EXPERT REVIEWS

Nutrient supplementation approaches in the treatment of ADHD

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Attention-deficit/hyperactivity disorder (ADHD) is a chronic, debilitating psychiatric illness that often co-occurs with other common psychiatric problems. Although empirical evidence supports pharmacological and behavioral treatments, side effects, concerns regarding safety and fears about long-term use all contribute to families searching for alternative methods of treating the symptoms of ADHD. This review presents the published evidence on supplementation, including single ingredients (e.g., minerals, vitamins, amino acids and essential fatty acids), botanicals and multi-ingredient formulas in the treatment of ADHD symptoms. In most cases, evidence is sparse, mixed and lacking information. Of those supplements where we found published studies, the evidence is best for zinc (two positive randomized, controlled trials); there is mixed evidence for carnitine, pycnogenol and essential fatty acids, and more research is needed before drawing conclusions about vitamins, magnesium, iron, SAM-e, tryptophan and *Ginkgo biloba* with ginseng. To date, there is no evidence to support the use of St John's wort, tyrosine or phenylalanine in the treatment of ADHD symptoms. Multi-ingredient approaches are an intriguing yet under-researched area; we discuss the benefits of this approach considering the heterogeneous nature of ADHD.

KEYWORDS: ADHD • botanicals • carnitine • essential fatty acids • minerals • nutrition • pycnogenol • supplements • vitamins • zinc

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood disorders, characterized by problems with inattention, hyperactivity and impulsivity [1]. It is now accepted that ADHD can be a chronic condition across the lifespan [2]. Worldwide prevalence rates are estimated to be 5.29% [3] and it is now believed that as many as 4–5% of adults may suffer from ADHD [4,5]. The disorder is more commonly diagnosed in boys, with male-to-female ratios estimated at 2:1–9:1 [6]. Overall, it is viewed as treatable but not curable; its heterogeneous etiology complicates the effectiveness of those treatments that are available.

Stimulant medications, such as methylphenidate (Ritalin™), pemoline (Cylert™) and dextroamphetamine (Dexedrine™), with or without cognitive–behavioral therapy, are the most common and most studied treatments for childhood ADHD [7,8]. However, despite modern psychopharmacological advances, only 30–70% of adults with ADHD respond to these types of interventions [9,10], a rate lower than that observed in ADHD children. Additionally, many trials exclude patients with co-occurring disorders, so even less is known about medication treatment in these individuals. These limitations make it difficult to establish who would benefit from drug treatment given that trial participants are often quite different from those seen in the community. Side effects associated with pharmacological treatments for ADHD can also be concerning, as they include cardiovascular risks (methylphenidate [11]) and suicide attempts (US FDA warning on Strattera®/atomoxetine [101]).

Alternative treatments

Complementary and alternative methods (CAM) for treating ADHD are often sought by families wanting treatments with fewer side effects or remedies they consider 'safer' than medication [12]. It is important for clinicians to ask patients and their families whether they are using any supplements, given that these can influence medication treatment. Bussing *et al.* found, in a sample of 822 families, that 12% of children diagnosed with ADHD used CAM, and 7% of parents who suspected ADHD in

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their child used them [13]. Other studies confirm the high rate of CAM use with children and lack of disclosure to medical practitioners [14,15]. Stubberfield and colleagues found that 65% of their sample of children with ADHD were using some form of alternative therapy [16].

Psychiatry has been slow to embrace nutritional approaches to ADHD, despite a wealth of data showing that children are not receiving the recommended daily allowances of nutrients [17]. The negative studies on megavitamins (e.g., Grenblatt [18] and Haslam [19]) have not assisted the field in moving forward to investigate such treatments. Although there is much research on medication, there has been very little on nutrient interventions, which is probably partially attributable to the fact that funds are rarely available for that type of study [20]. The lack of scientific data makes treatment decisions difficult for families, who may then resort to trial and error. More concerning, is that families often do not inform their medical practitioners of alternative treatments being used, placing children at unnecessary risk from potential interactions between conventional treatments and alternatives [12,14].

While families are trying many alternative treatments for ADHD, including regulation of diet, biofeedback and massage, this review focuses specifically on nutrient approaches. We review three nutrient-based approaches: single-ingredient interventions, botanicals and multi-ingredient formulas. Only published studies with ADHD samples were reviewed, including those where participants had other co-occurring diagnoses. Three designs were included case studies, open-label trials (OLTs) and randomized controlled trials (RCTs). Electronic literature searches were performed to find all reviews completed for supplements tested in the treatment of ADHD. The MEDLINE (via PubMed), PsycINFO and PsycARTICLES databases, as well as the Cochrane Library were searched for all research articles published up to October 2008. Nutrient supplement terms included in the search were based on known clinical trials, anecdotal reports of leading researchers and clinicians in the field of ADHD treatment, as well as the authors' knowledge of the topic. In addition to the nutrient ingredients included in this review, our search terms included glutamine, phosphatidyl, grape seed extract, primrose oil, flaxseed, melatonin, taurine, inositol, gamma-amino-butyric acid (GABA), 5-HTP, chromium polynicotinate, vitamin E, inositol, selenium, taurine, lemon balm, grapine and Huperzine A. All reference sections of review articles on ADHD and alternative treatments were also scanned for additional studies. This review summarizes outcomes from all the 27 human studies found on nutrient supplements in the treatment of ADHD. Despite poor methodologies in some studies, we attempted to be inclusive given the overall dearth of studies conducted in the area. Given the variability in quality, we classified the studies according to a simple coding system (i.e., effect, no effect or unclear); however, it is cautioned that cross comparisons cannot be performed given that RCTs have a different methodological rigor compared with OLTs. Table 1 presents studies using single ingredients; Table 2, studies using botanicals and Table 3, studies using multi-ingredient approaches.

Single ingredients

Vitamins

Pyridoxine (Vitamin B_6)

Pyridoxine is essential for neurotransmitter synthesis and normal brain development. Only one study has investigated its effect on hyperactivity and apparently has not been replicated or extended. Coleman *et al.* conducted a small 21-week double-blind (3 weeks in each condition), crossover RCT comparing low/high dose of pyridoxine with low/high dose of methylphenidate with three placebo conditions in six hyperactive children: nonsignificant trends suggested that pyridoxine and methylphenidate were more effective than placebo in suppressing the symptoms of hyperkinesis [21]. Although the evidence does not support therapeutic benefit from pyridoxine supplementation alone, it has not been tested adequately.

Minerals

Iron

Iron is essential for normal brain growth, neurotransmitter synthesis and catabolism, and many cellular metabolic processes. Iron deficiency can cause abnormal dopaminergic neurotransmission because it modulates dopamine and norepinephrine production as a cofactor for tyrosine hydroxylase, and has been speculated to contribute to the pathophysiology of ADHD [22]. Symptoms of iron deficiency can include decreased attention, arousal and responsiveness. In a controlled group comparison study, 53 children diagnosed with ADHD had significantly lower serum ferritin levels than 27 controls; in addition, the serum ferritin levels were significantly correlated with inattentive ADHD symptoms (but not hyperactivity) as measured by the Conners' Parent Rating Scale [22].

