Attention Deficit Hyperactivity Disorder (ADHD)

Clinically proven alternatives for treating inattention, hyperactivity, and impulsivity

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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 yperactivity.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. everal recent studies have shown that symptoms and impairments related to childhood ADHD can persist into adulthood, either wholly or partially.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 yperactivity, 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 on society.4 The Global Burden of Disease
Study in 2010 reported estimates of 26 million children and adolescents with ADHD worldwide and 491,500 disability-adjusted life years.5

Critics of the concept of ADHD claim that it is not a clear-cut psychiatric disorder but is instead a scapegoat for the 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. Importantly, 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 these diagnoses 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. Shockingly, only 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's 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 tends to be 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 recently 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 – WHAT ARE THEY
Stimulant drugs are the first-line therapy for ADHD for both

children and adults. Several studies indicate that these drugs, which include amphetamines, methamphetamines, 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 direct health risks as well as the risk for addiction, and because there is evidence that the extent of the side-effects is underestimated.19–21

Amphetamines and Methamphetamines

Amphetamines and the related stimulants, methamphetamines, achieve at least some of their effects on ADHD by boosting the transmission of both dopamine and norepinephrine in the prefrontal cortex.22,23 These drugs act directly on dopamine and norepinephrine transporters by serving as pseudo-substrates at the binding sites of these transporters.24 They also increase dopamine release that occurs in response to stimuli from the environment and enhance the release of catecholamines.22,24,25

Methamphetamines, known also by the trade names Desoxyn and Methedrine, are available as oral tablets that are generally taken once or twice a day. They are not widely prescribed and are only approved for use against ADHD and obesity.26

Compared to methamphetamines, there are many more prescription options for amphetamines, which come in immediate and extended release tablets, as well as in solution form. Two of the amphetamine brands that are available in both immediate and extended release form are Adderall and Dexedrine.

Adderall

Adderall and Adderall XR are immediate and extended release amphetamine medications, respectively.24 The immediate release Adderall is formulated with amphetamine as tablets, which are available in 5 milligram (mg), 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, and 30 mg doses. The extended release version, which combines amphetamine and dextroamphetamine, comes as a capsule, which may be 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg.

A meta-analysis of the use of Adderall has suggested that it can improve symptoms of inattention, hyperactivity-impulsivity, and aggression.27 However, some studies on the effect of Adderall have found that nearly one quarter of study participants given the drug did not respond to it.28 Additionally, the drug poses concerns related to psychological events like psychosis, slowed growth in children, and substance abuse in adolescents and adults.29

Dexedrine

Dexedrine, a dextroamphetamine tablet formulation, is an immediate release amphetamine, and Dexedrine SR, an amphetamine capsule, is an extended release option.24 Both forms have 5 mg and 10 mg formulations, and Dexedrine SR also has a 15 mg option.

Research has indicated that Dexedrine is not prescribed as frequently as other ADHD medications. Nonetheless, comparative studies have shown that it can be as effective as other medications in treating symptoms of ADHD but also suffers some of the same limitations.30

Other Immediate Release Amphetamines

Some amphetamine brands are only available as immediate release medications.24 These include Evekeo, Dextrostat, and Zenzedi, all of which are offered as 5 mg and 10 mg tablets, as well as Procentra, which is a 5 mg/milliliter (mL) solution. Zenzedi has additional 2.5 mg, 7.5 mg, 15 mg, and 20 mg options as well.

Each of these immediate release amphetamines has been shown to improve ADHD symptoms.31 There are data suggesting that these drugs can be well-tolerated and that their efficacy can last throughout the day.32,33 Nonetheless, these drugs are also associated with some adverse side effects, such as anxiety, reduced appetite, headache, irritability, and abdominal pain.32,34

Other Extended Release Amphetamine Drugs

As with immediate release amphetamine therapies, there are also brands that offer only extended release options.24 Adzenys XR is an amphetamine formulated as an orally disintegrating tablet, which comes in the following mg doses: 3.1, 6.3, 9.4, 12.5, 15.7, and 18.8. Dyanavel XR is offered as a 2.5 mg/ML suspension, and Vyvanse – the only U.S Food and Drug Administration (FDA) approved lisdexamfetamine – comes in capsules that differ by 10 mg and range from 20 mg to 70 mg.

