

Complementary Medicine for Children and Young People Who Have Attention Deficit Hyperactivity Disorder

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Authors and Disclosures

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Abstract and Introduction

Abstract

Purpose of review Despite effectiveness of medication in treating children and young people who have attention deficit hyperactivity disorder (ADHD), concerns about the effects of medication on children's developing brains, adverse side-effects, possibility of long-term use, and compliance issues have all contributed to the continuing search for alternative therapies. This article reviews the latest scientific evidence of the effectiveness and safety of these treatments in ADHD. **Recent findings** Although there is evidence from a large randomized controlled study that neuro-feedback has positive effects on reducing children's symptoms of ADHD, most recent randomized controlled trials have generally yielded negative results. Some positive results exist from a pilot study of repetitive transcranial magnetic stimulation. However, the sample size was far too small to enable any conclusions to be drawn about the evidence. Findings from the recent randomized controlled trials of supplements of essential fatty acids in children who have ADHD clearly demonstrated lack of superiority compared with placebo. **Summary** Notwithstanding efforts made to increase the scientific rigor of previous studies, more recent studies have generally been unsuccessful in demonstrating adequate treatment effects of complementary medicine on children who have ADHD. Currently, there is no proof that complementary medicine provides a better alternative for children who have ADHD than treatments that are currently available within multimodal therapy.

Introduction

Attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed neurobehavioral disorder of childhood (3–8%).[[] Previous reports document trends of increasing prevalence during the past decade and increases in use of medication for ADHD.

Previous studies firmly placed medication management as a cornerstone in treating children and young people who have ADHD. However, despite strong effect sizes, not all children respond to medication (15–30%), and some experience significant adverse effects, which limits the use of medication. In addition, both society and parents may have attitudinal difficulties with regard to giving medication to children, or to the risk of drug diversion. These limitations have encouraged researchers, clinicians and families to search for additional treatment options.

Complementary medicine is a group of diverse medical and healthcare systems, practices

and products that are not generally considered part of conventional medicine.[6] Complementary medicine is an increasing feature of healthcare practice, but considerable confusion remains about its effectiveness and what positions the disciplines included under this term should hold in relation to conventional medicine.

The frequency of use of complementary medicines in children who have ADHD ranges between 12 and 64%. However, there has been controversy about the effectiveness and safety of use of this group of interventions. Moreover, some philosophy-based complementary treatments do not lend themselves well to conventional evaluation, as the belief system associated with each is such an important component of the therapy.

This article reviews the latest studies (from January 2008 through to early 2011) on the use of complementary medicines in ADHD and examines their efficacy and safety profile.

Polyunsaturated Fatty Acids

Phospholipids containing polyunsaturated fatty acids (PUFAs), such as omega-3 and omega-6 (essential fatty acids), are integral parts of the neuronal cell membranes of the brain, and it has been hypothesized that they may have a role in facilitating transmission of signals between neurons. Some studies have found an association between PUFA intake and neuropsychiatric disorders, in particular depression. The observation of a systematic association between having symptoms of ADHD and low PUFA status has led to the hypothesis that PUFAs might be involved in the etiology of ADHD. Animal models have linked hyperactivity to reduced omega-3 PUFA in the frontal cortex.[

Some intervention trials of PUFA that were published before 2008 on children who had ADHD have shown positive treatment effects, and similar results were obtained for the second phases of the single-crossover trials, which were single-blind. Controlled trials, however, were generally unsuccessful in demonstrating any treatment effects beyond those of placebos, and some suggested inferiority.

A multisite Swedish treatment study using an RCT design has been conducted that compared the effects of omega-3 fatty acid with placebo. A 0.5 g dose of eicosapentaenoic acid (EPA) or placebo was administered over a 15-week period to 92 children (7–12 years) who had ADHD. The children were stimulant naive. The primary outcome measure was the Conner's Rating Scale. The study did not show that EPA had any advantage over placebo. In summary, this was a well-designed prospective, randomized, placebo-controlled, double-blind study, which produced negative results.

