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REVIEW ARTICLE

Micronutrient Deficiencies in ADHD: A Global Research Consensus

Author(s): James M. Greenblatt, MD[1]; Desiree D. Delane [1]

[1] Walden Behavioral Care, 9 Hope Avenue, Suite 500, Waltham, MA, 02453

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Introduction

Clinical diagnoses of Attention Deficit Hyperactivity Disorder (ADHD) in children, adolescents, and adults have grown remarkably over the last fifty years. Officially recognized in the United States as a medical condition in 1968 by the Diagnostic and Statistical Manual for Mental Disorders (DSM) for the primary symptoms of inattention, hyperactivity, and impulsivity in children, ADHD has gradually spread around the world to reach even underdeveloped nations with equally significant prevalence (Conrad & Singh, 2018; Scheffler et al., 2007). At the same time, diagnostic criteria have been further expanded and specified for adolescents and adults with the acknowledgement that ADHD persists throughout the lifespan (Epstein, 2013). Currently, eighteen core symptoms describe at least forty attention-related behavioral disorders, and dynamic DSM criteria evolve with efforts to categorize the nebulous condition (Epstein, 2013). Globally, ADHD prevalence is estimated at 9.5% for children and adolescents and almost 3% in adults (Doshi et al., 2012; Fayyad et al., 2017).

Until the 1990s, international diagnosis and treatment of ADHD was uncommon. Rapid growth and spread of technology and communication channels, particularly in the healthcare and pharmaceutical industries, introduced Western psychiatry to almost every corner of the globe, contributing to the medicalization of ADHD and other mental health issues (Conrad & Singh, 2018). Estimates for the economic costs of ADHD range from $140 to $260 billion in the US alone, including additional education and medical care for children and loss of productivity and income in adults (Doshi et al., 2012). Adult ADHD is highly comorbid with medical and mental health conditions, generating further individual and public health costs with significant social ramifications (Fayyad et al., 2017). Long-term, individuals with ADHD attain fewer academic achievements, earn lower incomes, and have less-successful relationships (J. R. Galler et al., 2012).

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Variations in global ADHD reports are primarily attributed to distinct cultural differences in recognizing, acknowledging, and diagnosing behavioral symptoms (Hinshaw et al., 2011). Yet the pervasiveness of ADHD across age, gender, time, and ethnicity imply common risk factors influencing its pathology. Research consensus points to genetic, environmental, and social contributors to risk. More controversial assessments indicate that vitamin and mineral deficiencies may also play a prominent role (Khan, 2017). Although highly complex and variable, data suggests several diet-related factors that overlap and interact to influence ADHD symptoms, including chronic inflammation, oxidative stress, neuroplasticity, mitochondrial dysfunction, and microbiome profile. A bi-directional relationship between dietary quality and mental health risk is evident, and there is little doubt that nutrition serves a significant role in brain health (Marx, Moseley, Berk, & Jacka, 2017; Rodriguez, 2017).

Malnutrition and Long-Term Outcomes of ADHD

Ongoing scientific research in laboratory and clinical settings demonstrates that ADHD pathology primarily involves dopaminergic and noradrenergic systems, implying a key role for the micronutrient cofactors that help to synthesize and regulate these neurotransmitters. Furthermore, data informing DSM criteria recognize distinct neurobiological and genetic profiles involving specific regions of the brain (Epstein & Loren, 2013). ADHD is marked by behavioral symptoms that reflect neurochemical imbalances. In addition to nutrition, genetics, environmental, and social exposures, developmental conditions before and after birth may predispose an individual to ADHD. Epigenetic pressures during these critical periods of development induce lasting physiological changes (Greenblatt, 2017b). The continuum of ADHD symptoms and impairments suggests that epigenetic influences create unique needs or excesses producing neuropsychological disruption (Epstein & Loren, 2013).

Janine Galler made enormous contributions to the study of malnutrition's long-term effects on behavior. Beginning in 1967, Galler followed 129 children born healthy and at normal birth weight who then experienced severe protein-energy restriction in their first year of life (Galler, et al., 1983). Follow-ups over the next forty years consistently reflected the adverse effects of malnutrition in early life on intelligence quotients (IQ), with academic, vocational, and social impacts. Ongoing assessment of the participants' surrounding environments established that maternal, prenatal, and postnatal factors overruled current conditions to predict IQ and behavior. Although physical growth deficiencies corrected over time with proper nourishment, cognitive and emotional consequences persisted. Previously malnourished children showed a reduced ability to respond to stress and adapt to changing environments, symptoms that are commonly associated with ADHD (Galler et al., 2012).