These drugs have been shown to reduce symptoms of ADHD in children, even as young as preschool age. They have also been shown in certain studies to be well-tolerated.35,36

Methylphenidate

Methylphenidate is another stimulant used to treat ADHD, and it blocks the reuptake of both dopamine and norepinephrine. More specifically it works on central adrenergic brain cells by inhibiting presynaptic dopamine transporters, enhancing the concentration of dopamine in the synaptic cleft and thus increasing dopamine neurotransmission.23 The drug has a similar action on the norepinephrine system, but its influence is not as strong as it is on the dopaminergic system.24

As is the case with amphetamines, methylphenidate drugs are offered in both immediate release and extended release formulations.37 The brands Ritalin and Methylin offer both types of formulation. The brand Focalin offers a formulation of dexmethylphenidate, which is similar to methylphenidate, in both immediate release and extended release varieties. The immediate release is available in 2.5 mg, 5 mg, and 10 mg tablets, and the extended release comes in capsules of 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg. The drug is also provided through a transdermal patch with the brand name Daytrana.38,39 The patch initially administers 10 mg of methylphenidate each day but can be titrated to 15 mg, 20 mg, and 30 mg doses.

Ritalin

Ritalin, which is the most recognizable methylphenidate brand, comes in immediate release tablets that may be 5 mg, 10 mg, or 20 mg. The extended release medications, Ritalin SR and Ritalin LA, come in a 20 mg tablet or a capsule that can be 20 mg, 30 mg, or 40 mg.24

Ritalin appears enhance cognitive performance by modulating neuronal activity in brain networks involved in attention.40 Though it may be sufficient to achieve certain outcomes in ADHD patients, it should be noted that it is not necessary. For instance, a recent study showed that while combining non-pharmacological with Ritalin in children with ADHD more efficiently improved behavior, the non-pharmacological approaches alone were also effective.41

Though Ritalin has held a place as a mainstay treatment for ADHD, there is significant tension in the medical community around its use.42 Of particular concern is the potential for substance abuse. As Ritalin prescribing frequency has increased, so too has abuse of the drug.43 When taken intranasally, the effects of Ritalin are much like those of cocaine, in terms of both their type and their rapid onset.

Methylin

Methylin tablets are offered as both immediate release and extended release medications in 10 mg and 20 mg doses. Immediate release options also include a 5 mg tablet, chewables that comes in 2.5 mg, 5 mg, and 10 mg doses, as well as a solution offered in 5 mg/mL and 10 mg/ML doses.24 Given that methylin is another formulation of methylphenidate, its risks and limitations mimic those of Ritalin.

Other Extended Release Methylphenidate Drugs

There are several other methylphenidate brands that offer only extended release formulations. These include Metadate ER, Metadate CD, Quillivant XR, Quillichew ER, and Concerta. These extended release drugs have been shown to reduce symptoms of ADHD in children and adolescents.44,45 Data suggest that these medications can combat symptoms in the morning, afternoon, and evening, and that they may be well-tolerated.46 Though these drugs are similar to Ritalin, it is generally assumed that they are less likely to be abused or suffer from dosing limitations because of their extended release nature.47

STIMULANT DRUGS – WHAT ARE THE RISKS?

Psychosis

While each stimulant drug carries its own risks, all stimulants increase children's likelihood of experiencing psychosis and other psychiatric challenges.48 In addition, stimulants have been associated with the development of stuttering,49 and new data show that these drugs affect the brain development.50

Somatic Disease

In addition to psychiatric diseases, stimulants likely contribute to the heightened risk amongst those with ADHD for other somatic diseases.51 Indeed, psychostimulants used to treat ADHD have been shown to increase both heart rate and blood pressure.52 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.

Whereas some of those with ADHD diagnoses are known to abuse stimulant drugs, 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.53,54 On the contrary, an ADHD diagnosis is a risk factor for substance abuse in adults. Other psychiatric conditions increase this risk. New data also show that childhood methylphenidate use increases the likelihood of using antidepressants in adolescence.55

Tolerance

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.56–58 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 ADHD patients who have never taken medication for their disorder.57

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 most 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.59

Eating Disorders and Insomnia

Also problematic is that most of the efficacious (higher dose) psychostimulants are associated with anorexia, weight loss, and insomnia.58,60 In children with ADHD, higher doses of methylphenidate are associated with parent ratings of increased insomnia and decreased appetite.61 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.62

Poorer School Performance

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.63–67 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, 63–67 making them potentially more credible.