Recently, Belanger *et al.* conducted a 16-week, randomized double-blind, one-way, crossover study of 37 French Canadian primary school children who had ADHD. An n-3 PUFA supplement was compared with n-6 PUFA (sunflower oil), acting as placebo. Although this was a small study ($N = 37$), with 30% dropout, eight patients displayed a statistically significant clinical improvement, particularly on the inattention, global DSM-IV and total Conner's subscales. Twelve patients reported minimal amelioration and six patients did not improve. The patients tolerated the n-3 PUFA supplement without any adverse effects.

Johnson *et al.* conducted a randomized, 3-month, omega 3/6 placebo-controlled, one-way

crossover trial with 75 children and adolescents (8–18 years), followed by 3 months with omega 3/6 for all. Exclusion criteria for the study included the use of any psychoactive drugs 3 months before the study. The first phase, which ended with a dropout rate of 22%, demonstrated significant treatment effects in the Clinical Global Impression scores but not in ARSs. Similar results were obtained for the second (open-label) phase of the study. The authors concluded that the study results were essentially negative, and that they did not support the superiority of PUFA over placebo. Raz *et al.* randomized 73 children aged 7–13 years, who had ADHD but who were not on medication, to either short-chain PUFA supplementation or placebo groups, for a period of 7 weeks. The study used as measures teacher and parental questionnaires, as well as an objective continuous performance test [Test of Variables of Attention (TOVA)]. Fourteen percent of the sample did not complete the study. The study failed to demonstrate a benefit of PUFA supplementation over placebo on any of the measures used.

In summary, despite improvements in study design, more recent studies fail to support the use of PUFA supplements as a primary or supplementary treatment for children who have ADHD.

Chiropractic Care

Chiropractic care focuses on the musculoskeletal system and, in particular, the spine and its disorders. Its intentions are to optimize functioning of the nervous system, which this discipline takes as the key to maintaining or restoring health. A recent systematic review found that chiropractors treat a wide variety of pediatric health conditions (i.e. enuresis, asthma, infant colic). However, their interventions are supported by only low levels of scientific evidence, and most of it is derived from clinical experience, descriptive case studies and very few observational and experimental studies. Since 2008, four case reports on chiropractic care for children who have ADHD, and a case series, have been published. All supported the positive effects of its use. Alcantara and Davis published a retrospective case series on four boys aged 9–13 years, two of whom were on medications for ADHD at the start of chiropractic care. Their responses were monitored using a 15-item parent/teacher ADHD questionnaire (previously unpublished and not validated). According to the authors, all patients showed an improvement in their symptoms of ADHD (i.e. hyperactivity, impulsivity and inattentiveness) following the course of their chiropractic care. However, our conclusion is that, to date, there is no good evidence of the effectiveness of chiropractic care for ADHD.

Electro-acupuncture

Stimulation of acupoints by inserting a needle is called acupuncture, and it is part of traditional Chinese medicine. Electro-acupuncture is a modification of acupuncture in which the needles inserted are attached to pulsating electrical current to provide stimulation to the acupoints. Acupuncture is commonly used by patients who have chronic conditions, that is, chronic pain disorders, although data supporting its use are limited. The theories of traditional Chinese medicine propose that ADHD represents the connection of congenital constitutional insufficiency, postnatal loss of nourishment, affect-mind dissatisfaction and trauma, and the origin of the illness is thought to be in the kidneys, heart, liver and spleen. Based on these theories, the acupoints such as Shen-Ting and Tai-Yang are chosen for treating ADHD.

In China, Li *et al.* recruited 213 preschoolers who had ADHD diagnosed by DSM-IV criteria.

