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Nutritional Supplements for the Treatment of Attention-Deficit Hyperactivity Disorder

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Synopsis

Polyunsaturated fatty acid supplementation has demonstrated evidence of efficacy in meta-analysis of randomized, placebo-controlled trials in ADHD. The benefits of polyunsaturated fatty acid appear small compared to the effect sizes observed for traditional pharmacological treatments of ADHD. Some evidence suggests that polyunsaturated fatty acid formulations with higher eicosapentaenoic acid may be more effective in improving ADHD symptoms. Melatonin appears to be effective in treating chronic insomnia in children with ADHD but appears to have minimal effects in reducing core ADHD symptoms. Iron and zinc supplementation may have benefit in reducing ADHD symptoms in children with or at high risk of deficiency. Data demonstrating efficacy of iron, zinc or magnesium in non-nutrient deficient ADHD populations is lacking. Many other natural supplements are widely utilized in the United States despite minimal evidence of efficacy and possible side-effects.

Keywords

Attention-Deficit Hyperactivity Disorder; omega-3 fatty acids; polyunsaturated fatty acids; zinc; magnesium; Gingko biloba

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common and impairing health condition affecting school-aged children.[1, 2] Pharmacotherapies are currently considered the cornerstone of evidence-based treatment for ADHD. Over 70% of children with ADHD respond to psychostimulant medications.[3] Other medications such as atomoxetine, alpha-2 agonists, bupropion and tricyclic antidepressants have also demonstrated efficacy in treating ADHD.[4–6] However, many families elect not to use traditional pharmacotherapies to treat ADHD. This decision is often related to concerns over possible short-term side effects or doubts regarding long-term efficacy or effects on development of these medications.[7–10]

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Instead, alternative and complementary treatments such as natural supplements are often used by families to treat ADHD.[11]

Despite a modest evidence-base compared to conventional treatments for ADHD, complementary and alternative treatments are commonly used by children with ADHD. Although few population-based, epidemiologic studies have been performed in the area, current evidence suggests that 12–64% of children with ADHD use some form of complementary medicine.[12] Examination of adolescent dietary supplement use in the National Health and Nutrition Examination Survey (NHANES), a series of nationally representative surveys of the civilian, non-institutionalized population in the United States administered by the National Center for Health Statistics, suggested that adolescents with ADHD were roughly 10% more likely to use dietary supplements than adolescents without ADHD.[13]

The goal of this review is to synthesize and evaluate the scientific evidence regarding the potential efficacy and side-effects of natural supplements and herbal remedies for ADHD. We additionally will provide clinicians with recommendations regarding their potential use and role in overall ADHD treatment.

Methods

PubMed and Cochrane Central Register of Controlled Trials was searched on March 24, 2014 using the search strategy “Attention Deficit Disorder with Hyperactivity”[Mesh] AND (“Dietary Supplements”[Mesh] OR “Zinc”[Mesh] OR “Magnesium”[Mesh] OR “Iron” [Mesh] OR “Hypericum”[Mesh] OR “Ginkgo biloba”[Mesh] OR “Vitamins”[Mesh].” The search was further limited to clinical trials, reviews and meta-analysis. Trials were included are cited in this review if they (1) examined treatments for ADHD, (2) were randomized and (3) placebo-controlled trials. References in reviews and systematic reviews in the area generated by the search strategy were also reviewed for additional eligible trials.[14–24] Trials were additionally required to involve a therapy of interest, which for the sake of this article includes vitamins, minerals, natural supplements and herbal remedies. Specifically excluded from this review are non-pill-based treatment modalities such as neurofeedback, behavioral therapies, restriction or food color exclusion diets and chiropractic interventions.