A recent study in Europe examining the treatment emergent adverse events (TEAEs) in children and adolescents with ADHD using amphetamine drugs found that 89% of the participants reported TEAEs, with nearly 1 in 10 participants experiencing a serious TEAE.68 Those 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, and 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.69 It is therefore important to consider the underlying reasons for this distinction in amphetamine prescription rate for ADHD and what insights can be gleaned from comparative analyses of the relevant outcomes.

NON-STIMULANT DRUGS

In cases where the person with ADHD or their family members do not want to pursue stimulant drugs as a treatment option, or where stimulant drugs are contraindicated, poorly tolerated, or do not invoke an adequate clinical response, non-stimulant drugs may be prescribed. These drugs tend to work via presynaptic mechanisms related to catecholaminergic system.70 Atomoxetine (ATX), guanfacine (GXR), and clonidine are three non-stimulant drugs that have been approved by the FDA for the treatment of ADHD. These drugs are also known by their trademark names: Strattera, Intuniv, and Kapvay, respectively.71 In addition to these non-stimulant drugs, people with ADHD are also sometimes prescribed medications that are conventionally used for depression.

Strattera

Strattera, which is a selective norepinephrine reuptake inhibitor, was the first nonstimulant 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. Dosing is variable, but the maximum daily dose for children and adolescents weighting up to 70 kilograms (kg) that is approved by the FDA is 1.4 mg/kg. For anyone weighting over 70 kg, the approved dosage is up to 100 mg per day.72 Though 80 mg per day has been recommended for adults with ADHD, actual use by people with a prescription for Strattera appears to be, on average, about 60 mg per day.73

This drug has been shown to reduce ADHD symptoms within the first week of treatment.72 This non-stimulant drug is also associated with improved morning and evening behavior related to ADHD in children. Another benefit of Strattera is that, unlike stimulant drugs, it does not have positive reinforcing effects and so is not associated with addiction.74

Though the mechanism of action of Strattera is unclear, Strattera is known to be highly selective for and have high affinity to norepinephrine transporters and have been shown to suppress the uptake of norepinephrine.75 It is therefore generally thought that its effects in patients with ADHD relates to its ability to increase levels of norepinephrine in the prefrontal cortex.

Strattera 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.72

Intuniv

Sometimes used in combination with Strattera, Intuniv is a selective adrenergic-receptor agonist in an extended release formulation.76 Like Strattera, it is also indicated as a monotherapy but only for youths aged 6 to 17. However, a recent randomized, double-blind, placebo-controlled trial published in the *Journal of Clinical Psychiatry*, showed for the first time that guanfacine extended-release significantly improved ADHD symptoms in adults and that the drug tended to be safe.77

In this study, 101 adult ADHD patients were given titrated doses of the drug starting at 2 mg per day and moving to 4 mg and 6 mg per day, while 100 adult ADHD patients were given placebo. After 5 weeks of dose optimization, drug doses were tapered. Patients who took the guanfacine extended-release displayed significantly greater improvements in the Japanese version of the ADHD-Rating Scale-IV than did those taking placebo. These improvements were seen in overall scores as well as in sub-scores on inattention and hyperactivity.

Though Intuniv has been shown to improve ADHD symptoms in in both the morning and evening,78,79 there have been no studies that directly compare the efficacy of Intuniv to other active treatments, and indirect analyses provide inconsistent views on the relative efficacy of Intuniv.80 Additionally, studies have shown that Intuniv does not successfully overcome certain symptoms of ADHD, such as impulse control.81

It may be the case that the value of Intuniv derives from its superior effects in specific contexts. For instance, some data suggest that Intuniv may help children with co-morbidities like chronic tic disorders or oppositional symptoms who have not been responsive to other treatments.82

This drug, which is available in 1 mg, 2 mg, 3 mg, and 4 mg tablets, appears to work by stimulating postsynaptic adrenergic receptors and enhancing signaling of pyramidal neurons of the prefrontal cortex.70,83 The result of this modification to neural activity is often improved memory and attention.

