs, soy, yeast, nuts, and chocolate are eliminated. Numerous studies on the OAD reported significant reductions in hyperactivity in children with ADHD when specific food items were eliminated from the diet using an open-label protocol.[11] In most studies, symptoms recurred when children were subsequently challenged with the eliminated food item following a placebo-controlled protocol. The significance of findings on elimination diets is limited by study design flaws, including heterogeneity of patient populations, absence of standardized outcome measures, high dropout rates and, in some studies, nonblinded raters.

Although research findings are mixed, sugar has long been suspected as an underlying causative factor in ADHD. In a 9-week placebo-controlled study, children without ADHD who were randomized to diets high in sucrose, aspartame, or saccharin showed no differences in behavior.[12] The expectations of parents may bias the perceptions of their children's behavior following the consumption of large quantities of sugar. In one controlled trial, mothers who believed their child had eaten sugar were more likely to label their child's behavior as hyperactive.[13]

In their comprehensive review of nonpharmacological therapies for ADHD, Weber and Newmark[14] remarked that the study design did not adequately control for fruits, juices, or other dietary sources of sugar and suggested that future studies should not focus primarily on sugar but rather on a possible link between high-glycemic-index foods and hyperactivity. Large prospective controlled studies on dietary restrictions as therapeutic interventions in ADHD have been elusive because of difficulties in controlling eating behavior in both children and adults.[15]

EEG biofeedback. Children and adults with ADHD often have abnormal patterns of brain electrical activity; underarousal in frontal and midline cortical regions is found in up to 90% of cases, and frontal hyperarousal is especially noted in individuals who have not responded to stimulants.[16] Electroencephalographic (EEG) biofeedback is aimed at normalizing EEG activity by correcting the brain's state of relative underarousal, thereby optimizing cognitive and behavioral functioning.[17]

Two EEG biofeedback protocols have been extensively studied as treatments of ADHD. With sensorimotor rhythm (SMR) training, the goal is to reinforce EEG activity in the faster beta frequency range (16 to 20 Hz) in the midline cortical regions, and it is targeted at reducing symptoms of impulsivity and hyperactivity. In contrast, theta suppression aims to reduce EEG activity in the slower theta frequency range (4 to 8 Hz) and is used primarily to treat symptoms of inattention.

Controlled studies that compared EEG biofeedback to a stimulant medication with a wait list report consistent beneficial clinical effects and EEG normalization with SMR and theta suppression EEG biofeedback protocols.[18,19] However, causal relationships between improvements in attention and increased or decreased alpha activity (12 to 18 Hz) have not been clearly established. The significance of most findings on EEG biofeedback is limited by study design flaws that include small study sizes, heterogeneous populations, absence of a control (ie, sham biofeedback) group, inconsistent outcome measures, self-selection bias (the majority of enrolled subjects were highly motivated to receive treatment), and limited or no long-term follow-up.

Natural products used to treat ADHD. The finding that children with ADHD have lower plasma concentrations of certain essential fatty acids (EFAs) than those in a healthy population has led to the hypothesis that fatty acid deficiencies during critical developmental phases increase the risk of acquiring ADHD.[20,21] Few controlled studies have examined the effect of EFAs in children with ADHD, and findings are inconsistent.

One study on EFAs as an adjunctive therapy to stimulant medications found no differential benefit of EFAs compared with stimulants plus a placebo.[22] Another adjunctive study found only modest improvements over placebo in disruptive behavior and attention.[23]

In a placebo-controlled trial on EFAs as a stand-alone treatment of ADHD, parents of children in the treatment group reported more improvement than did parents of children receiving a palm oil placebo.[24] This study has been criticized because a high dropout rate biases findings in a positive direction.[14] The use of olive oil as a placebo may mask the beneficial clinical effects of EFAs because an active constituent of olive oil is converted into oleamide, which is known to affect brain function.[25] It has also been suggested that the relatively short durations and low doses of EFAs used in these studies may not be adequate to result in changes in neuronal membrane structure required for clinical improvement.[22]

The issue of dosing has been addressed by a small open-label study (N = 9) in which children with ADHD were given supplemental

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high-dose eicosapentaenoic acid/docosahexaenoic acid (EPA/DHA) concentrates (16.2 g/d) while they continued to take stimulant medications. Most children were rated by a blinded psychiatrist as having significant improvements in both inattention and hyperactivity that correlated with reductions in the arachidonic acid to EPA ratio at the end of an 8-week treatment.[26] Large prospective trials in different age-groups are needed to replicate these findings before omega-3s can be generally recommended for ADHD.