Later, 33 of them were excluded for various reasons (i.e. no written consent, did not finish full course of the treatment, etc.). These preschoolers were allocated randomly into an experimental group ($n = 92$), in which the children received electro-acupuncture and behavior therapy, and a control group, in which the children received sham electro-acupuncture and behavior therapy ($n = 88$). Change in the core symptoms of ADHD, a standard enacted by the national traditional Chinese medicine committee, was the main outcome measure. The efficacy of treatment was evaluated after 12 courses of treatment and after follow-up lasting half a year (10 cases were lost during the follow-up). On both occasions, core ADHD symptoms were significantly lower in the experimental group than in the control. However, the actual effect size was not provided in the study. Although the findings are interesting and the sample was relatively large, it is not clear how many children (or their parents) refused this quite invasive form of treatment (electro-acupuncture) and the dropout rate was quite high ($n = 43$; 20%). Moreover, neither the magnitude of the effect nor the validity of the main outcome measure is clear. Thus, our opinion is that the very positive results reported after the study should be interpreted with caution and, currently, there are no studies that provide strong evidence for using electro-acupuncture for treating children who have ADHD.

Repetitive Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive intervention that creates weak electric current to cause activity in a target area in the brain. Dopaminergic activity in the prefrontal cortex is affected in ADHD, and rTMS affects dopaminergic secretion in the prefrontal cortex. One small study has suggested promising results. Thirteen adults, who had ADHD diagnosed on DSM IV criteria, participated in a double-blind randomized crossover study that compared sham-brain stimulation and rTMS. There was a specific beneficial effect on the patients' attention 10 min after a real rTMS course with no effect evident in the sham rTMS. Larger double-blind randomized, sham-controlled studies are necessary to provide evidence for the effectiveness of rTMS in treating children who have ADHD.

Anthroposophic Therapy

According to anthroposophic theory, there is a complex equilibrium between two polar systems: the 'nerve-sense system' (low metabolic rate, mediator of consciousness) and the 'metabolic-limb system' of the abdominal organs and limbs (high metabolic rate, minimal consciousness, mediator of voluntary movement). According to anthroposophic theory, this equilibrium can be distorted in human disease and the ADHD symptom of hyperactivity is seen as reflecting a predominance of the metabolic-limb system. This imbalance is sought to be regulated by special anthroposophic therapies.

Hamre *et al.* conducted a 2-year prospective cohort study to obtain information on anthroposophic therapies for children who had ADHD symptoms and who were managed in routine outpatient conditions in Germany. Patients received anthroposophic therapies medication alone (i.e. Aurum/stibium/Hyoscyamus pillules) ($n = 4$) or were referred to anthroposophic art therapy, eurhythmy movement exercises or rhythmical massage therapy ($n = 21$) or received a combination of anthroposophic therapy medications and therapies ($n = 36$). The standardized response mean effect size for the comparison over 0–24 months was 0.45 according to the FBB-HKS total score. However, there were many limitations to the study that included selection bias, absence of a control group, only 67% of the sample meeting DSM-IV criteria for ADHD, 15% having pervasive developmental disorder and 18%

not meeting strict criteria for diagnosis of ADHD; in addition, 18% of the participants were on stimulants. Finally, the study assessed anthroposophic therapies as a whole system. Taking into account that 56 different anthroposophic therapy medications were prescribed at enrolment, the lack of subgroups analysis is the major drawback of this study. In our opinion, the current level of evidence is insufficient to allow the efficacy of this modality of treatment to be evaluated.

Meditation

Meditation has been gaining momentum as a method for relaxation, stress reduction and improving general well being. There are different types of meditations; of particular interest is mindfulness, which emphasizes an observant and nonreactive stance toward one's thoughts, emotions and body states. It has been found efficacious in reducing relapse rates of depression.