Only two studies were found that treated children with ADHD using iron. One was an OLT with 14 nonanemic boys with ADHD who were treated for 30 days with an iron preparation called Ferrocal [23]. Although there was a significant increase in blood serum ferritin levels after supplementation, only the Conners' Parent Rating Scale score decreased, not the Teacher's. Konofal *et al.* reported a RCT of 23 children with low serum ferritin levels (<30 mg/ml) and ADHD at screening who were treated either with oral ferrous sulphate or placebo for 12 weeks [24]. Although there was a significant improvement over time on two clinician-based scales (the ADHD Rating Scale administered to parents, and the Clinical Global Impression – Severity score), there was no change on either the Conners' Parent or Teacher Rating Scales. Effect sizes were large between iron supplementation and placebo on the ADHD Rating Scale (Cohen's d = 0.81). Furthermore, the oral ferrous sulfate was generally well tolerated in the trial, except in one patient who dropped out. We cannot determine the longer term impact of iron supplementation and whether such treatment can induce hemosiderosis, a serious health problem caused by iron overload.

High levels of lead are known to be associated with symptoms typical of ADHD (e.g., hyperactivity and inattention) and some have hypothesized that supplementation with minerals, such as iron, calcium and zinc, can decrease lead absorption. However, a study of 602 lead-exposed Mexican children did not find that iron and zinc supplementation had an effect on parent and

Table 1. Intervention studies with single nutrients.

Study	Intervention (daily dose)	Sample (age, years)	Design	Length of trial (weeks)	Results	Effect	Ref.
Vitamins							
Coleman *et al.* (1979)	Pyridoxine (10 and 15 mg/kg)	n = 6; hyperkinetic children with low serotonin; 83.3% boys (8–13)	RCT comparing low/high pyridoxine with low/high methylphenidate with 3 placebo conditions in a crossover design	21 (3 weeks in each condition)	Nonsignificant trend indicating pyridoxine and methylphenidate > placebo on symptoms of hyperkinesis	Unclear	[21]
Minerals							
Sever *et al.* (1997)	Iron (5 mg/kg)	n = 14; nonanemic boys with ADHD (7–11)	Case series	4	Parent Conners' rating improved; no change on teacher rating	Unclear	[23]
Konofal *et al.* (2008)	Iron (80 mg as ferrous sulfate)	n = 23; nonanemic children with ADHD; 78% boys (5–8)	RCT with 3:1 ratio of supplement:placebo	12	Iron > placebo on clinician ADHD rating scale and CGI ratings, but not Parent or Teacher Conners'	Unclear	[24]
Kozielec and Starobrat-Hermelin (1997)	Magnesium (3 mg/lb)	n = 75; magnesium-deficient hyperactive children (7–12)	RCT with 2:1 ratio of magnesium:no supplement	24	Magnesium > no supplement; significant decrease in hyperactivity on magnesium, controls worsened over 6 months	Effect	[27]
Bilici *et al.* (2004)	Zinc (150 mg as zinc sulfate)	n = 400; ADHD children; 82% boys (6–14)	RCT	12	Zinc sulfate > placebo for hyperactivity, impulsivity and impaired socialization; no improvement in attention	Effect	[35]
Akhondzadeh *et al.* (2004)	Zinc (55 mg as zinc sulfate) adjunct to methylphenidate	n = 44; ADHD children; 59% boys (5–11)	RCT	6	Zinc sulfate > placebo on parent and teacher ratings	Effect	[36]
Amino acids							
Wood *et al.* (1985)	DL-phenylalanine (50-400 mg three-times daily)	n = 19; ADD adults, residual type; 38.5% male (23–35)	Double blind crossover trial with placebo followed by OLT for responders	2 then 12 weeks OLT	DL-phenylalanine > placebo on mood and mood lability, but benefits not maintained at 3-month follow-up	No effect	[37]
Nemzer *et al.* (1985)	L-tyrosine (140 mg/kg) vs tryptophan (100 mg/kg) vs D-amphetamine (5/10 mg)	n = 14; ADHD children; 79% boys (7–12)	Double blind, 4-condition placebo-controlled latin square design	4 (1 week on each condition)	Tyrosine = placebo; tryptophan > placebo for parent ratings but not teacher ratings	Unclear for tryptophan; no effect for tyrosine	[38]

AA: Arachidonic acid; ADD: Attention-deficit disorder; ADHD: Attention-deficit/hyperactivity disorder; ALC: Acetyl-L-carnitine; CGI: Clinical Global Impression Scale; Conners: Conners' Rating Scales; DHA: Docosahexanoic acid; EPA: Eicosapentaenoic acid; GLA: γ-linolenic acid; OLT: Open-label trial; RCT: Randomized controlled trial; SAM-e: *S*-adenosy-L-methionine.

Table 1. Intervention studies with single nutrients.

Study	Intervention (daily dose)	Sample (age, years)	Design	Length of trial (weeks)	Results	Effect	Ref.
Amino acids (cont.)							
Reimherr *et al.* (1987)	L-tyrosine (50–150 mg/kg)	n = 12; ADD, residual type; 50% males (21–45)	1-week single-blind placebo washout; those unimproved entered 8-week OLT	1, then 8 weeks open-label trial	L-tyrosine therapeutically beneficial after 2 weeks; tolerance developed for all responders	No effect	[39]
Shekim *et al.* (1990)	SAM-e (2400 mg)	n = 8; adult males with ADHD (age not reported)	OLT	4	75% of participants improved in attention, hyperactivity and impulsivity	Effect	[40]
Carnitine							
Van Oudheusden and Scholte, (2002)	Carnitine (100 mg/kg)	n = 26; boys with ADHD (6–13)	RCT with double crossover	24	Carnitine > placebo on parent and teacher ratings of ADHD behaviors	Effect	[42]
Arnold *et al.* (2007)	ALC (500–1500 mg twice daily)	n = 112; children with ADHD; 74% boys (5–12)	RCT	16	No group differences on parent and teacher ratings; however, those with inattentive ADHD ALC > placebo	No effect	[41]
Torrioli *et al.* (2008)	ALC (20–50 mg/kg)	n = 63; boys with ADHD and fragile X syndrome (6–13)	Parallel multicentered RCT	52	ALC > placebo in terms of decreased hyperactivity/ inattention but questionable clinical significance	Unclear	[43]
Essential fatty acids							
Voigt *et al.* (2001)	DHA (345 mg), adjunct to stimulant medication	n = 63; children with ADHD; 70% boys (6–12)	RCT	12	DHA concentrations increase; however, no correlation with behavior measures, no improvements on ADHD scales or laboratory measures	No effect	[52]
Hirayama *et al.* (2004)	Whole foods fortified with DHA (514 mg) & EPA (100 mg)	n = 40; children with ADHD; 80% boys (6–12)	RCT	8	No differences on parent/teacher ratings of ADHD, improvements noted on some cognitive measures for controls	No effect	[53]

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Table 1. Intervention studies with single nutrients.