Interventions

Dietary Supplements

Polyunsaturated Fatty Acids—Polyunsaturated fatty acids (PUFAs) are a well-studied complementary treatment for ADHD. Omega-3 fatty acids cannot be synthesized by humans and are required in our diet. In the Western diet, omega-6 fatty acids or their precursors (e.g. linoleic acid) are much more abundant than omega-3 fatty acids or their precursors (e.g. alpha-linolenic acid).[25] A high omega-6 to omega-3 ratio can alter cell membrane properties and increase production of inflammatory mediators because arachidonic acid, an omega 6 fatty acid found in cell membranes, is the precursor of inflammatory eicosanoids, such as prostaglandins and thromboxanes.[26] By contrast, omega-3 fatty acids are anti-inflammatory.[26] Therefore, a high dietary omega-6 to omega-3 fatty ratio could promote

neuroinflammation. Increased omega-3 fatty acid concentration in the diet may also act by altering central nervous system cell membrane fluidity and phospholipid composition which may alter the structure and function of the proteins embedded in it.[27] By this mechanism, increased omega-3 fatty acid concentrations in cell membranes have been shown to affect serotonin and dopamine neurotransmission especially in the frontal cortex and may be of importance in ADHD pathogenesis.[28] Omega-3 fatty acids may also potentially act in reducing oxidative stress, which has been demonstrated to be elevated in ADHD.[29]

An initial meta-analysis involving ten trials including 699 children with ADHD demonstrated a significant benefit of PUFA supplementation compared to placebo. The benefits of PUFA supplementation were small (compared to the effect sizes observed for conventional pharmacological treatments for ADHD) but statistically significant.[17] Additionally, meta-regression demonstrated a significant relationship between eicosapentaenoic acid (EPA) dose within supplements and measured efficacy.[17] Two update systematic reviews using similar methodology have since confirmed the efficacy of PUFA supplementation for ADHD symptoms.[30, 31] One of these meta-analyses also confirmed the significant association between EPA dose and measured benefit in the treatment of ADHD. [31]

However, two recent systematic reviews have raised questions regarding the benefits of omega-3 supplementation of ADHD.[19, 32] The divergent results of these meta-analyses are attributable to methodological differences from the other systematic reviews. A recent Cochrane review in the area failed to demonstrate a significant benefit of omega-3 supplementation on most but not all outcome measures for ADHD.[19] As is traditional for Cochrane reviews, the authors did not pool results across different study designs (e.g. crossover vs. parallel-group trials) and this difference in methodology led to comparatively underpowered meta-analyses for many outcomes. Another recent systematic review, by contrast, added additional trials which examined the effects of omega-3 fatty acid supplementation on ADHD symptoms in other clinical populations (e.g. children with reading difficulties, developmental coordination disorders and dyslexia).[32] This meta-analysis found a significant benefit of PUFA supplementation but also noted evidence of publication bias in the literature that might be inflating effect estimates. Publication bias was detected through asymmetry in the funnel plot. However, the addition of trials involving subjects with primary diagnoses other than ADHD (included only in this meta-analysis) was likely responsible for asymmetry in the funnel plot (as none of the previous ADHD-only meta-analyses detected funnel plot asymmetry). One particular trial examining ADHD symptoms in children with reading disabilities included a larger number of participants (comprised 24% of the total weight of the meta-analysis) and demonstrated a minimal effect of PUFA supplementation in improving ADHD.[33] Inclusion of this large trial is responsible for the funnel plot asymmetry in the meta-analysis. However, it is quite plausible that children with primary reading disabilities would have less benefit from PUFA supplementation in improving ADHD symptoms (because they are secondary to reading difficulties or less severe than in a ADHD clinical population).

Cumulative evidence suggests that there is currently CEBM level-1 evidence demonstrating the efficacy of omega-3 fatty acids for the treatment of ADHD. Current evidence would

recommend supplementation with a dose of 1–2g daily with a substantial content of EPA within the omega-3 formulation. However, evidence supporting supplementation much less clear when examining ADHD symptoms in children with other primary disorders (such as dyslexia, developmental coordination disorder and with reading impairments). Table 1 summarizes the results of randomized, placebo-controlled trials of nutritional supplements in ADHD.