Herbal preparations

In a 4-week study, 36 children with ADHD were randomized to an herbal preparation containing *Ginkgo biloba* and *Panax quinquefolius* (American ginseng) or to a combination of the herbal preparation and stimulant medication.[27] Beneficial effects in attention and impulsivity were observed in children taking the herbal preparation alone; however, the absence of a comparison group (ie, taking a stimulant only) and small study size limit the significance of the findings.

Findings of several open studies suggest that a standardized extract of *Pinus pinaster* (French maritime pine) bark is an effective treatment of ADHD, although to date, only 1 double-blind placebo-controlled trial has been published.[28] Children and adolescents randomized to a standardized extract of French maritime pine bark (Pycnogenol, 1 mg/kg/d for 1 month) experienced significant improvements in hyperactivity, inattention,

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Table Nonconventional and integrative treatments of ADHD[48]

Nonconventional therapy	Research methods	Significant findings	Comments
Dietary changes	Double-blind placebo-controlled challenge cross-over trial (N = 300, ADHD children), phase 1 elimination, phase 2 challenge[49]; double-blind placebo-controlled challenge cross-over trial, phase 1 open elimination followed by challenge (N = 56, 4 - 12 y with behavioral problems)[50]	75% improved with restricted diet, however symptoms recurred when food colorings and additives reintroduced; improved behavior and attention scores	No description of recruitment or eligibility of nonresponders in phase 2; more restrictive than Feingold but less restrictive than OAD protocol
EEG biofeedback	1-y clinical trial stimulants vs EEG biofeedback + stimulants (N = 100, 6 - 19 y)[17]; 12-wk clinical trial EEG biofeedback SMR and beta rhythms 3/wk or stimulants (N = 34, 8 - 12 y)[51]	Symptoms improved with stimulants but only biofeedback group sustained improvement without stimulants at 1-y follow-up; Conners scores significantly improved in EEG biofeedback group	Group assignments based on parental preference; average of 43 sessions required for sustained improvement
Herbal preparations	4-wk RCT (N = 34, ADHD children) randomized to *Ginkgo biloba* + American ginseng or ongoing stimulant medication + herbals; 1-mo RCT (N = 61) standardized extract of French maritime pine bark (1 mg/kg/d)[29]; RCT (N = 85, healthy men and women) extract of *Ginkgo biloba* and *Bacopa monnieri* or placebo[30]	No improvements in ADHD symptoms; significant improvements in hyperactivity, inattention, and visual-motor coordination; no improvements over placebo in short-term memory, working memory, executive processing, etc	No comparison group treated with stimulants only; large studies needed to replicate findings; study population consisted of normal individuals; large prospective dose-finding trials on ADHD patients needed
Trace elements	12-wk RCT (N = 400, children and adolescents) high-dose zinc (150 mg/d) or placebo[33]; 12-wk RCT non-anemic ADHD children with low serum ferritin levels treated with oral iron (80 mg/d) or placebo[52]	Significant improvement in hyperactivity and impulsivity but not inattention; improvements with iron comparable to those with stimulants	High dropout rate limits significance; large prospective studies needed to confirm efficacy and determine optimal dosing
EFAs	2-mo double-blind placebo-controlled randomized trial (N = 40, 6 - 12 y), diet consisted of DHA-enriched foods or olive oil–enriched foods[53]; 8-wk open pilot study (N = 9) children given high-dose EPA/DHA concentrates (16.2 g/d) then rated by blinded psychiatrist; 16-wk pilot study (N = 112, ADHD children) randomized to ALC (500 - 1500 mg bid) or placebo	Short-term memory improved in control group but not DHA group; no differences in parent or teacher ratings of behavior or cognition; significant improvements in behavior and inattention correlated with reduced AA to EPA ratio and global severity of illness scores; no serious adverse effects reported	Olive oil may not be inert; some subjects had comorbid Asperger, conduct, learning, and mood disorders; no placebo group; some subjects had comorbid conduct disorder or oppositional-defiant disorder (which also improved during study); dietary intake not recorded at baseline or during study; supplement intake not closely monitored
ALC		ALC superior to placebo in inattentive-type ADHD but not combined-type ADHD	Large prospective trials needed
Yoga and massage	In 2 small controlled studies, ADHD children stable while receiving medications were randomized to yoga or regular massage therapy[45,46]	Trend toward reducing severity of ADHD symptoms with regular yoga and massage	Possible group expectation effects; large prospective studies needed