Study	Intervention (daily dose)	Sample (age, years)	Design	Length of trial (weeks)	Results	Effect	Ref.
Essential fatty acids (cont.)							
Sinn & Bryan, (2007), Sinn *et al.* (2008)	EPA (558 mg), DHA (174 mg), GLA (60 mg) or above plus micronutrients	n = 132; children with ADHD; 46% boys (7–12)	RCT with 3 arms followed with 15-week single blind extension	15 plus 15 extension	Both active treatment groups (no difference between groups) > placebo on parental measures of inattention, hyperactivity, impulsivity, switching and controlling attention; all other cognitive measures showed similar changes across all groups; no change on teacher ratings	Effect	[54,55]
Richardson and Puri, (2002)	EPA (186 mg), DHA (480 mg), GLA (96 mg), vitamin E (60 IU), *cis*-linoleic acid (864 mg), AA (42 mg), & thyme oil (8 mg)	n = 41; children with learning difficulties and ADHD symptoms; 85% boys (8–12)	RCT	12	Active treatment > placebo on 2 out of 7 measures of ADHD symptoms	Unclear	[56]
Stevens *et al.* (2003)	EPA (80 mg), DHA (480 mg), AA (40 mg), GLA (96 mg), and vitamin E (24 mg)	n = 50 children with ADHD and thirst/dry skin; 87% boys (6–13)	RCT	16	Active treatment > placebo on conduct problems as measured by parents and attention problems as measured by teachers; 11 other measures not significant	Unclear	[45]

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teacher ratings of inattention and hyperactivity [25]. Currently, the potential beneficial effect of oral iron supplementation alone is weak based on these small trials but may be helpful for those children identified as iron deficient.

Magnesium

Magnesium is a required cofactor of many enzyme systems and it plays a major role in neurotransmitter synthesis. Severe deficiency can cause neuromuscular hyper-reactivity and irritability. Starobrat-Hermelin documented deficiencies in magnesium, copper, zinc, calcium and iron in the 116 children she identified with ADHD [26]. Kozielec and Starobrat-Hermelin reported an intra-erythrocyte magnesium deficiency in 95% of the 116 ADHD children (aged 9–12 years) who they examined in terms of blood serum, red blood cells and hair using atomic absorption spectroscopy [27]. They followed these findings with a RCT, supplementing 50 magnesium-deficient hyperactive children with magnesium for 6 months, while 25 magnesium-deficient children with ADHD received nothing [28]. The trial was not blind and there was a further complication in that children in both groups were taking neuroleptic medications. After 6 months, those receiving the magnesium supplementation showed significant improvements on all scales assessing hyperactivity, whereas the control children worsened over the same duration. While supplementation with magnesium shows some initial promise, RCTs are needed to better identify its impact on ADHD symptoms.

Zinc

Zinc is essential for normal growth, immune function and neurological development. It is also an essential cofactor for metabolism relevant to neurotransmitters (e.g., zinc is necessary for converting vitamin B_6 to its active form, pyridoxal phosphate, which in turn is necessary for the conversion of tryptophan to serotonin), fatty acids, prostaglandins and melatonin, as well as indirectly affecting dopamine metabolism [29].

A number of researchers have reported that zinc deficiencies can lead to cognitive impairment and slowed information processing [30,31]. Almost 20 years ago, Arnold and colleagues determined that children with ADHD had lower zinc levels in their urine compared with controls and that this level was related to stimulant response [32]. There could be several causes of zinc deficiency, including poor diet; poor absorption; infection,

allergy or other inflammation; and drug-induced effects (see [33] for a review). More recently, Arnold *et al.* determined that parent and teacher ratings of ADHD behaviors were negatively correlated with zinc serum [34].

Bilici *et al.* conducted a RCT using zinc supplementation alone as a treatment for ADHD [35]. The 12-week trial consisted of a double-blind 1:1 randomization to either zinc sulfate (n = 202) or sucrose placebo (n = 198). The drop-out rate was high (107 in the supplement group and 100 in the placebo group). A significant improvement on ADHD rating scales was noted on measures of hyperactivity, impulsivity and socialization (but not attention) in the supplemented group compared with the placebo group. A number of limitations were noted, including the generalizability (i.e., children with any co-occurring condition were excluded), the fact that some were on medications and others were not, and the very high drop-out rate. Akhondzadeh *et al.* conducted a 6-week, double-blind RCT [36] comparing zinc with placebo in 44 children taking methylphenidate. Based on the DuPaul ADHD Rating Scale, they determined that those receiving zinc plus methylphenidate improved significantly more than those receiving methylphenidate and placebo, suggesting that the supplement might be boosting the effect of the medication.

With only two studies investigating zinc supplementation for ADHD, definitive conclusions are not possible, although these initial results suggest more research is warranted. Low zinc could be an effect, a cause or could simply co-occur with ADHD. For those considering zinc supplementation, it is important to note that high doses can be harmful. For example, at 50–150 mg/day, zinc can cause gastrointestinal problems and headaches, and doses of 300 mg/day can suppress immune function [33].

Amino acids

Phenylalanine

Amino acid precursors have been the subject of clinical interest given that they form the building blocks of neurotransmitters. For instance, phenylalanine is the initial precursor of dopamine and phenethylamine. Over 20 years ago, adults with ADHD were randomized in a 2-week, double-blind, crossover study of DL-phenylalanine versus placebo [37]. In the 13 participants who completed the study, mood improved significantly; however, during a subsequent 3-month open-label extension, all improvements were lost. The authors reported that another OLT with L-phenylalanine produced no effect.

L-tyrosine & tryptophan

Tyrosine and tryptophan are amino acid precursors for catecholamine synthesis. We found two studies on L-tyrosine, both reported more than 20 years ago. Nemzer *et al.* conducted a double-blind study comparing L-tyrosine, tryptophan, dextroamphetamine and placebo in 14 ADHD children over a 1-week period for each condition [38]. Parent and teacher ratings and measures of attention were obtained at baseline and at the end of each condition. Tyrosine did not differ from placebo on any of the variables measured. However, tryptophan, while not significantly different from placebo on teacher ratings, was significantly better on parent ratings, suggesting it could be of benefit for those children with more home-based difficulties. Those taking amphetamine improved on all measures compared with placebo. Reimherr *et al.* conducted an 8-week OLT of L-tyrosine in 12 adults with ADHD residual type [39]. Although eight of those adults showed an initial positive response (within 2 weeks) with marked-to-moderate changes, after 6 weeks, they developed tolerance and the authors concluded that L-tyrosine was not effective in the treatment of ADHD.