Melatonin—Melatonin is a hormone secreted primarily by the pineal gland in response to variations in the circadian cycle and has been used for the last two decades for the treatment of sleep disorders in adults and children. In contrast to most available sleep medications, melatonin has little dependence potential, is not associated with habituation and typically produces no hangover. Given its reported hypnotic effects, relatively benign side-effect profile and over-the-counter availability, melatonin has been widely utilized in the United States.[34] Melatonin has been demonstrated in meta-analysis of randomized placebo-controlled trials to decrease sleep latency, increase total sleep time and improve sleep quality in both children and adults with primary sleep disorders.[35] Given that sleep problems are common in children with ADHD and are hypothesized to possibly be related to the pathogenesis of the disorder there remains the possibility that melatonin may help improve both sleep problems and ADHD symptoms in children with both conditions. It has been hypothesized that a subset of children with ADHD experience chronic sleep-onset insomnia that leads to excessive daytime sleepiness associated with disinhibition, hyperarousal, and problems with executive function that mimics ADHD. Two, randomized placebo-controlled trials of melatonin have been conducted in children with ADHD and sleep problems. An initial cross-over study in 27 stimulant-treated children with ADHD and sleep-onset insomnia demonstrated a significant benefit of melatonin in improving sleep outcomes (decreased sleep onset latency) but not ADHD symptoms.[36] The second trial which examined the efficacy of melatonin in reducing sleep problems in 105 children with ADHD and chronic sleep onset insomnia demonstrated a significant benefit of melatonin on primary sleep measures (decreased time to sleep onset and increased total sleep time) but demonstrated no effect on ADHD symptoms.[37] Taken together, these trials and meta-analysis suggest that melatonin has CEBM Level 1 evidence for reducing sleep-onset latency in children with chronic sleep-onset insomnia (regardless of a comorbid diagnosis of ADHD) but there is no evidence to suggest melatonin improves ADHD symptoms. Melatonin should be prescribed in a single, night-time dose of 3–6mg (depending on child's weight) approximately 30 minutes before bedtime.

Carnitine—Carnitine is a small-molecule necessary for energy production, specifically involved in oxidation and transport of fatty acids. An initial randomized, double-blind, placebo controlled crossover trial of L-carnitine in 24 children with ADHD failed to demonstrate a significant difference compared to placebo.[38] Similarly, two other randomized, placebo-controlled trials of acetyl-L-carnitine in children with ADHD have also failed to demonstrate any evidence of efficacy in treating children with ADHD.[39, 40] Based on currently available trial data in children with ADHD, there is no evidence to suggest carnitine is a more effective treatment for ADHD than placebo.

Minerals

Iron—Iron is a cofactor for tyrosine hydroxylase, the rate-limiting enzyme of monoamine synthesis and thus is critical for dopamine and norepinephrine production. In a recent meta-analysis of case control studiespatients with ADHD have been demonstrated to have lower serum ferritin levels compared to healthy controls.[41] A small, pilot, randomized, placebo-controlled trial in 23 children with ADHD and abnormally low serum ferritin levels demonstrated a significant improvement in ADHD symptoms in children randomized to ferrous sulfate (80mg/day) compared to placebo.[42] Further trials are needed to establish whether iron supplementation has any clinical utility beyond ADHD patients with evidence of iron deficiency.

Zinc—Zinc is a cofactor for enzymes that are important for cell membrane stabilization, and in the metabolism of neurotransmitters, melatonin and prostaglandins. Zinc has indirect effects on dopamine metabolism and antioxidant functions.[15] Chinese children with zinc deficiency have demonstrated impaired neuropsychological function and growth that improved with zinc repletion.[43] Symptoms of zinc deficiency can include inattention, jitters and delayed cognitive development, which mimic the symptoms of ADHD. Zinc intake is primarily from the diet and its main sources include red meat, poultry, beans, fortified breakfast cereals and dairy products. Zinc deficiencies can be due to insufficient dietary intake or malabsorption (diarrhea, lack of intestinal absorption, liver or kidney disease, sickle-cell anemia or other chronic disease). Zinc deficiency is fairly common in some areas of the developing world but is uncommon is the United States. Case-control trials in several areas of the world (Isreal, Turkey and Poland) have demonstrated lower zinc levels in children diagnosed with ADHD compared to healthy controls.[44–46] These results have not been replicated in samples in the United States, although overall meta-analysis suggests a significant association between low zinc levels and a diagnosis of ADHD.[15, 16, 41]

