Attention Deficit Hyperactivity Disorder (ADHD)

Where are we, and what have we learned?

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Evidence-Based Use of Supplements

ABSTRACT

The goal of this paper is to present an objective up-to-date evaluation of the existing data and research as it pertains to Attention Deficit Hyperactivity Disorder (ADHD). Given the rapid expansion of the field and the associated data and literature, the hope is to help healthcare professionals synthesize current knowledge on ADHD and improve their ability to think critically about the condition. The aim is to provide insight that extends beyond the context of what may be seen in individual clinics and to provide valuable and current information on the pros and cons of existing main line treatments and other potential adjunctive or stand-alone options.

What is ADHD?

ADHD is a neuropsychiatric disorder characterized by symptoms of inattention with or without evidence of impulsivity and hyperactivity.1 Historically, ADHD has been widely recognized and described as a condition affecting school-aged children, but it is now increasingly accepted as a valid diagnosis in adults as well. Several recent studies have shown that symptoms and impairments related to childhood ADHD can persist into adulthood, and thus adults can experience partial remission or the full condition.2

ADHD is a chronic condition in children that can start at 2 to 4 years of age and is composed of a persistent pattern of hyperactivity, impulsiveness, and a lack of focus. Importantly, in ADHD, these symptoms are more frequent than is usual for age-matched children and result in significant deficiencies in school or work performance, as well as in daily activities.3 ADHD is one of the most common neurodevelopmental disorders of adolescents and children, and it imparts social and economic burdens on the health system and society.4 The Global Burden of Disease Study in 2010 reported estimates of 26 million children and adolescents with ADHD worldwide, as well as estimates 491,500 disability-adjusted life years.5

Critics of the concept of ADHD have always claimed that it is not a clear-cut psychiatric disorder but is instead simply a social stigma attached to children who are behaviorally difficult. The current argument is that ADHD is a descriptive diagnosis where the severity of behavior allows it to be differentiated from normal behavior. Those on each side of the argument about the legitimacy of ADHD agree that both over-diagnosis and under-diagnosis occur frequently.6,7

How Often and by Whom is ADHD Diagnosed?

Though physicians or clinical psychologists are responsible for official ADHD diagnoses, teachers have taken on an increasingly larger role as "disease spotters."8–10 In a review of 491 primary care doctors who had diagnosed ADHD in Washington, D. C., almost half of the diagnoses of ADHD in children had first been 'suggested' by teachers. A teacher was the most likely person to be the first to recommend a 'diagnosis' of ADHD. Whereas 46.4% of ADHD diagnoses were first recommended by a teacher, only 30.2% were first recommended by a parent. A shocking 11.3% of these cases were first identified as potential ADHD cases by physicians.11 Thus, teachers seem to have become the primary diagnosticians of ADHD in children.

The teacher's role as the diagnostician has been investigated more for ADHD than for any other disorder affecting children. The most recent version of the Diagnostic and Statistical Manual of Mental Disorders (DSM), DSM-V, assigns teachers an active role in ADHD diagnosis by using assessment instruments such as the Conners' Teacher Rating Scale, which incorporates teacher reports of behavior into clinicians' diagnoses.12

As part of their role in diagnosing ADHD, teachers have also become responsible for explaining the disorder to parents and guiding parents and children through the diagnosis and treatment process. In the U.S., there are resources for teachers, including educational programs offered by the organization known as Children and Adults with Attention Deficit/Hyperactivity Disorder (CHADD).13–15 CHADD is the U.S.'s largest advocacy group for ADHD-affected persons. It acts as the chief editorial consultant of a special issue on ADHD in *Health in Action*, a publication of the American School Health Association.16

Between 2004 and 2005, 22% of CHADD's total revenue was provided by the pharmaceutical industry,13 which may contribute to the surprising observations that ADHD is diagnosed in the U.S. more than in European countries and that those rates are increasing. Recent data have also shown that children born in August are more frequently diagnosed with ADHD than children born in September. Because September 1 is the cut-off for kindergarten entry, those born in August are the youngest in their classes and thus likely the farthest behind developmentally and behaviorally.17 Experts suggest that these younger children are prone to misdiagnosis of ADHD as a result of what are actually normal behaviors for their age. This phenomenon has

arecently garnered widespread attention, with an opinion piece on the topic published by health policy researchers in late 2018 in the *New York Times*.18

How is ADHD Treated, and are Treatments Safe and Effective?