S-adenosyl-methionine

S-adenosyl-methionine (SAM-e) is a methyl donor and, therefore, plays an important role in many metabolic pathways through the process of methylation; for example, it participates in the synthesis and catabolism of biogenic amines [40]. Shekim *et al.* conducted a 4-week OLT in eight adults with ADHD using oral SAM-e titrated up to a maximum of 2400 mg/day. Reduced problems with concentration, restlessness, self-control and impulsivity were reported by 75% of the participants. Although these researchers indicated that they were planning to conduct a RCT, we were unable to locate such a study.

Carnitine

Acetyl-L-carnitine (ALC) is a small water soluble molecule that plays an important role in the metabolism of fatty acids and is biosynthesized from the amino acids lysine and methionine. It binds fatty acids (such as arachidonic acid [AA] and docosahexanoic acid [DHA]) to assist with mitochondrial oxidation, thereby generating metabolic energy, and it can also remove potentially toxic metabolic intermediates, such as carboxylic acids. It is suspected of influencing cholinergic and dopaminergic neurochemical pathways, which are both implicated in ADHD. Humans synthesize approximately a quarter of their carnitine and then obtain the rest from their diet [41].

Several RCTs of carnitine have been reported in childhood ADHD. Van Oudheusden and Scholte used a randomized, double-blind, placebo-controlled double-crossover trial with 26 ADHD boys (22 of whom completed the trial) [42]. The active ingredient was a maximum of carnitine 4 g. The trial consisted of three 8-week phases, balanced for order: either carnitine–placebo–carnitine or placebo–carnitine–placebo. Carnitine was well tolerated and associated with significantly better scores on both the Conners' Parent and Teacher Rating Scales. Despite the significant difference, only 54% of those taking carnitine were considered 'responders' based on the Parent Scale and only 50% based on the Teacher Scale (in contrast to 13 and 17% of those on placebo, respectively). Overall, carnitine showed promise in this study for improving attention and reducing aggression in boys with ADHD.

By contrast, Arnold and colleagues conducted a 16-week double-blind, multisite, placebo-controlled trial with 112 children with ADHD using a soluble strawberry flavored powder of ALC in doses ranging from 500 to 1500 mg twice-daily (an amount up to 25% less than the Van Oudheusden and Scholte study) or a matching placebo [41]. Although no safety problems were identified, the main analyses revealed no group differences and, indeed, the mean changes on ADHD rating scales by both parents and

teachers were small for both groups. In addition to administering lower doses of ALC, this study differed from the previous in that the ALC contained an additive (strawberry flavoring) that may exacerbate ADHD symptoms in some children. However, two interesting secondary findings were noted: superiority of ALC over placebo in those children with the inattentive subtype of ADHD, and an unexplainable geographical effect in that the response to the active ingredient varied depending on site location.

Finally, Torrioli *et al.*, using a sample of 63 (51 completed) boys with both ADHD and fragile X syndrome, conducted a double-blind, parallel, multicenter comparison of ALC with placebo [43]. The children were not taking stimulants during the trial. Although the authors concluded that ALC improved hyperactivity over the 1-year period, their reports of statistical analyses directly comparing the placebo and the active ingredient were inconsistently reported. The means on the hyperactivity symptom were lower after 12 months, but only for parent ratings and it is unclear whether the change is clinically meaningful. Although more clinically significant changes were noted on measures of adaptive behavior, the conclusions need to be cautiously interpreted. Furthermore, the only data they provided on ADHD symptoms were a global measure of both hyperactivity and inattention and, therefore, it is impossible to assess which specific ADHD symptoms improved. In summary, the findings for carnitine are mixed, with two positive trials (but one with some methodological problems) and one negative trial using an ALC supplement containing an additive that may have contributed to the negative outcome.

Essential fatty acids

More research exists on essential fatty acids (EFAs) and ADHD than any other nutrient. EFAs consist of two groups: omega-3 and omega-6. Omega-3s, such as DHA, play a vital role in brain development and function. For instance, dopamine-producing nerve endings are composed of up to 80% DHA [44]. These fatty acids are also necessary for the formation of prostaglandins, leukotrienes and thromboxanes, hormones involved in the regulation of bodily functions. Some research has reported that at least 40% of children with ADHD symptoms exhibit thirst and dry skin, and lower AA and DHA in their plasma phospholipids [45].

An interest in the role that fatty acids play in the symptoms of ADHD has spanned at least three decades. Colquhoun and Bunday suggested that hyperactive children were deficient in EFAs, based on the observations of food allergies (that can impair the body's ability to use EFAs effectively), abnormal thirst and zinc deficiencies [46]. They hypothesized that hyperactive children may have greater difficulty absorbing EFAs from the intestine or may have inherited a metabolic defect that results in a need for more EFAs than normal. Their preliminary study of EFA supplementation using primrose oil (which contains an omega-6 called gamma-linolenic acid [GLA]) resulted in anecdotal reports of improvements in half of the 25 children studied. Arnold and colleagues, 10-years later, studied 16 boys with ADHD in a crossover comparison of GLA, D-amphetamine and placebo, and reported that higher behavioral problems were correlated with lower levels of GLA [47]. However, they did not compare conditions. More recent research supports an association between the genes responsible for the breakdown of fatty acids (desaturase genes) with ADHD [48]. A dysfunction in the desaturase genes would presumably result in lower levels of long-chain polyunsaturated fatty acids in the blood, which has been found in those with ADHD [49].

In contrast to many other types of supplements, an impressive number of well-designed trials exist on EFA supplementation in many mental disorders including ADHD, as well as a number of reviews specifically dedicated to this topic [50,51].

The two RCTs that have been conducted with DHA alone have not shown benefit for improving symptoms of ADHD. Voigt *et al.* conducted a 12-week, double-blind RCT comparing DHA to placebo with 63 children diagnosed with ADHD [52]. A total of 54 children completed the study. All participants were concurrently being treated successfully with stimulant medications. Although plasma DHA increased in those treated with DHA, there was no statistical improvement in any of the objective assessments or symptom reports of ADHD symptoms. It is possible that the supplementation with stimulants created ceiling effects (individuals who had not responded to stimulants were excluded from the study) such that EFA-specific effects were difficult to detect.