Randomized, placebo-controlled trials of zinc supplementation either as an adjunct to psychostimulant treatment or as monotherapy have provided conflicting evidence of efficacy. These discrepant results are likely related to differences in underlying study quality and prevalence of zinc deficiency in the study populations.[15] A completers analysis of 193 (out of 400 randomized) Turkish children with ADHD demonstrated a significant benefit of 150mg of zinc sulfate per day compared to placebo after 12 weeks of treatment.[47] However, these positive results need to be treated with an abundance of caution given the high-drop rate and the non-intention to treat analysis. A small, randomized placebo-controlled trial of Zinc sulfate 55mg/day demonstrated that zinc augmentation of methylphenidate (1mg/day) was more effective than placebo augmentation in 44 Iran children with ADHD after 6 weeks.[48] A more recent randomized, placebo-controlled trial examined the addition of zinc sulfate 10mg/day (compared to placebo) as an adjunct to methylphenidate (0.3mg/kg/d) in 40 Chilean children with ADHD.[49] This trial demonstrated no significant differences between zinc supplementation and placebo on attentional measures but did demonstrate a trend towards greater improvement with zinc supplementation on Connor's attentional measures that did not reach statistical significance. Zinc plasma levels were normal in the sample at baseline and decreased throughout the trial in both the placebo and zinc supplementation groups. A randomized, placebo-controlled trial examining the efficacy of

zinc glycinate (15–30mg/day) monotherapy over 8 weeks in 52 American children with ADHD[50] failed to demonstrate any benefit of zinc supplementation over the 8 weeks of treatment on any ADHD rating scales. Additionally, measures of zinc were not appreciably affected by supplementation. However, when children were given d-amphetamine over the next 5 weeks of the trial lower doses of d-amphetamine (37% reduction compared to placebo) were needed to achieve the same clinical effects in the zinc supplementation group.

Taken together, these data suggest zinc supplementation may be a reasonable treatment option in areas where zinc deficiencies are common, in patients with demonstrated (or at a high risk) for zinc deficiency. However, evidence is insufficient to recommend zinc supplementation in American children where zinc deficiencies are rare and trial results have been negative. Also, the dosing and form of zinc supplementation has varied widely between trials so an optimal dosing strategy is not apparent.

Magnesium—No randomized, placebo-controlled trials have demonstrated the efficacy of magnesium supplementation compared to placebo. Currently there only exists CEBM Level IV evidence based on controlled cohort studies suggesting magnesium supplementation may be beneficial in treating ADHD. Furthermore, there is significant evidence that at high doses (>10mg/kg/d) magnesium can be toxic so magnesium supplementation if employed should only be given at moderate doses (<200mg/d).[16] The side-effects of magnesium supplementation at appropriate doses can include nausea, diarrhea and cramps. Magnesium overdoses are potentially fatal. A recent systematic review in this area expands on the evidence regarding magnesium supplementation more in depth.[14]

The rationale for use of magnesium supplementation comes from a few case-control trials that have demonstrated reduced serum levels of magnesium in patients with ADHD compared to healthy controls.[51–53] The association between lower magnesium levels and ADHD has not been consistently found and overall meta-analysis of case-control studies does not suggest an association with ADHD.[41, 54, 55] Magnesium is a cofactor for many enzymes and has been demonstrated to interact with many monoamine receptors relevant in ADHD pathophysiology (serotonin (5-HT1A and 5-HT2A and 5-HT2C), noradrenergic (alpha1 and alpha2) and dopamine (D1 and D2) receptors in mouse models.[56] A single, double-blind placebo-controlled trial demonstrated that psychostimulants increased serum magnesium levels in ADHD after 3 weeks of treatment.[57] Multiple, uncontrolled trials have demonstrated a reduction in magnesium levels in children with ADHD compared to controls and that the deficiency in magnesium and ADHD symptoms improved after a few months of magnesium supplementation (typically 6mg/kg/d of Mg along with 0.6mg/kg/d of vitamin B6). However, randomized, blinded trials in the area are lacking.