ADHD, attention-deficit/hyperactivity disorder; OAD, oligoantigenic diet; EEG, electroencephalographic; SMR, sensorimotor rhythm; RCT, randomized clinical trial; EFAs, essential fatty acids; DHA, docosahexaenoic acid; EPA,eicosapentanoic acid; ALC, acetyl-L-carnitine; AA, arachidonic acid.

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ADHD

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and visual-motor coordination over those receiving placebo; however, symptoms returned to pretreatment baseline levels after a 1-month washout.[28] One case of mild gastric discomfort was reported, and there were no serious adverse effects. Well-designed controlled studies are needed to replicate these preliminary findings.

Bacopa monnieri (Brahmi) is an Ayurvedic medicinal herbal preparation that is widely used as a tonic and memory enhancer. In a small, 12-week double-blind randomized clinical trial (RCT), 36 children who had ADHD and who were randomized to bacopa 50 mg twice a day showed significant improvement over those receiving placebo in tests of sentence repetition, logical memory, and pair-associative learning.[29] Large placebo-controlled trials are needed to confirm the safety and efficacy of bacopa as a treatment of ADHD.

Supplementation with trace elements

Zinc. Children who have ADHD frequently have abnormally low plasma zinc levels, which may interfere with optimal information processing and correlate with the severity of inattentive symptoms.[30,31] Zinc supplementation is a widely used alternative treatment of ADHD; nevertheless, few studies have been done and findings are inconsistent. In a large 12-week double-blind placebo-controlled trial (N = 400), children and adolescents who were randomized to a high dose of zinc (150 mg/d) experienced significant improvement in hyperactivity and impulsivity but not inattention over those receiving placebo.[32] A high dropout rate limits the significance of these findings.

In another study, the addition of zinc to methylphenidate therapy resulted in greater improvement than methylphenidate alone.[33] Large prospective studies are needed to replicate these preliminary findings and to confirm optimum dosing of zinc sulfate.[34]

Iron. The incidence of iron deficiency as measured by serum ferritin levels may be higher in children with ADHD than in a matched population of children without ADHD.[35] Abnormally low serum ferritin levels may be associated with relatively greater hyperactivity in non-anemic children with ADHD but not with differences in cognitive performance tasks.[36] In an open trial, non–iron-deficient children given oral iron for 1 month were perceived as less hyperactive and distractible by teachers—but not by parents.[37]

In a small, 12-week placebo-controlled trial, non-anemic children with ADHD who had abnormally low serum ferritin levels were randomized to oral iron (ferrous sulfate, 80 mg/d). Progressive improvements in the severity of ADHD symptoms were observed relative to placebo throughout the study: the effect was comparable to clinical improvements obtained with stimulants.[35] Large controlled studies are needed to confirm putative beneficial effects of iron supplementation in ADHD and to determine optimal dosing.