Stimulant Drugs
Stimulant drugs are the first-line therapy for ADHD for both children and adults. Several studies indicate that these drugs, such as amphetamine and methylphenidate, are beneficial in helping to mitigate ADHD symptoms. However, the literature on the long-term safety, side-effects, and efficacy of these drugs is controversial. Treatment of ADHD with psychostimulants is criticized because stimulants pose health risks including the risk for addiction, and because the extent of the side-effects is underestimated.19–21

Psychostimulants used to treat ADHD have been shown to increase both heart rate and blood pressure,22 and children taking stimulants for ADHD have a significant risk of experiencingpsychosis.23 Specifically, those taking psychostimulants for ADHD have experienced rises in heart rate of 3 to 10 beats per minute, rises in systolic blood pressure of 3 to 8 mmHg, and rises in diastolic blood pressure of 2-14 mmHg.

While some of those with ADHD diagnoses are known to abuse amphetamines and methylphenidate, these drugs are also abused by adolescents and adults who have not been diagnosed with ADHD.19 Although meta-analyses of children and adolescents diagnosed with ADHD and treated with psychostimulant drugs show less risk of future substance abuse, the same is not true for adults diagnosed with ADHD and treated with psychostimulants.24,25 On the contrary, an ADHD diagnosis is a risk factor for substance abuse in adults. Other psychiatric conditions increase this risk.

Higher doses of stimulant drugs used to treat ADHD exacerbate the side effects. Unfortunately, increasingly higher doses are often needed as those taking these drugs develop tolerances to them.26–28 Indeed, the Multimodal Treatment Study of Children with ADHD (MTA), the largest ADHD treatment study in history, found that psychostimulants have less efficacy over time. According to the data, there are people who have been taking psychostimulants for years who have the same symptom levels "as those who had never been medicated."27

This apparent need for higher psychostimulant dose over time has led the American Academy of Child and Adolescent Psychiatry (AACAP) to recommend dose increases as needed. Their guidelines state that the majority of children will eventually need higher drug doses during the course of their treatment. Of particular concern, though, is that because low brain dopamine levels are believed to be the cause of ADHD, decreasing the brain's sensitivity to dopamine is just the opposite of what ADHD patients need and could theoretically lead to the worsening of ADHD symptoms.29

Also problematic is that most of the efficacious (higher dose) psychostimulants are associated with anorexia, weight loss, and insomnia.28,30 In children with ADHD, higher doses of methylphenidate are associated with parent ratings of increased insomnia and decreased appetite.31 Recent research has also begun to demonstrate the potential cognitive handicap provided by methamphetamines that may prevent normal cognition from developing and lead to impaired cognitive performance in those taking these drugs.32

Teachers too likely see the effects of higher doses of methylphenidate. A 2017 Netherlands study of methylphenidate use in children confirms earlier studies of long-term drug failure and concludes that the use of methylphenidate is associated with poorer school performance.33–37 Though the evidence that long-term use of methylphenidate use impairs student performance contradicts earlier positive reports of the drug's effects, these more recent studies involve longer timeframes and larger study populations, 33–37 making them potentially more credible.

A recent study in Europe examining the treatment emergent adverse events (TEAEs) in children and adolescents with ADHD who use amphetamine drugs found that 89% of the participants reported TEAEs, with nearly 1 in 10 participants experiencing a serious TEAE.38 The TEAEs included:

-Increases in systolic blood pressure and diastolic blood pressure, which were reported by 22.4% and 38.8% of participants, respectively.

-Reductions in appetite, which occurred in nearly half the participants, as well as weight loss, experienced by 18.2% of the participants.