Herbal Supplements

Gingko Biloba—*Gingko biloba* is a natural supplement proposed topromote brain blood flow and inhibit platelet activation.[16] *Gingko biloba* has been touted as a treatment for dementia and memory impairment although systematic reviews assessing the efficacy of *Gingko biloba* for improving cognitive function have not been supportive of these claims.[58] A single, 6-week, randomized, methylphenidate-controlled trial in children with ADHD

demonstrated the superiority of methylphenidate to *Gingko biloba* in terms of improving ADHD symptoms.[59] Although, significantly worse than methylphenidate, the improvement over time with *Gingko biloba* was non trivial (pre-post effect size=0.5). Thus, although it is clear that *Gingko biloba* is less effective than conventional pharmacological treatment for ADHD, it remains unanswered whether *Gingko biloba* has any benefit compared to placebo. Increased bleeding risk with *Gingko biloba* treatment makes its current use for ADHD unadvised.[16]

St. John's Wort: *Hypericum perforatum*—St. John's Wort is a natural supplement that has been demonstrated to inhibit reuptake of serotonin, norepinephrine, and dopamine.[60] The potential mechanism of action of St. John's Wort is similar to two commonly used ADHD medications, atomoxetine (a norepinephrine reuptake inhibitor) and bupriopion (a norepinephreine and dopamine reuptake inhibitor).[60] A well-designed, randomized, placebo-controlled trial of 54 children with ADHD failed to demonstrate a significant benefit or a trend towards benefit in children taking St. John's Wort compared to placebo over 8 weeks of treatment.[24] Therefore, despite a plausible biological rationale for efficacy of St. John's Wort for ADHD, current evidence suggests that St. John's Wort is no better than placebo. St. John's Wort further has significant interactions with medications commonly prescribed for ADHD, depression and anxiety that has caused serotonin syndrome in rare cases. Additionally, sun sensitivity is a known side-effect of St. John's Wort.

Pycnogenol: Pinus Mainus—Pycnogenol is a standardized extract from the bark of the French maritime pine. The potential mechanism of action of Pycnagenol is unclear but case reports and case series have suggested that its use is associated with improvements in ADHD symptoms as a monotherapy or as an adjunct to psychostimulant medications. An initial, randomized, placebo- and methylphenidate-controlled crossover trial of Pycnogenol failed to demonstrate a significant benefit of Pycnogenol compared to placebo. The results of this trial were more consistent with a failed trial rather than convincing evidence of inefficacy given that (1) the trial also failed to demonstrate a benefit of methylphenidate and (2) the trial demonstrated a medium, albeit, non-significant benefit of Pycnogenol in improving inattention symptoms of ADHD.[61] A subsequent, 4-week randomized, placebo-controlled trial of 61 children with ADHD randomized to either Pycnogenol (1mg/kg/day) or placebo in a 2.5:1 ratio demonstrated a significant benefit of Pycnogenol in improving ADHD symptoms on Child Attention Problems (CAP) teacher rating scale.[62] Pycnogenol did not significantly reduce ADHD symptoms according to Connor's Parent and Teacher Ratings but by in large the trends for improvement were in the same direction as the CAP. Lower catecholamines were also demonstrated in the urine of the patients prescribed Pycnogenol in the trial suggesting that Pycnogenol may act by affecting catecholamine formation or metabolism. Further research is needed to definitively evaluate the safety and efficacy of this compound before use in patients with ADHD could be recommended.