In addition to questions over the efficacy of Intuniv, it is also unclear how safe the drug is. While some studies have found Intuniv to be well-tolerated,78 with the most commonly reported adverse side-effects being fatigue and headache,84 other studies have identified more concerning undesirable side-effects, including hypotension, sedation, and bradycardia, and found that these side-effects are common.80

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

Kapvay

Kapvay 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 Kapvay ADHD in the medical literature, the data thus far suggest that Kapvay is associated with mproved sleep duration, and like other non-stimulant drugs, Kapvay may be well-tolerated.85

An alpha-2 adrenergic agonist, Kapvay is thought to influence ADHD symptoms by enhancing noradrenergic sympathetic transmission and thereby improving functioning in areas of the prefrontal cortex that are critical for attention and behavior.86 While Kapvay can improve certain symptoms of ADHD, it is also associated with side effects, the most common of which appears to be somnolence.87 ADHD is also associated with headache, hypotension, bradycardia, and clinically significant changes in electrocardiographic results.86 The drug is available as 0.1 mg tablets.88

A recent study showed that the primary driver for prescribing this drug over other ADHD medications was its cost-effectiveness. The second most common reason this drug was prescribed was because the patient had a history of seizures, which is a contraindication for methylphenidate.89 Interestingly, the authors of this study found that nearly one quarter of all children who took this non-stimulant medication experienced sedation, which may account for what in other studies has been interpreted as improved sleep duration. Withdrawal syndrome is also common for those who abruptly stop taking Kapvay. Withdrawal has been observed in up to 80% of these cases.90

Antidepressant Drugs

Though they have been shown to be less effective than stimulant medications in treating ADHD symptoms like those related to attention and cognition, antidepressants are sometimes used to address hyperactivity and impulsivity in ADHD patients and likely achieve at least some of their effects via their influence on the dopamine system .91 In the case that antidepressants are prescribed, the patients are likely to be refractory to stimulant drugs.92 While antidepressants are limited in what they can do for ADHD patients, they also pose the same risks that they do for patients who take them for depression.

NON-PHARMACOLOGICAL 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.93,94

According to a 1999 survey, parents of 64% of children with ADHD chose non-prescription alternative medicine treatments to address their children's ADHD.95 Research shows that alternative therapies are as effective as prescription drugs, with a slight trend towards more effective results in the non-prescription group.95,96 Alternative therapies are discussed below.

Sleep

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.97,98 Indeed, healthy sleep patterns are crucial to successful long-term ADHD intervention and overall long-term health as well.

Technology

Though alterations to sleep and dietary intake appear to be the most promising non-pharmacological ways to improve ADHD symptoms, new technologies are also being developed to address the disorder. For instance, a new device aimed at helping those with ADHD by delivering low-level electrical pulses to targeted areas of the brain, has recently been approved by the FDA.99

There has been a wealth of research on the impact of dietary ingredients on different aspects of ADHD and related symptoms. New data have shown that when children with ADHD are treated with micronutrients or medication, ADHD symptoms improve. However, unlike with medication, children using micronutrients to address their ADHD symptoms do not experience deteriorations in their moods and anxiety.100

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.69

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 improvements in memory-impaired adults.101,102 Recent research has shown that the substance can provide neuroprotection and improve cognitive deficits.103,104 Indeed, its impact on Alzheimer's disease pathology has led researchers to suggest that it may contribute to an effective drug treatment for Alzheimer's and other forms of dementias.105,106

In one study, 31 children previously diagnosed with ADHD were given 225 milligrams (mg) of Bacopa monnieri extract daily fora 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.67,107

A new and comprehensive literature survey has helped to clarify these beneficial impacts of Bacopa monnieri. Bacopa monnieri appears to work through several signaling pathway to mitigate harmful oxidative stress.108

Magnesium Alone and Magnesium – Vitamin B6 Combinations

Magnesium levels are demonstrably lower in children diagnosed with ADHD, as evidenced by measures of magnesium collected from the hair, nails, and blood serum of these children.58 Indeed, recent meta-analyses based on exhaustive literature reviews corroborated this point.109,110 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.111 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.

Recent research into the role of nutrition on ADHD has also shown that magnesium appears to influence the gut microbiome in a way that could impact ADHD symptoms.112 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.111,113–115 These findings are perhaps unsurprising given that disorders of vitamin B6 metabolism are common among those with ADHD.116

Data shows 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.114 One study on 40 children with ADHD showed that 8 weeks of a magnesium-B6 regimen reduced ADHD symptoms including hyperactivity, aggressiveness, and inattention.114 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.115

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.117 This study was the first to compare vitamin D receptor levels in those with and without ADHD. More recent research has also suggested that vitamin D may impact ADHD through its effects on dopamine levels.118

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.119 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.120 Another recent study showed that vitamin D supplementation also improves ADHD symptoms without serious adverse side effects in those who also take methylphenidate for their ADHD.121