The acute period of malnutrition experienced by Galler's study participants manifested in smaller brain volumes and fewer neural connections, resulting in language delays and sensory integration (Galler et al., 1983). Behavioral outcomes in 60% of individuals included problems with attention, memory, and restlessness affecting school performance during childhood, and resulting in reduced academic and vocational achievement, lower socioeconomic status, and contributing to greater comorbidity with mood disorders and substance abuse patterns in adulthood. ADHD symptomology in childhood and adolescence persisted into middle-adulthood; 69% of the eighty remaining 40-year-old participants had clinical ADHD symptoms, implying permanent neurological compromise occurred during the critical first year of postnatal brain development (Galler et al., 2012).

Findings from Galler's study of the long-term impacts of malnutrition and persistent ADHD symptoms have been supported by more recent international research investigations. Walker, et al, followed 129 Jamaican children with stunted growth for over ten years and reported poor psychological function in adolescence, including greater hyperactivity, anxiety, depression, and poorer self-esteem (Walker, et al, 2007). A 2009 World Health Organization mental health survey of over 600 adults from the Americas, Europe, and the Eastern Mediterranean demonstrated that inappropriate and irresponsible behaviors in adulthood were predicted by attention problems in adolescents. More than half of the participants continued to meet DSM diagnostic criteria for ADHD, independent of both age and gender (Galler et al., 2012).

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Global malnutrition remains a significant issue, requiring speculation that it is related to the growing prevalence of ADHD. Poor nutritional status in children with ADHD has been shown in studies around the world. A major review of 50 years of United Nations data by Beal, et al, reported that approximately 11% of the global population is undernourished despite increases in per capita energy availability (Beal et al., 2017). A 2017 dietary comparison in Japan between 54 children with ADHD and healthy controls indicated that over 50% had suboptimal nutrition compared to 11% of typically developing children, and that 11% of ADHD children showed muscle wasting, indicating severe malnutrition (Sha'ari et al., 2017). Both diet quality and intake are factors in micronutrient deficiencies. In fact, while developing countries primarily experience deficiencies due to inadequate food intake, some micronutrients are lacking as a result of poor diet quality in high-income nations such as the United States (Beal et al., 2017).

Public health outcomes following the implementation of national food fortification programs and results of micronutrient supplement trials lend further support for the role of nutrition in reducing mental illness. As of 2011, fortification of food supplies, particularly in developing countries, has dramatically lowered malnutrition rates and micronutrient deficiencies from 27% to 14%. Notably, low zinc, magnesium, and iron status, often associated with ADHD, are significantly improved through both increased dietary quantity and quality (Beal et al., 2017). Many studies have demonstrated improved cognition, mood, and behavior in both children and adults treated with micronutrient supplements (Gordon et al., 2015; Rucklidge et al., 2011).

Growing Use and Reliance on Pharmacology

ADHD medications are a global boon, with prescription rates and spending around the world rising three- and nine-fold, respectively, since the 1990s. Indeed, use of these medications is directly correlated with national GDP, reinforcing the profitable medicalization of ADHD (Scheffler et al., 2007). With the US taking the lead in medication use, Europe has quickly followed suit, with prescriptions rising between 10% and 300% (Bachmann et al., 2017; Furu et al., 2017). Standard care involves a cascade of consensus in which a spectrum of symptoms and situations is neatly lumped under a subjective umbrella and treated with a few lucrative drugs (Hoffer, 2008). Despite an all-time high of psychiatric drug treatments, a multitude of research shows that current ADHD medications are ineffective in at least half of patients (Marx et al., 2017; Rodriguez, 2017).

Typical pharmacological treatment of ADHD involves stimulant- and non-stimulant-based drugs, and are often combined or exchanged in attempts to optimize dose while minimizing side effects. In addition to limited efficacy, side effects of ADHD drugs are often serious and disruptive, requiring continuous experimentation and often resulting in discontinuation (Catala-Lopez et al., 2017; Rosen, 2017). A systematic review by Hennissen, et al, reported that both stimulant and non-stimulant drugs significantly increase the risk for cardiovascular events in children adolescents (Hennissen et al., 2017). ADHD patients of all ages are commonly prescribed multiple medications to manage side effects or comorbid conditions, creating a vicious cycle of drug and side effect management (Winterstein, 2017). Overdose and substance abuse are frequent, especially among adolescents and adults, with profound social consequences (McCabe et al., 2017). Developmental effects on children and their long-term outcomes in adults are topics that continue to draw considerable attention from both professionals and patients, underlying the importance of evaluating and balancing the potential benefits and harms of these substances (Catala-Lopez et al., 2017; Karlstad et al., 2016).

Concerns and debates over the ethical and social consequences of pharmacology use in ADHD continue unabated (Singh et al., 2013). Limited efficacy and debilitating side effects of current drug treatments for ADHD call for specific, objective diagnostic markers and more precisely targeted treatment strategies. Large variations in diagnosis and prescription rates, environmental risk factors, healthcare training and clinical practices, and cultural beliefs across the world require ecological sensitivity and new perspectives in identifying and managing behavioral disorders (Singh et al., 2013). The "substitution principle" maintained in the Swedish healthcare system legally requires the priority use of safer substances. With overwhelming support for the role of diet in physical and mental health, it is worthwhile to prioritize nutrition and call upon orthomolecular theories with a deep history of success to address the global impact of ADHD (Hoffer, 2008).