Hirayama *et al.* also investigated DHA supplementation using a 2-month, placebo-controlled, double-blind study with 40 ADHD children (of whom eight were suspected ADHD patients, but diagnosis was not confirmed) [53]. Treatment consisted of either foods (e.g., soybean milk, steamed bread and bread rolls) containing DHA-rich fish oils for 2 months, or indistinguishable foods without fish oil (olive oil was used instead) for the control group (n = 20). Six of the participants were taking stimulant medications during the trial. DHA supplementation did not improve ADHD symptoms, nor did it affect other cognitive measures, such as visual short-term memory, errors of commission and visual perception. Indeed, improvements were noted in visual memory and commission errors in the control group only. The olive oil placebo is problematic, however, in that it may contain active ingredients.

Sinn and Bryan investigated 132 children who were assigned to one of three arms in a randomized, placebo-controlled, double-blind intervention for 15 weeks: placebo, EFAs alone or EFAs plus micronutrients [54]. After 15 weeks, all children were given the combined EFA plus micronutrient supplement single blind (only the researcher was aware). A total of 104 children completed the trial. Significant treatment effects were observed with medium-to-large effects on all parental measures of ADHD. There was no additional benefit to the micronutrient supplementation, although the researchers speculated whether the doses were high enough for the treatment of clinical conditions. No changes were noted on the Conners' Teacher Rating Scale. Interestingly, after 15 weeks, symptoms continued to improve and those who were originally in the placebo group showed a positive response on the active treatment. Overall, 30–40% of children over 15 weeks and 40–50% of children over 30 weeks improved as defined by standard deviation greater than 1 in scores on parental measures. A follow-up paper reported on the effect of the treatment on cognitive variables [55]. The only improvement observed was in the ability to switch and control attention, an improvement noted only in the treatment groups.

Richardson and Puri studied children with learning difficulties (mostly dyslexia) who also had ADHD symptoms, but lacked a diagnosis [56]. In total, 41 children were randomly assigned to either EFA supplementation or placebo for 12 weeks and 29 completed the trial. Only parent ratings were obtained and, at post-treatment, there was significant improvement on seven of the 14 scales for active treatment compared with none for placebo. Group differences were observed on three of the 14 scales (inattention, Conners' ADHD index and the psychosomatic scale) although statistical corrections were not made despite multiple comparisons; furthermore, the clinical changes were small. It is important to note that a group difference was noted on the ADHD index not because there was a significant change in the treatment group but because the placebo group got worse over time, making it difficult to attribute the group difference to the intervention. Also, none of the children had been diagnosed with ADHD and again, an olive oil placebo was used. As a result, these findings need to be interpreted cautiously. In a different study, Richardson and Montgomery looked at ADHD symptoms in a group of children diagnosed with developmental coordination disorder [57]. This RCT using dietary supplementation with omega-3 and -6 fatty acids versus placebo did show improvements in the active group on measures of ADHD symptoms.

Stevens *et al.* conducted a 4-month, double-blind, parallel treatment comparing EFAs plus vitamin E (used as a preservative) with an olive oil placebo in children with ADHD who also reported excessive thirst or dry skin [45]. Children continued to take other medications for the duration of the trial. A total of 50 children were randomized: 18 completed the active treatment and 15 completed the placebo treatment. Both groups benefited, but there was no clear superiority of the active intervention compared with the placebo. Although EFAs were nominally better on many outcome measures, the treatment difference was significant on only two of the 16 outcome measures: conduct problems as rated by parents and attention problems as rated by teachers. However, there were significant correlations between behavioral improvement and the magnitude of increase in vitamin E, EPA and DHA concentrations in the blood. The researchers wondered whether their 'placebo' (olive oil) was an active ingredient: olive oil does provide some EFAs, as evidenced by the fact that the children receiving the placebo showed improved plasma phospholipid EFA composition. It is also possible that vitamin E played an active role in change.

Overall, the findings on EFAs in connection with ADHD symptom reduction are promising but mixed. Problems with design remain, including: lack of investigations into the effect of supplementation on omega-6:omega-3 ratios; high attrition rates; variation in the type of EFA intervention used; presence of stimulant medications; lack of positive outcome data from more than one source; inconsistent consideration of dietary patterns; diagnostic discrepancies; effect of co-occurring disorders and lack of strict classification; and the challenge of finding an appropriate placebo (e.g., olive oil contains oleic acid, which is a precursor to oleamide, which can have psychoactive effects) [58,59]. Owing to the varied interventions, no conclusion can be drawn about which omega-3, if any, is most effective [50]. More trials are needed to determine whether EFAs have the potential to be a useful adjunctive treatment or possible treatment on their own.

Botanicals

The use of plants as remedies for mental health concerns is not new. For centuries, native people around the globe have utilized plants and plant extracts to improve mood, facilitate concentration and alleviate stress [60,61]. Today, the wisdom of traditional healing practices is beginning to be understood in light of scientific knowledge of how certain botanicals may aid in the treatment of health conditions.

Pinus pinaster *bark extract (Pycnogenol®)*

A standardized extract of French maritime pine bark (*Pinus pinaster*), known by its trade name, Pycnogenol® (Pyc), is a concentrate of polyphenols, mainly procyanidins and phenolic acids, recognized antioxidants or free radical scavengers [61]. In terms of its effect in the treatment of ADHD, Pyc is believed to act as a vasodilator that may improve cerebral blood flow to certain parts of the brain thought to be impaired in ADHD [62,63]. Pyc is also believed to regulate the metabolism of catecholamines, which may, in the case of their excess, contribute to oxidative stress through auto-oxidation. Through the modulation of catecholamine levels, Pyc may serve as an antioxidant and also improve ADHD symptoms [64].

Two RCTs examined the role of Pyc in alleviating ADHD symptoms: one with children, one with adults. In the first, 61 children with ICD-10 diagnoses of either hyperkinetic disorder, hyperkinetic conduct disorder or attention deficit without hyperactivity, were randomized to either Pyc or placebo for 1 month, followed by assessment after a 1-month treatment washout [65]. Only participants free from other psychiatric disorders and medical problems were included, although 13 of the children had learning disabilities. Four participants dropped out. No serious side effects were reported. In two cases where minor gastric discomfort occurred, participants still completed the trial. A significant reduction in symptoms was noted in the treatment group on the teacher-rated child attention problems for hyperactivity and inattention, with symptoms returning to pretreatment levels after the washout. Symptoms also decreased slightly in the treatment group compared with baseline and placebo, as rated by parents and teachers on the Conners' measures, but did not reach significance. These symptom reductions were not observed in the placebo group. Finally, significant improvements on visual–motor coordination and concentration tasks were observed in the Pyc group compared with pretreatment, as well as with placebo. Treatment was not significantly effective for girls, but, as only six females were in the Pyc group, it is not known whether these were truly gender-specific effects [65].

As part of this same study, the researchers looked at the urinary catecholamine concentration compared with 17 healthy, age-matched controls with no psychiatric diagnoses [64,66]. Children with ADHD had significantly higher concentrations of epinephrine and norepinephrine in their urine at baseline compared with healthy controls. Furthermore, in the children with ADHD,

Table 2. Intervention studies with botanicals.