L-Theanine

L-Theanine is an amino acid that is present in significant amounts in green tea. This compound has been found to have a calming effect and is used to improve cognitive and mental performance.122,123 Alpha-wave predominance in the brain is

associated with a state of relaxation, and people experience a shift toward more alpha-wave production within 40 minutes of taking 50 to 200 mg theanine doses. The effects appear to last up to eight hours and are dose-dependent.124,125 A double-blind, placebo-controlled study on boys diagnosed with both ADHD and sleep disorders also demonstrated that L-theanine significantly increases sleep efficiency as well as time spent asleep.126

Grape Seed Extract

Grape seed extract is one of the most potent antioxidant extracts from plant sources, even more potent than pine bark extract,127 providing, for instance, excellent protection against oxidative stress and free radical-driven tissue injury.128

Grape seed is highly bioavailable and provides greater protection against free radicals and damage to cell membranes and DNA than vitamins C and E, when the vitamins are taken individually or 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.129

Children diagnosed with ADHD demonstrate higher levels of lipid peroxides than do controls and are at greater risk for developing cardiovascular disease.130–132 Potent antioxidants like grape seed extract that provide protection against excessive oxidative stress and cardiovascular risk factors are therefore likely to be beneficial for those with ADHD.133,134

Vitamin C

Vitamin C is the most prevalent water-soluble antioxidant in the human body.135 It inhibits the first step in developing coronary artery disease - LDL-cholesterol oxidation - and plays a major role in other protective mechanisms against heart disease, such as lowering C-reactive protein.135 Vitamin C may therefore help to mitigate the enhanced cardiovascular risks that ADHD patients experience.135–137 Because humans cannot synthesize vitamin C, they must get this critical vitamin from their diets.136,137 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.138 Children with more severe iron deficiencies are more likely to also experience more severe ADHD symptomology,139 and iron deficiency in infancy has been shown to be predictive of social and behavioral problems in adolescence.140 Lower serum ferritin levels are correlated with more severe ADHD symptoms as measured by the Conners' Parent Rating Scale.141 Iron deficiency has not only been observed in children with ADHD but has also been shown to be higher in adults with ADHD than in those without the disorder.142 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.143

Based on these findings, it has been suggested the iron supplementation may reduce symptoms of ADHD, and there is evidence that such supplementation is effective.144 Iron supplementation that leads to higher levels of blood iron is also associated with better performance on the Conners' Parent Rating Scale.145 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.146

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.147 Human trials have provided scientific evidence for the impact of lemon balm, demonstrating its ability to improve mood, reduce stress, and help induce sleep.148–150 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.150 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.151 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.152 Further, once the melatonin was discontinued, the children's sleep and behavioral problems returned 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.153–155

Zinc Sulfate

Zinc deficiency appears to contribute to the etiology of ADHD.156 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.157 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.158

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 through double-blind randomized trial data 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).159,160

There is an abundance of primary data, as well as evidence from large meta-analyses that saffron can positively affect symptoms of depression and anxiety.161–166 In addition, research has shown that saffron can exert benefits that are comparable to anti-depressant drugs without the unwanted side effects associated with the pharmaceuticals.167,168 Given the significant comorbidity of ADHD and depression – and the apparently high risk for depression amongst young people with ADHD - saffron may be particularly useful for ADHD patients experiencing both classic ADHD symptoms as well as depressive symptoms.169–173

Omega-3 Fatty Acids

Omega-3 deficiencies have been observed in those with ADHD.174 Even maternal consumption of omega-3 fatty acids has been implicated in the disorder.175 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.176 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.177 Some of the specific benefits that have been observed with omega-3 supplementation in those with ADHD are cognitive effects, including enhanced visual learning, reading, and memory, as well as improvements in hyperactivity, impulsivity, and

attention.178

Omega-3 supplementation appears to enable the reduction of stimulant medication doses in those with ADHD.178, 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.180,181

Phosphatidylserine

Phosphatidylserine has been shown to improve ADHD symptoms in children, including symptoms related to cognition.182 Some research suggests that phosphatidylserine supplementation may be particularly effective for ADHD children who are emotionally and behaviorally dysregulated.177

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. They argue that many of 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 to 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. This notion is consistent with expert guidelines that recommend a stepwise approach to ADHD treatment that begins with non-drug interventions.170

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 be sufficient for achieving systemic levels of the included ingredients that are required for a therapeutic effect. 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 of healthier sleep habits.

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 a 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 these types 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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