Recently, Zylowska *et al.* have conducted the first uncontrolled feasibility pilot study of an 8-week mindfulness training program with 24 adults and eight adolescents who had ADHD diagnosed on the basis of DSM-IV criteria. Symptoms of ADHD were assessed using the ARS IV (adults) and comparable items from the Swanson, Nolan and Pelham Rating Scale (SNAP-IV) (adolescents). Before and after improvements in self-reported symptoms of ADHD and test performance on tasks measuring attention and cognitive inhibition were noted. The study was limited by the small sample size, lack of control group, selection bias (participants were women, white, educated and from medium to high socioeconomic status), presence of higher rates of comorbidity, greater levels of overall functioning than what is commonly seen in the ADHD samples and a majority of participants (63%) being on stimulant medications. However, the results of this study supported the feasibility of mindfulness meditation in a subset of adults and adolescents who have ADHD. Singh *et al.* provided mindfulness training to two mothers, and subsequently to their sons who had ADHD. Training mothers in mindfulness increased their child's compliance in the short term, but, probably, insufficiently to make a substantial difference in mother–child relationships.

Grosswald *et al.* conducted a 3-month noncontrolled open pilot study to test the feasibility of transcendental meditation on 10 students aged 11–14 years, who had a diagnosis of ADHD. The practice of the transcendental meditation technique involved two components: a suitable sound or 'mantra', specifically chosen to facilitate the process of settling the mind, and a precise yet effortless technique for using the sound which leads to the experience of quieter aspects of persons' awareness. After 3 months of intervention, there was a statistically significant decrease of scores on the Child Behavior Checklist and the Achenbach Youth Self-Report ADHD Problems scale. Limitations of this research included small sample size, no control group, co-morbid psychiatric disorder and lack of a standardized ADHD scale. In addition, eight out of 10 students were taking stimulants. We conclude that the evidence base for effectiveness of meditation is very limited.

***Hypericum perforatum* (St John's Wort)**

Extracts from St John's wort, also known by its Latin botanical name *Hypericum perforatum*, have been studied extensively for the treatment of depression. *Hypericum perforatum* has been found to inhibit reuptake of serotonin, norepinephrine and dopamine. It is because *Hypericum perforatum* is believed to act as a norepinephrine reuptake inhibitor that Weber *et*

al. [51] hypothesized that *Hypericum perforatum* may be beneficial in treating people who have ADHD. They carried out a double-blind randomized placebo-controlled trial on 54 children aged 6–17 years who had ADHD. The patients were not on any other medications for ADHD. No significant difference was found after 8 weeks of the trial between the two groups on the ARS IV and the Clinical Global Impression Improvement Scale. The study did not find positive results for the efficacy of *Hypericum perforatum* in treating ADHD, although the sample size was small and the trial was short. Another study of *Hypericum perforatum* was of three 14–16-year-old male psychiatric outpatients. It reported significant improvements in patients' mean scores of Conner's factors of hyperactivity, inattention and immaturity. However, the study was essentially a case series report. Our conclusion is that, overall, the evidence to support use of *Hypericum perforatum* as a treatment for ADHD is very limited.

Iron Supplementation

In the past, a few studies reported that iron deficiency was correlated with the severity of symptoms of ADHD; thus, it was proposed that iron supplementation might reduce symptoms of ADHD in patients who had low ferritin levels. In 2008, Konofal *et al.* carried out the first double-blind, randomized, placebo-controlled trial of oral ferrous sulfate on the symptoms of ADHD in 23 children (aged 5–8 years) who were iron deficient but not anemic. Children who received iron supplementation therapy reported significant improvement on total symptom score and on the hyperactive/impulsive and inattentive subscales of the ARS; however, their improvement on the Conner's Parent Rating Scale (the primary outcome measure) and the Conner's Teacher Rating Scale associated with iron supplementation therapy failed to reach significance. Interestingly, restless legs symptoms were improved in the treatment group, but not in the group given a placebo. As previously reported, restless legs may mimic, may be mimicked by, or may hide evening motor activity of children who have ADHD.[56] Therefore, there is a possibility that the improvement of restless legs symptoms was actually accounted for by the improvement of attention deficit hyperactivity disorder motor activity in the evening. These results should encourage further research in this area. However, currently, there are not enough data to support us to recommend the use of iron in treating ADHD.