Interestingly, 31% of adults in the U.S. diagnosed with ADHD were prescribed amphetamines, while only 9.4% of European adults diagnosed with ADHD were given amphetamines.39

Non-Stimulant Drugs
In cases where stimulant drugs are contraindicated, poorly tolerated, do not invoke an adequate clinical response, or where the person with ADHD or their family members simply do not want to pursue stimulant drug use, non-stimulant drugs have been prescribed. Atomoxetine (ATX), guanfacine (GXR), and clonidine are three non-stimulant drugs that have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of ADHD. These drugs are also known by their trademark names: Strattera, Intuniv, and Kapvay, respectively.40

ATX, which is a selective norepinephrine reuptake inhibitor, was the first non-stimulant that was approved for the treatment of ADHD in the U.S. and is indicated as a monotherapy for adults as well as children who are at least 6 years of age. ATX has been shown to reduce ADHD symptoms within the first week of treatment.41 This non-stimulant drug is also associated with improved morning and evening behavior related to ADHD in children. Another benefit of ATX is that, unlike stimulant drugs, it does not have positive reinforcing effects and so is not associated with addiction .42

ATX can lead to some adverse side-effects. For adults and children who experience side-effects, both nausea and reduction in appetite are common. Children with adverse side-effects also frequently experience abdominal pain and headaches, whereas adults with side-effects may endure insomnia, dry mouth, or erectile dysfunction.41

GXR is a selective adrenergic-receptor agonist in an extended release formulation. Like ATX, it is also indicated as a monotherapy but for youths aged 6 to 17. Though GXR has been shown to improve ADHD symptoms in children and adolescents in both the morning and evening,43,44,

there have been no studies that directly compare the efficacy of GXR to other active treatments, and indirect analyses provide inconsistent views on the relative efficacy of GXR.45

It may be the case that GXR is more valuable than other treatments in specific contexts. For instance, some data suggest that GXR may help children with co-morbidities like chronic tic disorders or oppositional symptoms who have not been responsive to other treatments.46

In addition to questions over the efficacy of GXR, it is also unclear how safe the drug is. While some studies have found GXR to be well-tolerated,43 with the most commonly reported adverse side-effects being fatigue and headache,47 other studies have identified more concerning undesirable side-effects, including hypotension, sedation, and bradycardia, and found that these side-effects are common.45

Research has shown that the side-effects associated with GXR can limit its tolerability and that discontinuing the drug can also lead to troubling symptoms, such as rebound hypertension and tachycardia, particularly if GXR use is abruptly discontinued. Further complicating our understanding of the impact of GXR is that its mechanism of action in ADHD is unclear.

Finally, clonidine can serve as both a monotherapy and as an adjunctive therapy for those with ADHD. Though there is relatively little coverage of the use of clonidine in ADHD in the medical literature, the data thus far suggest that clonidine is associated with improved sleep duration, and like other non-stimulant drugs, clonidine may be well-tolerated.48

Non-Prescription Alternative Treatments
Although pharmacological treatments for ADHD symptoms for most children work in the short-term, 20 to 30% of children are non-responders or cannot tolerate the side-effects of these drugs. The same is true for adults diagnosed with ADHD.49,50

According to a 1999 survey, parents of 64% of children with ADHD chose non-prescription alternative medicine treatments to address their children's ADHD.51 Research shows that alternative therapies are as effective as prescription drugs, with a slight trend towards more effective results in the non-prescription group.51,52 Sleep and dietary strategies are two promising ways to pursue the improvement of ADHD symptoms.

Both children and adults diagnosed with ADHD demonstrate unhealthy sleep patterns, and any comprehensive treatment regimen must not only help to reduce ADHD symptoms of poor concentration, poor focus, impulsivity, and hyperactivity but must also help to correct and reestablish better sleep patterns. Indeed, healthy sleep patterns are crucial to successful long-term ADHD intervention and overall long-term health as well.