Study	Intervention (daily dose)	Sample (age, years)	Design	Length of trial (weeks)	Results	Effect	Ref.
Trebatická *et al.* (2006)	Pyc (1 mg/kg)	n = 61; children with ADHD, including 18 with specific learning disabilities; 82% boys (6–14)	RCT: 4 weeks treatment or placebo plus 4 weeks washout	8	Pyc > placebo: decrease in hyperactivity noted by teachers and parents of boys; increased attention, visual–motoric coordination & concentration; relapse occurred with washout	Effect	[65]
Tenenbaum *et al.* (2002)	Pyc (1 mg/lb) or methylphenidate (10–45 mg)	n = 24; adults with combined type ADHD; 46% men (24–53)	RCT with crossover: 3-week trial of each treatment with 1-week washout	12	methylphenidate = Pyc = placebo	No effect	[70]
Lyon *et al.* (2001)	*Panax quinquefolium*: 'American ginseng' (200 mg) and *Ginkgo biloba*, (50 mg twice daily)	n = 36; children with ADHD; 25 were also taking stimulant medication (3–17)	OLT	4	Some improvement in seven symptom categories assessed on Conners' Parent Rating Scale but unclear owing to concurrent use of stimulant medications; some children worsened during the trial	Unclear	[74]
Weber *et al.* (2008)	*Hypericum perforatum*: 'St John's wort' (300 mg three-times daily)	n = 54; children with ADHD; 63% boys (6–17)	RCT	8	Neither treatment nor placebo significantly improved ADHD symptoms. No significant difference between two groups on percentage improving on CGI	No effect	[75]

ADHD: Attention-deficit/hyperactivity disorder; CGI: Clinical Global Impression Scale; RCT: Randomized controlled trial; OLT: Open-label trial; Pyc: Pycnogenol®.

norepinephrine urinary concentrations positively correlated with degree of reported hyperactivity. These findings are consistent with previous studies reporting abnormal metabolism of catecholamines in children with ADHD [67,68]. Following Pyc treatment, a significant reduction of dopamine and a trend toward reduction in epinephrine and norepinephrine were noted. In addition, a significant increase in the ratio of reduced versus oxidized glutathione was found, suggesting that Pyc may reduce oxidative stress by normalizing catecholamine concentrations in children with ADHD, which may, in turn, reduce hyperactivity [64,69].

Tenenbaum *et al.* conducted a RCT of Pyc with 24 adults with ADHD combined type, randomized to 3 weeks each: Pyc, methylphenidate or placebo, with a 1-week washout between each period [70]. The results, taken from a range of measures, both self-reported and from observers, indicated that neither methylphenidate nor Pyc was superior to placebo, but all three treatments (placebo included) produced group gains over baseline. Explanations for this finding include too brief a treatment, too low a dose and too small a sample, as well as the possibility of no effect of treatment. Of note, however, is the report that several participants chose to continue on Pyc after the trial and some showed clinically significant symptom improvement on Pyc, as well as on methylphenidate [70].

Panax quinquefolium *(American ginseng)* & Ginkgo biloba

Both of these extracts have been shown to increase cerebral dopaminergic activity in animals studies [71,72], an area of suspected deficit in people with ADHD [73]. In a 4-week open study, 36 children with ADHD were given a product containing ginseng extract and *Ginkgo biloba* extract twice daily [74]. Children on medication such as stimulants were included (n = 25) if symptoms of ADHD were poorly controlled in spite of the medication. Five participants reported adverse events during the course of the study but completed anyway. In two cases, the adversity experienced was attributed to the treatment itself: greater emotionality and impulsivity in one and an increase in hyperactive behavior in another, although both of these participants reported symptom improvement in other areas. Improvement was defined as a change in individual symptom or global scores of at least 5 points in the direction of normal range, based on age and gender. To a varying degree (31–47%), improvement was reported in all seven ADHD indices measured at weeks 2 and 4 on the Revised Conner's Parent Rating Scale (long form) [74]. There are a few limitations to these findings, including: a number of the children who improved were also taking stimulant medication, so any potential benefit of the botanical supplement must be considered with this in mind; and 3–15% of the children had a negative outcome, as measured by an increase in T-score on aspects of the Revised Conner's Parent Rating Scale (long form) by 5 points. Finally, the findings are limited by the uncontrolled nature of an open trial of such short duration. Nevertheless, the findings seem to warrant further research, although none has been reported in the ensuing 8 years.

Hypericum perforatum *(St John's wort)*

One RCT using *Hypericum perforatum* or St John's wort for ADHD was found [75]. St John's wort has been noted to increase the levels of serotonin, dopamine and norepinephrine in the brain [76,77]. Deficiencies in these neurotransmitters, particularly dopamine and norepinephrine, have been implicated in ADHD symptoms, such as inattention and impulsivity [78]. Based on this knowledge, a norepinephrine-reuptake inhibitor, atomoxetine, has been developed and approved for ADHD treatment in the USA [78].

In an 8-week RCT, 54 children with ADHD were randomized to St John's wort extract 300 mg standardized to hypericin 0.3% or a placebo three-times daily. Participants were included if scores were greater than 1.5 standard deviations above age and gender norms on the ADHD Rating Scale-IV and were free of other ADHD medications during the trial. Concurrent use of multivitamins and EFAs was allowed as long as the treatment had been consistent for the previous 3 months and was expected to remain at the same levels. One participant in the placebo group dropped out owing to an adverse event. No significant difference was found in either of the two measures used: the ADHD Rating Scale-IV or the Clinical Global Impression Improvement Scale, indicating that St John's wort did not improve ADHD symptoms.

Multi-ingredient formulas

Research with multi-ingredient formulas in the treatment of ADHD is relatively rare, although such combination therapies have been found to be effective in the treatment of cognitive deficits and antisocial and disruptive behaviors [79–81]. A number of studies were reported in the individual supplementation section of this review, which added ingredients to the treatment approach initially studied. It is important to consider these in our overall interpretation of the studies and, more generally, in our appreciation of the multinutritional approach to the treatment of ADHD. For example, one of the first reports on EFA supplementation used a combination of ingredients for at least one of their participants (EFA with zinc, vitamin C, pyridoxine and niacin) [46]. Sinn and Bryan had a third arm in their study on EFAs which consisted of a multivitamin/mineral tablet plus fatty acids but found no additive benefit over the EFA-only arm; however, they acknowledged that the dose may have been too low to reach any conclusions about specific ingredients in the tablet [54]. Stevens *et al.* [45] and Richardson and Puri [56] added vitamin E, although Stevens *et al.* mentioned that it was used as a preservative; *G. biloba* and ginseng were used in combination in Lyon *et al.*'s OLT [74].