Zinc Supplementation

In the past, several studies have reported evidence of lower zinc tissue levels in children who had ADHD, compared with normal controls. It has been hypothesized that zinc supplementation may reduce symptoms of ADHD in patients who have low zinc levels. Recently, Uckardes *et al.* have conducted a double-blind randomized, placebo-controlled trial in Turkey to determine the effect of zinc supplementation on behavior in low-income school-aged children (218). Children in the study group received 15 mg elemental zinc syrup per day for 10 weeks and the children in the placebo group received syrup but without zinc. The mean scores on the Conner's Rating Scale for Parents relating to attention deficit, hyperactivity, oppositional behavior and conduct disorder decreased significantly in the study and placebo groups after supplementation. Interestingly, serum zinc levels were normal in both groups before the intervention and increased after supplementation in both groups. Of note, a caloric spectrophotometer was used instead of an atomic absorption spectrophotometer due to the limited budget of the study. DiGirolamo *et al.* conducted a 6-month randomized, double-blind, controlled trial comparing zinc supplementation with a placebo (glucose) in 674 Guatemalan children in grades 1–4. The groups given zinc and

placebo did not differ significantly in any behavioral measures at baseline or at follow-up: this included parent-reported scores for their children's behavioral problems. Whereas older studies have reported a correlation between zinc deficiency and ADHD symptoms, a RCT of zinc supplementation therapy that was conducted recently failed to demonstrate a benefit for zinc supplementation.

Magnesium

Huss *et al.* carried out an observational, longitudinal study to investigate the possible effects of a commercial dietary supplement containing a combination of omega-3 and omega-6 fatty acids and magnesium. Of children who had elevated scores initially, 73.7% remained below the threshold on SNAP-IV (a screen for inattention and hyperactivity) following 12 months of taking the supplement. In our opinion, the positive results should be interpreted with caution, as this study had a lot of shortcomings: the lack of a control group and no control of treatment allocation; no control for socioeconomic status; the validity of the compliance reports was limited, as data could not be cross-validated by pill counts or other methods of compliance control; eligibility for participation was based on the presence of symptoms of inattention and behavioral problems rather than on a confirmed ADHD diagnosis; and co-morbidities.

Ginkgo biloba

The *Ginkgo biloba* tree is one of the oldest living species and traditionally Ginkgo leaf has been used in herbal medicine to treat poor circulation. Niederhofer *et al.* described six outpatients who were diagnosed with ADHD and whose mean total score and subscores on the Wender Utah Rating Scale for ADHD improved significantly after they took *Ginkgo biloba* for 1 month. Less optimistic findings were reported from a recent RCT. Salehi *et al.* conducted a double-blind, randomized, parallel group comparison of *Ginkgo biloba* and methylphenidate in 50 children and adolescents who met DSM-IV, Text Revision (DSM-IV-TR) criteria for diagnosing ADHD. The authors reported that *Ginkgo biloba* had no comparable efficacy in comparison with methylphenidate in treating ADHD.

Dietary Interventions

Since the Feingold Diet in the 1970s, which promoted elimination of artificial food additives, coloring and flavoring from affected persons' diets, the discussions about food and ADHD have accelerated.

Pelsser *et al.* conducted an open-label controlled trial into the effects of food on ADHD in 24 children (age between 3.8 and 8.5 years) who were randomized to a waiting-list (control) group or an intervention group. Children in the intervention group were put on an elimination diet consisting of rice, turkey, lamb, vegetables, fruits, margarine, vegetable oil, tea, pear juice and water. The intervention group showed a 62.6% improvement on the Abbreviated 10-item Conner's Scale (ACS) and a 70.3% improvement on the ARS Number of ADHD criteria. The scores of the waiting-list group increased by 4.4% (ACS) and decreased by 2.2% (ARS Number of ADHD criteria). However, the study was a small open-label controlled trial, without placebo.