Acetyl-L-carnitine is required for energy metabolism and synthesis of fatty acids. Findings from a small study suggest that acetyl-L-carnitine significantly reduces the severity of ADHD symptoms. However, study design flaws, including failure to report pretreatment and posttreatment symptoms, limit the significance of the findings.[38] In a multisite, 16-week pilot study, 112 children with ADHD, aged 5 to 12 years, were randomized to placebo or to acetyl-L-carnitine (500 to 1500 mg bid).[39] The Conners parent and teacher rating scales administered at baseline, and at 8, 12, and 16 weeks showed the superiority of acetyl-L-carnitine over placebo in inattentive-type children; however, there was no improvement over placebo in combined-type children. Significant adverse effects were not reported. Future studies are warranted to examine specific therapeutic effects of acetyl-L-carnitine in the inattentive type of ADHD. Findings of a small randomized placebo-controlled study suggest that acetyl-L-carnitine given in doses of 50 mg/kg/d improves symptoms of hyperactivity in young boys with fragile X syndrome and ADHD.[40]

Homeopathic remedies

Homeopathic remedies are widely used in the United States and other countries to treat or self-treat ADHD. A recent systematic review of RCTs on homeopathic treatments in ADHD concluded that there is no evidence of beneficial effects of homeopathy on symptom severity, core symptoms, or the course of ADHD.[41]

Frei and colleagues[42] have pointed out that conventional RCT study designs may interfere with the goal of demonstrating clinically relevant treatment effects of specific homeopathic remedies for ADHD. They suggest that long-term studies are needed that incorporate an initial open-label phase to identify the optimal treatment for each patient who can then be randomized to his or her optimum remedy or to a randomly selected homeopathic preparation in a subsequent placebo-controlled phase.

Yoga and massage

In a small pilot study, children with ADHD randomized to yoga experienced more significant reductions in symptoms over time than children assigned to a conventional exercise group. Children who continued to take stimulants while practicing yoga experienced the greatest improvements.[43] Two small controlled studies suggest that yoga and regular massage therapy may reduce the severity of ADHD symptoms.[44,45] Large prospective studies are needed to confirm beneficial effects and test for possible group expectation effects of yoga and massage in ADHD.

As many as 80% of patients who use herbal preparations and other natural products regard these therapies as the primary treatment of their [ADHD] symptoms.

Green play environments

A recently proposed theory conceptualizes ADHD as the result of attention fatigue caused by limited contact with green spaces during early childhood development. Findings of a large observational study suggest that children with ADHD who spend more time playing outdoors in natural environments may experience fewer and less severe symptoms of ADHD.[46] These findings have been criticized because of design flaws, including a highly heterogeneous population that included children with severe symptoms or comorbid oppositional-defiant disorder, absence of independent raters, absence of a comparison group, and reliance on the impressions of parents using nonstandardized rating scales.[47]

Summary of key findings

To be most effective, the integrative management of ADHD should be individualized, taking into account the specific causes of the syndrome in each patient, including genetic factors, perinatal insults or toxic exposure, food sensitivities, and social factors. Stimulant and nonstimulant medications are often beneficial and are well tolerated for a significant percentage of children, adolescents, and adults with ADHD. When stimulants are ineffective, poorly tolerated, or refused by the patient (or the patient's parents), validated EEG biofeedback protocols—including SMR training for primarily hyperactive-type ADHD and theta suppression for primarily inattentive-type ADHD—are reasonable alternatives.

The **Table** summarizes significant research findings for the nonconventional and integrative therapies for ADHD discussed in this article. Dietary restrictions on food colorings and additives or on foods that may be causing allergic reactions may significantly reduce symptoms of hyperactivity in some cases. Zinc supplementation may be helpful in cases when hyperactivity and impulsive behavior do not respond to stimulants alone. Emerging findings suggest that supplementation with iron and acetyl-L-carnitine may reduce symptoms of distractibility and inattention in some cases of ADHD. Large prospective placebo-controlled studies are needed before zinc, iron, or acetyl-L-carnitine can be generally recommended for the treatment of ADHD. High doses of omega-3 EFAs (up to 16 g/d) may have beneficial effects on symptoms of both inattention and hyperactivity. More studies are needed to determine the optimal form and dosing of omega-3s in children and adults in whom ADHD is diagnosed. Extracts of *Ginkgo biloba*, *Panax quinquefolius*, *Pinus pinaster*, and *Bacopa monnieri* may be beneficial; however, conclusive findings from large prospective controlled trials are needed before any of these herbal preparations can be recommended as adjunctive or first-line treatments.

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