A recent trial followed 40 children with clinical symptoms of ADHD over an 8-week period, during which time they received magnesium plus vitamin B_6 [82]. They were compared with 36 control children not receiving supplementation. Intraerythrocyte magnesium (Erc-Mg) and blood ionized calcium were measured, as well as behavior. During the supplementation, symptoms of hyperactivity and aggressiveness were reduced significantly and school attention improved. The therapy was then stopped and clinical symptoms returned together with a decrease in Erc-Mg values. Although this ABA (on–off–on) study highlights the therapeutic effect of Mg-B_6 supplementation, it was done in association with low intraerythrocyte magnesium values and, therefore, it may not generalize to a larger ADHD population. Furthermore, the children were young (mean age of the sample was 6 years) and the impact of other co-occurring behaviors was not considered.

Another recent 3-month OLT that combined flax oil and an antioxidant (vitamin C), studied 30 unmedicated children with ADHD and 30 normal controls [83]. The controls did not receive any treatment, but served as a comparison group for blood work. Fasting venous blood showed that presupplementation, children with ADHD had significantly lower red blood cell membrane lipid levels compared with the controls. At post-supplementation, there was a significant increase in EPA and DHA (both of which are omega-3s) and a decrease in AA (omega-6) in the children with ADHD. Scores on a parent-rated measure of ADHD behaviors showed a significant drop in inattention, impulsivity, hyperactivity, restlessness and self-control.

Kaplan and colleagues conducted an OLT with children with a variety of psychiatric disorders, including ADHD, bipolar disorder, anxiety, oppositional behaviors and Asperger's disorder [84]. Six of the 11 children in the trial had ADHD, although one of these dropped out. After 16 weeks of taking a supplement, distributed under the name of EMPowerplus, which consists of 36 ingredients: 14 vitamins, 16 minerals, three amino acids and three antioxidants [102], the children were rated as significantly improved in attention, anxiety, aggression, delinquency and mood. Few adverse effects were reported, and those that did occur were mild for all except two patients who were concurrently taking psychiatric medications. Indeed, Popper has warned against taking such supplements concurrently with medications owing to the hypothesized potentiating effect these combination formulas can have on the medication [85]. The trial is limited by observer and placebo/expectancy effects. More trials are currently underway with individuals with ADHD to better evaluate the effect this multi-ingredient supplementation approach has on the symptoms of ADHD. For example, unpublished pilot data on an OLT using this same multinutritional supplement with 14 adults with ADHD and mood instability showed significant improvement in all ADHD symptoms (although problems with inattention were less well controlled than hyperactivity and impulsivity), as well as stabilization of mood for all patients in the trial [86].

Harding and colleagues compared methylphenidate with dietary supplements in the treatment of ADHD symptoms in 20 children over a 4-week period [87]. Co-occurring diagnoses and use of other medications served as exclusion criteria. The dietary supplement consisted of many nutrients (i.e., taurine, glutathione, α-lipoic acid, garlic extract, glycine, five amino acids and 13 minerals), presumed gastrointestinal and immune support (*Lactobacillus acidophilus* and *Lactobacillus bifidus*, lactoferrin and silymarin), EFAs and phospholipids, iodine and tyrosine, all the B vitamins, and some phytonutrients. Their rationale for such a broad-based approach was that they were attempting to address all the nutritional deficits associated with ADHD. With ten children per group (based on parental

Table 3. Intervention studies with combination formulas.

Study	Intervention (daily dose)	Sample (age)	Design	Length of trial (weeks)	Results	Effect	Ref.
Mousain-Bosc *et al.* (2006)	Mg–vitamin B_6 (6 mg/kg Mg; 0.6 mg/kg vitamin-B_6)	n = 76 children; 40 with ADHD, 68% boys (mean age: 6.49 years); 36 controls, 61% boys (mean age: 4.37 years)	OLT with controls as comparisons	24	Erc-Mg lower in ADHD children at baseline compared with controls; improved hyperactivity, aggressiveness and attention; increase in Erc-Mg values; regression in symptoms when supplement discontinued	Effect	[82]
Joshi *et al.* (2006)	ALA (from flax oil; 200 mg) and vitamin C (25 mg twice-daily)	n = 60 children; 30 with ADHD, 75% boys (mean age: 7.5 years for boys, 8.5 for girls); 30 controls	OLT with controls	12	Post-supplementation levels of RBC membrane fatty acids higher than both pretreatment and levels in control group; significant decrease in ADHD symptoms, specifically inattention, impulsivity, hyperactivity restlessness and self-control as rated by parent	Effect	[83]
Kaplan *et al.* (2004)	36 ingredient formula containing minerals, vitamins, amino acids and antioxidants	n = 11 children with mood and behavioral problems, including 5 with ADHD; 63.6% boys (8–15 years)	OLT	16	Significant improvement on 7 of 8 CBCL scales, including attention; significant improvement in measures of mood	Effect	[84]
Harding *et al.* (2003)	Combined vitamin, mineral, amino acid, probiotic, EFA and phospholipid treatment	n = 20 children with ADHD, 10 per group (7–12 years)	Parent choice of either methylphenidate or nutritional supplement	4	Both groups benefited significantly from treatment as measured by neurocognitive tasks; no group differences	Effect	[87]
Patel and Curtis (2007)	Comprehensive nutritional/environmental/chelation treatment	n = 10 children with ADHD and autism, 90% boys (4–10 years)	OLT	12–24	Significant improvement in urinary lead concentrations; all children reported improved attention & concentration; 7 out of 10 reported improved ADHD symptoms	Effect	[88]

ADHD: Attention-deficitr/hyperactivity disorder; ALA: α-linolenic acid; CBCL: Child Behavior Checklist; EFA: Essential fatty acids; Erc-Mg: Intraerythrocyte magnesium; OLT: Open-label trial; RBC: Red blood cell.

choice), both groups showed significant improvement on neurocognitive tests that measure auditory response control, auditory attention, visual attention and visual response control. The nutrient group did as well as the methylphenidate group. However, there were no measures of behavioral change in ADHD symptoms and the sample size may have been too small to detect group differences.

Patel *et al.* reported an open-label pre-pilot observational study with an even more comprehensive approach [88]. Ten children with both autism and ADHD were treated for 3–6 months with vitamins (A, B-complex), seven minerals, coenzyme Q10, amino acids and peptides, some EFAs, milk thistle, α-lipoic acid, digestive enzymes, and probiotic bacteria. In addition, the parents of these children received instructions on controlling environmental factors (i.e., mites, exposure to pesticides, toxins and cleaners), an organic diet, gastrointestinal support, antigen injection therapy (to address dust mite allergens, molds, foods and chemicals), chelation therapy and injection one- to three-times per week with glutathione and methylcobalamin (vitamin B_{12}). They also continued their usual therapies (e.g., speech and occupational therapy). Although significant changes were observed in urinary lead levels, no other heavy metals were significantly different from baseline (although near significant drops [$p < 0.1$] were noted in cadmium and mercury). The researchers reported that on parental questionnaires, there was an 'average' improvement in concentration and attentional problems (range: 40–100% improvement) and an average decrease of hyperactivity-related problems (range: 0–95% improvement); however, they did not report the actual tests used to measure behavior change, how they defined improvement or any statistical tests. Based on the extensive and varied therapies the children received (ranging from psychosocial to supplementation), it is impossible to evaluate the specific effect of the nutritional supplements on behavior change. Furthermore, the ecological validity of the program would make it very difficult to replicate. The findings from this study and the previous one raise the possibility

that only a multimodal treatment can effectively address all the symptoms associated with this heterogeneous disorder, but the research has many limitations.