Conclusions

Table 2 provides an appraisal of available evidence and recommendations regarding use for supplements contained in this review. Two dietary supplements, omega-3 fatty acids in treating ADHD symptoms and melatonin in treating sleep-onset insomnia in children with

ADHD (but not primary ADHD symptoms) have strong supportive evidence of efficacy. However, many other dietary and herbal supplements have widespread use in the United States for ADHD despite minimal evidence of efficacy. Some herbal remedies such as Gingko biloba, and St. John's Wort are fairly frequently used to treat ADHD despite non-existent to negative evidence of efficacy and clear evidence for possible side-effects. Given the widespread use of many dietary supplements by families of children with ADHD (and possible interactions with many traditional medications), it remains imperative that clinicians inquire about their use with families and coordinate pharmacological management of ADHD with them. Polyunsaturated fatty acids, especially omega-3 fatty acids, have fairly convincing evidence of efficacy in treating ADHD across a sizable number of randomized, controlled trials. That being said, the efficacy of omega-3 fatty acids for ADHD appears well below the treatment gains achieved from traditional medications for ADHD such as psychostimulant medications. The use of omega-3 fatty acids in the treatment of ADHD should generally be reserved for mild cases of ADHD and as an adjunctive treatment in more severe ADHD cases. Melatonin appears to be an excellent option to treat sleep problems in ADHD (stimulant-induced or not) if behavioral treatments have been unsuccessful and reducing or adjusting psychostimulant medication use is not feasible.

Future Directions

Rigorous, randomized, placebo-controlled clinical trials examining the efficacy of dietary supplements in the treatment of ADHD are needed. Many of these supplements are commonly utilized by families despite a lack of convincing evidence of efficacy. The dearth of quality clinical trials in this area highlights an area of need for future federally and foundation funded research.

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Glossary

ADHD	Attention-Deficit/Hyperactivity Disorder
CAP	Child Attention Problems
EPA	Eicosapentaenoic Acid
NHANES	National Health and Nutrition Examination Survey
PUFAs	Polyunsaturated Fatty Acids

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Key Points

- Polyunsaturated fatty acid supplementation appears to have modest benefit for improving ADHD symptoms.
- Melatonin is effective in improving chronic insomnia in children with ADHD but has little evidence for efficacy in improving core ADHD symptoms.
- Many other supplements are commonly used despite little evidence of efficacy and evidence of possible side-effects.

Table 1

Randomized, Placebo-Controlled Trials of Natural Supplements for ADHD

Author	Year	N	Age Range	Dosing (mg/d)	Duration	Comparison	Result
Polyunsaturated Fatty Acids							
Milte	2012	90	7–12	EPA Enriched:EPA 1109, DHA 108 DHA Enriched: EPA 264, DHA 1032	16 weeks	placebo	EPA=DHA = placebo
Stevens	2003	50	6–13	EPA 80, DHA 480	16 weeks	placebo	PUFA = placebo
Raz	2009	63	7–13	LA 960, ALA 120	7 weeks	placebo	EFA = placebo
Sinn	2007	104	7–12	fish oil 2400 including EPA 558, DHA 174	15 weeks	placebo	PUFA > placebo
Voigt	2001	54	6–12	DHA 345	16 weeks	placebo	DHA = placebo
Richardson	2005	102	5–12	EPA 558, DHA 174	12 weeks	placebo	PUFA>placebo
Richardson	2002	41	8–12	EPA 186, DHA 480	12 weeks	placebo	PUFA =placebo (but greater improvement on some ADHD outcomes)
Johnson	2009	75	8–18	EPA 558, DHA 174	12 weeks	placebo	PUFA = placebo
Belanger	2009	26	6–11	EPA 500–1000, DHA 200–400 mg	16 weeks	placebo	PUFA = placebo
Gustafsson	2010	92	7–12	EPA 500, DHA 2.7	15 weeks	placebo	EPA > placebo
Aman	1987	31	X	Efamol - LA 2160, GLA 270	4 weeks	placebo	EFA = placebo
Manor	2012	147	6–13	EPA+DHA 120	15 weeks	placebo	PUFA = placebo
Perera	2012	94	6–12	omega-3 600, omega-6 361 (+MPH)	6 months	placebo (+MPH)	PUFA>placebo
Arnold	1989	18	6–12	Efamol - LA 2160, GLA 270	3 months	placebo, d-amphetamine	D-amphetamine>efamol=placebo
Yehuda	2011	78	9–12	LA 1440; ALA 180	10 weeks	placebo	PUFA>placebo
Zinc							
Zamora	2011	40	7–14	10 (+ MPH)	6 weeks	placebo + (MPH)	zinc=placebo
Arnold	2011	52	6–14	15 or 30	8 weeks	placebo	zinc=placebo
Bilici	2004	193	6–14	150	12 weeks	placebo	zinc > placebo
Akhondzadeh	2004	44	5–11	55 (+ MPH)	6 weeks	placebo + (MPH)	zinc > placebo
Iron							
Konofal	2008	23	5–8	80	12 weeks	placebo	iron > placebo
St. John's Wort: Hypericum perforatum							
Weber	2008	54	6–17	900	8 weeks	placebo	Hypericum perforatum = placebo