Howard *et al.* examined the dietary patterns of 1800 adolescents from the long-term Raine Study. The study looked at the dietary patterns among the adolescents and compared each

adolescent's dietary information against whether or not he or she had received a diagnosis of ADHD by the age of 14 years. One hundred and fifteen adolescents had been diagnosed who had ADHD. Having an ADHD diagnosis was associated with taking a diet that was high in takeaway foods, processed meats, red meat, high-fat dairy products and confectionery (the so-called western diet). However, this was a cross-sectional study, and it remains unclear whether or not a poor diet leads to ADHD or whether ADHD leads to poor dietary choices and cravings.

Very recently, Pelsser *et al.* have reported from an open-label randomized crossover study on the 'impact of nutrition on children with ADHD'. The restricted elimination diet had a significant beneficial effect on ADHD symptoms in 32 (64%) of 50 children aged 4–8 years, and reintroducing foods led to significant behavioral relapses in clinical responders. Blood tests, which assessed IgG levels against foods, did not predict which foods might have a deleterious effect on the children's behavior. This open-label RCT was carried out with masked measurements by an independent pediatrician but not parents, teachers, and researchers. Thus, parents cannot be ruled out as a possible cause of the improvements in their children's behavior. Moreover, the authors admitted that they could not rule out a possibility that the behavior improvements might have been caused by increased attention paid to the child in the group that received the elimination diet.

Conclusion

Most recent studies on complementary medicine as treatments for children and young people who have ADHD have tried to replicate some success demonstrated by earlier studies that used complementary medicine for ADHD. The differences are that the more recent researchers have endeavored to improve the methodology (e.g. through lower dropout rates, careful diagnosis, randomization and blindness management).

Of the complementary medicines which have been investigated in the recent studies, the evidence is best for neurofeedback. A large randomized controlled study showed that neurofeedback has positive effects on reducing symptoms of ADHD. The behavioral effects of neurofeedback training were maintained at 6-month follow-up and support for the intervention's neurophysiological mechanism of action was also provided. Although the effect was of moderate size (effect size = 0.6), it was smaller than the effects of medication. That research has not been followed by other positive studies. Thus, currently, there is some evidence that neurofeedback is beneficial, but there is no proof that neurofeedback provides a better alternative for individuals who have ADHD compared with other treatments that are available currently (i.e. a combination of medication and behavioral treatments).

Findings from the recent RCTs of PUFAs supplements in children who had ADHD are disappointing. All recent RCTs have demonstrated clear lack of superiority for PUFAs over placebos. Interesting, but yet preliminary, results have been found in an rTMS study, and await larger-scale replications. One RCT showed that electro-acupuncture has positive effects on reducing ADHD symptoms. However, the study had serious methodical shortcomings and larger, more rigorous studies are needed before any definite recommendations can be made. A few pilot studies to test the feasibility of meditation training for adults and adolescents who have ADHD have been carried out recently with only modest results. *Hypericum perforatum* is believed to act as a norepinephrine reuptake inhibitor. However, a hypothesis that *Hypericum perforatum* may be beneficial in treating ADHD has

not been confirmed in a recent double-blind randomized placebo-controlled trial. A few older studies have pointed out that patients' serum ferritin levels and zinc levels were inversely correlated with their symptoms of ADHD. However, recent RCTs have failed to demonstrate a benefit for either iron or zinc supplementation over placebo. All but one recent RCTs on elimination diets did not generate recommendations for them being a generally applicable treatment for children who have ADHD.

In summary, our opinion is that, currently, there is not enough evidence to prove that complementary medicine provides a better alternative for individuals who have ADHD compared with treatments that are currently available as parts of multimodal therapy.