There has been a wealth of research on the impact of dietary ingredients on different aspects of ADHD and related symptoms. Though nearly 20% of those diagnosed with ADHD in Europe are given dietary supplements, supplements are given to only 10% of U.S adults diagnosed with ADHD. Remarkably, in the U.K. alone, 27.7% of ADHD patients are given supplements – almost three times as many as in the U.S.39

Below is a list of supplements whose use in the management of ADHD are supported with clinical data and that have the potential to work well together as a stand-alone cocktail treatment or adjunctively in patients who take pharmacological treatments.

Bacopa Monnieri Extract
Bacopa monnieri extract, or Brahmi, is a traditional Indian medicinal plant that has multiple effects on the central nervous system. Standardized extracts of this plant have been shown to enhance information processing in healthy volunteers and in memory-impaired adults.53,54

In one study, 31 children previously diagnosed with ADHD were given 225 milligrams (mg) of Bacopa monnieri extract daily for a total of 6 months. Symptoms of attention deficits were improved in 85% of the children. More than half of the children experienced reductions in impulsivity and psychiatric disturbances. In addition, learning improvements occurred in 78% of the children.55

In 2000 and 2002, two other studies were published that looked at the impact of Bacopa monnieri in children previously diagnosed with ADHD. The data from these studies corroborate the finding that Bacopa monnieri improves ADHD symptoms.37,56

Magnesium alone and Magnesium – Vitamin B6 Combinations
Magnesium levels are demonstrably lower in children diagnosed with ADHD, as evidenced by magnesium levels collected from the hair, nails, and blood serum of these children.58 Whether magnesium supplementation can alleviate ADHD symptoms has thus been of interest among ADHD researchers.

A study of 50 children diagnosed with ADHD and who were also deficient in magnesium examined the impact of 200 mg supplementation of elemental magnesium over a 6 month period.57 Compared to the children who did not receive magnesium supplementation, those taking the magnesium developed higher levels of magnesium in their hair, which was accompanied by a significant reduction in hyperactivity.

While magnesium supplementation reduces the symptoms of ADHD in children with the disorder, supplementation with a combination of magnesium and vitamin B6 has been shown to lower ADHD symptoms even further.57–60 These findings are perhaps unsurprising given that disorders of vitamin B6 metabolism are common among those with ADHD.61

Research has shown that not only does a magnesium-B6 regimen significantly reduce clinical signs of ADHD, but when the regimen is terminated, the symptoms reappear within a few weeks.59 One study on 40 children with ADHD showed that 8 weeks of a magnesium-B6 regimen reduced ADHD symptoms, including hyperactivity, aggressiveness, and inattention.59 Similarly, another study on 52 children with the disorder found that 1 to 6 months of a magnesium-B6 combination reduced the same symptoms, as well as hypertony, myoclony, and spasm.60

Vitamin D
Research has shown that vitamin D deficiency is more common in ADHD patients than in healthy controls.64,65 One study found that 64% of ADHD patients were not only deficient in vitamin D but were moderately or severely deficient, with serum levels between 10 and 20 nanograms per milliliter (ng/ML) or below 10 ng/mL, respectively.66 A

more recent comprehensive meta-analysis covering data from over 11,000 children also found that children with ADHD have significantly lower levels of vitamin D than those without ADHD.63

A 2018 study helped to clarify the mechanism responsible for lower vitamin D levels, as it revealed that children with ADHD not only had lower serum vitamin D levels but also lower vitamin D receptor levels.62 This study was the first to compare vitamin D receptor levels in those with and without ADHD.

The first study to measure the effects of vitamin D supplementation and its effects on ADHD found that supplementation improves cognitive function, inattention, hyperactivity, and impulsivity.68 A recent double-blind, randomized clinical trial also showed that oral vitamin D improves symptoms of ADHD, particularly symptoms of inattention, and that it is especially beneficial for those who previously had insufficient levels of vitamin D.67

L-Theanine
L-Theanine is an amino acid found in green tea in significant amounts. L-Theanine has been found to have a calming effect and is used to improve cognitive and mental performance.69,70 Alpha-wave predominance in the brain is associated with a state of relaxation, and theanine supplementation produces a shift toward more alpha-wave production within 40 minutes of taking it at dosages from 50 to 200 mg. The effects appear to last up to eight hours and are dose-dependent.71,72 A double-blind, placebo-controlled study on boys diagnosed with both ADHD and sleep disorders demonstrated that L-theanine significantly increases sleep efficiency as well as time spent asleep.73