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Author	Year	N	Age Range	Dosing (mg/d)	Duration	Comparison	Result
Polyunsaturated Fatty Acids							
Pycnogenol: Pinus Mainus							
Trebatická	2006	61	6–14	1 mg/kg/d	4 weeks	placebo	Pycnogenol > placebo
Tenenbaum	2002	24	24–53	pycnogenol 1 mg/lb/d	3 weeks	placebo	Pycnogenol = placebo=MPH
Carnitine							
Van Oudheusden	2002	26	6–13	100 mg/kg/d	8 weeks	placebo	l-carnitine = placebo
Abbasi	2011	40	7–13	1000–3000 +MPH (20–30 mg/d)	6 weeks	placebo + MPH (20–30 mg/day depending on weight)	ALC=placebo
Arnold	2007	16	5–12	1000–3000	16 weeks	placebo	ALC=placebo
Melatonin							
Van der Heijden	2007	105	6–12	3 or 6	4 weeks	placebo	Improved sleep latency, no effect on ADHD symptoms
Weiss	2006	19	6–14	5	10 days	placebo	Improved sleep latency, no effect on ADHD symptoms

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Table 2

Current Evidence Supporting Use of Natural Supplements in ADHD

Treatment	Dosing Recommendations	Duration	Comment
Level 1 Evidence for Effiacy (Based on Systematic Review of Randomized Controlled Trials)			
Omega-3 Fatty Acids	1–2 g/d (>400 mg EPA)	12–16 weeks	Smaller treatment beenfits compared to psychostimulants
Level 2 Evidence for Effiacy (Based on Multiple Randomized Controlled Trials)			
Melatonin (for Sleep)	3–6 mg (30 min before bed)	As needed	Effective in reducing sleep-onset latency. No evidence of benefit in ADHD.
Level 3 Evidence for Effiacy (Based on Non-Randomized Studies or Single Randomized Controlled Trial Prone to Possible Bias)			
Zinc	30–150 mg/d	8–12 weeks	Limited evidence in US and Western European populaitons. Some evidence of efficacy in areas with prevalent zinc deficiency.
Iron	10 mg/d (prevent deficiency) – 80mg/d (repletion)	12 weeks	Indicated for ADHD patients with evidence of iron deficiency
Pycnogenol	1 mg/kg/d	12 weeks	Small, positive, placebo-controlled RCT. Unclear biological mechanism of action.
Ningdong	5 mg/kg/d	8 weeks	Small, underpowered trial without statistical seperation from MPH. No placebo-controlled trials.
Level 4 Evidence for Effiacy (Case Series and Mechanism Based Reasoning)			
Magnesium	100–350 mg/d	12 weeks	Toxic in high doses.
Best Available Evidence Suggests Ineffective with Potential Adverse Effects			
St. John’s Wort: Hypericum perforatum			
Gingko biloba			
Carnitine			