Expert commentary

Individual nutrients

Despite the relative surge in studies over the last decade, the overall evidence for alternative medicines in the treatment of ADHD continues to be sparse and simply does not compare with the hundreds of well-conducted studies that have been published on conventional treatments. Based on this review, the individual nutrient with the most evidence of treatment efficacy is zinc; however, this conclusion is based on only two RCTs with different doses. A number of the other treatments reviewed show some promise, but conclusions remain tentative, given variations in outcome across the RCTs. For example, of the three RCTs conducted on carnitine, only one showed a clear positive effect, one was unclear owing to interpretation difficulties and the third showed no effect. Some emerging evidence has been found for iron (or ferrous sulphate): one RCT showed change on clinician measures but not parent or teacher measures. One RCT and one OLT have been conducted with magnesium; however, one of those trials used magnesium and vitamin B_6 and, therefore, more studies are needed to better understand its efficacy, either alone or in combination. Pycnogenol has some support; however, one positive and one negative trial with varied groups (children in one, adults in the other) and varied levels of power make it difficult to assess its efficacy. The fatty acid trials are also mixed: out of five RCTs (using different ingredients, concentrations and ratios of omega-3:omega-6), one was positive, two were negative and two were unclear, with improvement on some ADHD behaviors but not others. While the combination of ginseng and *G. biloba* showed positive effects in a 4-week OLT, several limitations existed, which call into question the efficacy of the treatment and the need for more research. Although one SAM-e trial was positive, it was conducted open label more than 18-years ago with no apparent follow-up. St John's wort, phenylalanine and tyrosine are not supported in their use for ADHD treatment by the trials reviewed. It is possible, however, that the design, methods, duration of the trials and the dose given contributed to these negative results.

Supplements, other than the ones reviewed here, have been mentioned in books and on the internet as advantageous in the treatment of ADHD, but we could not find any studies to support or refute their use as individual treatments. These included L-glutamine, chromium polynicotinate, vitamin E, inositol, selenium, taurine, grape seed, lemon balm, grapine and Huperzine A. The only references supporting their use were anecdotal from practicing clinicians.

One should be skeptical of a treatment if manufacturers claim the product works for everyone with ADHD or other health problems, uses only case histories or testimonials as proof or cites only studies with no control (comparison) groups. While testing a treatment without a control group is a necessary first step in investigating a new treatment, subsequent studies with appropriate control groups are needed to clearly establish effectiveness and to ensure that any effect found using an open-label method is not simply a result of the powerful placebo effect. Many of the studies meet this first criterion, but far fewer, the second.

Multinutrient interventions

In contrast to the mixed evidence on single nutrients, the very recent data on multinutrient supplementation appears to be more consistently positive, but more research is needed, particularly RCTs. As ADHD is a complex disorder with heterogeneous symptoms, it is not surprising that a multi-ingredient supplementation might be required for benefit. However, the data are sparse as this area of study is in its infancy.

Most scientific methodology alters a single variable at a time, so it is worth briefly considering the justification for multinutrient supplementation. Every neurotransmitter goes through many metabolic steps to ensure its synthesis, uptake and breakdown. Every one of those steps requires enzymes, and every enzyme is dependent upon multiple coenzymes (cofactors). A variety of vitamins and minerals are required as cofactors in most, if not all, of those steps. Consequently, as discussed elsewhere [89], one possible mechanism underlying psychiatric symptoms is inborn metabolic dysfunction associated with slowed metabolic activity due to suboptimal availability of vitamin and mineral cofactors [90]. Impaired brain metabolic activity associated with other disorders has already been shown to be correctable through nutrient supplementation [90]. One can thus envision multinutrient supplementation as providing sufficient cofactor that even enzymes with drastically reduced activity become so supersaturated that near-normal function is restored [90]. Other mechanisms have been hypothesized as explanations for the effect of nutrients on brain function, such as improved energy metabolism [41].

Key issues

- While single-nutrient approaches show variable effects, multinutrient approaches appear more consistently positive, although more studies are required.
- Emerging evidence supports the use of some minerals, botanicals, carnitine and essential fatty acids, although not all attention-deficit/hyperactivity disorder behaviors improve, results are varied, and methodological differences make it difficult to draw definitive conclusions.
- Evidence from this review does not support the use of St John's wort, tyrosine or phenylalanine in the treatment of attention-deficit/hyperactivity disorder symptoms.
- Most studies on nutritional approaches use children and predominantly male samples; therefore, generalizations of results to adults and females need to be made cautiously.
- Nutrient supplementation, specifically zinc, may boost the effect of conventional medicines.

Five-year view

Mainstream medicine has accepted the notion that pharmaceuticals are the preferred approach to the treatment of ADHD. This review reveals there is potential benefit from nutritional approaches, but much more research is required. One interesting theme that emerged was the narrow focus taken by many researchers in studying individual nutrients (with limited success) rather than a broad-spectrum approach investigating multi-ingredient formulas. Given that physiological function is best optimized by having all systems in balance, with different vitamin and mineral levels affecting the absorption and effectiveness of each other, one needs to question why ingredients are studied individually. Perhaps the single ingredient approach is too narrow.

Research on a multinutrient approach to treating ADHD is in its infancy. The multi-ingredient trials reviewed here all showed promise but suffered from small sample sizes, varied sampling procedures and inclusion criteria, and multiple assessment methods. Across all the studies, the effect of gender was not investigated and, indeed, given the high percentage of males across the studies, we cannot generalize these results to females. Equally, the majority of the studies reviewed used a child population, so the results must be applied to adults with caution. We know that methylphenidate is less effective with adults than children; the same could be true with nutrient supplementation.

Given the heterogeneous nature of ADHD, it is unlikely that a single universal treatment will be effective. As scientists become better at identifying subtypes of this disorder [91], identification of treatments specific to ADHD subtypes may become more viable. The success of a treatment is influenced by several factors, including an individual's expectations and response, the side effects experienced, a person's preconceived ideas and the burden placed on the patient by the treatment. For these reasons, the availability of a variety of empirically-supported treatment options will be beneficial to patients and their families in the long term.

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