Grape Seed Extract
Grape seed extract is one of the most potent antioxidant extracts from plant sources, even more potent than pine bark extract,74 providing, for instance, excellent protection against oxidative stress and free radical-driven tissue injury.75

Grape seed is highly bioavailable and provides greater protection against free radicals and damage to cell membranes and DNA than vitamins C and E, both singly and in combination. Scientific studies have shown that the antioxidant power of proanthocyanidins is 20 times greater than that of vitamin E and 50 times greater than that of vitamin C.76

Children diagnosed with ADHD demonstrate higher levels of lipid peroxides than do controls and are at greater risk for developing cardiovascular disease.77,78,79 Potent antioxidants like grape seed extract that provide protection against excessive oxidative stress and cardiovascular risk factors are likely therefore beneficial for those with ADHD.80,81

Vitamin C
Vitamin C is the most prevalent water-soluble antioxidant in the human body.82 It inhibits LDL-cholesterol oxidation, which is the first step in developing coronary artery disease, and plays a major role in other protective mechanisms against heart disease, such as lowering C-reactive protein.82 Vitamin C may therefore help to mitigate the enhanced cardiovascular risks experienced by ADHD patients.82–84 Because humans cannot synthesize vitamin C, they must get this critical vitamin from their diets.83,84 As such, supplementation is often necessary for adequate vitamin C consumption, which may be the case for some of those with ADHD.

Iron
Recent studies have found an association between ADHD and iron deficiency.85 Children with more severe iron deficiencies have been shown to also experience more severe ADHD symptoms,86 and iron deficiency in infancy has been shown to be predictive of social and behavioral problems in adolescence.87 Lower serum ferritin levels are correlated with more severe ADHD symptoms as measured by the Conners' Parent Rating Scale.88 Interestingly, people with restless leg syndrome (RLS) also often display low levels of ferritin, and those with RLS are more likely to also have ADHD.89

Based on these findings, it has been suggested that iron supplementation may reduce symptoms of ADHD, and there is evidence that such supplementation is effective.90 Iron supplementation that leads to higher levels of blood iron is also associated with better performance on the Conners' Parent Rating Scale.91 In one study, researchers provided children with 80 mg of iron per day and found that this iron supplementation improved ADHD symptoms. According to this study, iron therapy was also well tolerated.92ding to this study, iron therapy was also well tolerated.92

Lemon Balm Extract
Lemon balm, or *Melissa officinalis* has been used as an anti-anxiety, sleep-inducing, and memory-enhancing nutrient for over 2,000 years.93 Human trials have provided scientific evidence for the impact of lemon balm, demonstrating its ability to improve mood, reduce stress, and help induce sleep.94–96 For instance, one study that investigated the impact of lemon balm extract on 20 stressed volunteers over a 15 day period found that anxiety was reduced in 70% of the study participants and insomnia was reduced in 85% of them.96 Given that ADHD patients often experience stress and suffer from a high rate of insomnia, lemon balm extract is likely a helpful supplement for these patients.

Melatonin
The role of melatonin, a pineal gland hormone, has been studied in patients who suffer from sleep disorders, including insomnia, delayed sleep onset, and nighttime awakening issues.97 One study showed that when children took melatonin supplements at bedtime, they were able to fall asleep faster and also experienced additional health and behavioral benefits. However, once the melatonin was discontinued, the children's sleep and behavioral problems returned.98 The positive effects of melatonin are corroborated by earlier trials in children with ADHD, which help to confirm that melatonin is effective in treating insomnia.99–101

Zinc sulfate
Zinc deficiency appears to contribute to the etiology of ADHD.104 Over the course of a 6 week double-blind study of 44 children previously diagnosed with ADHD, zinc sulfate supplementation, given as an adjunct to methylphenidate, improved ADHD symptoms.105 Other research on the impact of zinc on those with ADHD over an 8 week period suggests that a daily dose of 30 mg is effective in reducing the amount of amphetamine needed to treat ADHD and that this dosage is well-tolerated and safe.106

Crocus Sativus
There is evidence to suggest that crocus sativus, also known as saffron, can be beneficial to those with ADHD. Specifically, crocus sativus has been shown to be as effective as methylphenidate in improving ADHD symptoms over a 6

week period, as measured with the Teacher and Parent Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV).107,108

Omega-3 Fatty Acids
Omega-3 deficiencies have been observed in those with ADHD.109 Though the evidence related to the influence of omega-3s on ADHD is mixed, certain studies suggest that multiple types of omega-3 fatty acids may be effective in treating ADHD symptoms in youths.110 A 30 week study on omega-3 fatty acids demonstrated potential therapeutic effects on ADHD symptoms in children, particularly in those who are hyperactive-impulsive.111 Some of the specific benefits that have been observed by omega-3 supplementation in those with ADHD are improvements in hyperactivity, impulsivity, and attention, as well as cognitive effects including enhanced visual learning, reading, and memory.112
Omega-3 supplementation appears to enable the reduction of stimulant medication doses in those with ADHD.112,113 Given this impact and the safety profile of omega-3s, experts have suggested that omega-3 supplementation may offer a suitable alternative to pharmacological interventions in those with ADHD.114,115

Phosphatidylserine
Phosphatidylserine has been shown to improve ADHD symptoms in children, including symptoms related to cognition.116 Some research suggests that phosphatidylserine supplementation may be particularly effective for ADHD children who are emotionally and behaviorally dysregulated.111

Conclusion
Diagnosis and treatment are not as clear-cut with ADHD as they are with many other conditions. Treating ADHD has been criticized as being an inadequate substitute for good parenting and education. Critics claim that treatment medicalizes a psychosocial problem without curing the underlying cause and that the long-term effects of this treatment are thus limited – and that given the nature of many of the treatments, these treatments may even jeopardize the health of those diagnosed with ADHD.

There are also many people who believe that ADHD treatment and alteration of parenting styles are not mutually exclusive and that simultaneously pursuing both routes can help to achieve the best results for the children. For those who feel the need for a strategy that goes beyond behavioral modification, the treatment options can be overwhelming.

Choosing a treatment regimen is further complicated by social pressure and incomplete scientific information. Nonetheless, the science to support the value of nutraceuticals in the treatment of ADHD in both children and adults is growing. Not only can nutraceuticals be effective in improving ADHD symptoms, but they can help bypass the risks, such as addiction, as well as the unwanted side-effects associated with other treatment options.

I suggest that healthcare providers recommend to parents of minor children and to adults diagnosed with ADHD that they use a "cocktail" of the nutraceuticals discussed in this paper, either as an initial stand-alone therapy or adjunctively with prescribed medications. Given the risks associated with both stimulant and non-stimulant prescription drugs, there is good reason to attempt to control ADHD with non-prescription options before resorting to pharmaceutical methods.

Unless behavioral problems are extreme enough to constitute emergency intervention, a cocktail of nutraceuticals should be tested over a 3 to 4 month period. This duration should allow systemic levels of the included ingredients to rise to levels required for therapeutic effects. During the time that the cocktail is used, sleep patterns should also be tracked so that any improvements can be noted. In particular, falling asleep faster, staying asleep longer, and sleeping for at least 8 hours (for adolescents) or 9 hours (for younger children) are signs that sleep habits are improving in those with sleep disturbances.

If after 3 to 4 months of the nutraceutical cocktail, more benefits are desired, then starting a drug naïve ADHD child or adult on a prescription drug or adding a prescription drug to their previous regimen may be justified. Any time a new intervention is added, behavior should be tracked and documented to ensure that insights related to the impact of each intervention are captured. Collecting this type of data will enable those with ADHD to customize their treatment such that they can optimize their outcomes and manage their ADHD in accordance with their preferences.

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