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Orthomolecular Approaches and Nutritional Psychiatry

Artificial criteria for diagnosing ADHD that lead to subjective, automated conclusions and ineffective, unsuccessful interventions call for a rejection of universal treatment models. Not only do symptoms vary widely between individuals, they are often fluid over time within the same individual (Epstein & Loren, 2013; Hoffer, 2008). Expanding global prevalence of ADHD and evidence for poor nutrition worldwide strongly reinforce the relationship between diet and brain function that has been a concentrated area of research in the 21st century (Logan & Jacka, 2014). New discoveries are leading to novel perspectives in psychiatry, shifting conventional paradigms and recommending methods once considered “alternative” (Sarris et al., 2015). Orthomolecular approaches to medicine and psychiatry have produced reliable clinical evidence for decades that has either been ignored or concealed (Hoffer, 2008).

Global research across diverse environments and cultures recognizes that diet is a modifiable risk factor in the prevention of physical and mental illness (Marx et al., 2017). Sarris, et al, boldly suggest that nutrition is “as important to psychiatry as it is to cardiology, endocrinology, and gastroenterology”, endorsing dietary augmentation with selected nutrient-based supplements to address deficiencies implicated in neuropsychopathology (Sarris et al., 2015). William Kaufman, a notable pioneer of vitamin therapy, demonstrated in thousands of clinical trials over 50 years that carefully selected supplements, even at high doses, are safe and effective for improving health and well-being in most individuals. He proposed that even healthy individuals likely do not receive adequate micronutrients from food and water alone (Benton, 1992; Kaufman, 2007; Popper, 2017). Variable growing conditions, locations, storage, and processing of foods can have profound impacts on nutrient content, and personal intake, digestion, metabolism and utilization determine individual needs. Chronic, low-level micronutrient deficiencies are likely at the root of many degenerative diseases (Kaufman, 2007).

Although virtually all vitamins and minerals play essential roles in determining brain health, magnesium, zinc, copper, iron, and Vitamin B6 appear to have substantial effects on ADHD symptoms (Khan, 2017; Zhou et al., 2016). Either deficiencies or excesses of these naturally-occurring substances affect brain areas that influence neurotransmitter control over behavior, mood, and intelligence (Benton, 1992). Oxidative damage by lead and other neurotoxins also deserve attention and recommend specific antioxidant nutrients such as vitamin C that provide protection (OMNS, 2007). The proposed biological mechanisms underlying ADHD and other mental health conditions have directed promising international research with both single-nutrient and broad-spectrum nutrient supplements. Data provides ample support for psychiatrists and other mental health professionals to adopt individualized nutritional strategies to successfully treat ADHD (Gordon et al., 2015; Rucklidge, 2017).

Neurotoxicity, Micronutrient Deficiency, and ADHD

While a host of causes are likely to produce the brain chemical imbalances and abnormalities linked to ADHD symptoms, toxic exposures and inadequate detoxification systems are likely considerable factors (Brown, 2016). An exceptionally high metabolic rate and concentration of lipids in the brain make it particularly vulnerable to oxidative damage and increase its demand for protective nutrients. Acute or cumulative exposures to environmental and dietary-sourced toxins during gestation, early childhood, and throughout life have been shown to substantially impact brain integrity. Toxicity from heavy metals, household and industrial chemicals, tobacco smoke, and pesticides has been strongly linked to behavioral problems and ADHD in children through disruption of hormones and nutrient metabolism (Slotkin, 2004). Brain imaging studies provide incontrovertible evidence, displaying structural damage and cell death of dopaminergic and cholinergic neurons (Yolton et al., 2014). More disturbingly, similar damage and adverse effects have also been linked to ADHD stimulant medications (Advokat, 2007).

A sufficient diet providing appropriate protein, carbohydrates, and fats promotes the brain’s structure and energy production, yet micronutrients, even in minute amounts, are critical for balancing neurochemicals and transmitting signals correctly. Additionally, detoxification pathways throughout the brain require adequate vitamin and mineral cofactors to protect and repair neurons from the oxidative effects of normal metabolism as well as from heavy metals and other neurotoxins (OMNS, 2007). Individual micronutrient status is also highly reactive to bioavailability and the

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presence of “anti-nutrients” that inhibit absorption. Establishing or restoring chemical homeostasis and facilitating optimal neurotransmission may require concentrated and purposeful nutrient provisions.

Some evidence suggests that broad-spectrum supplements have proven superior over single-nutrients in the treatment of ADHD and other psychiatric conditions. Three randomized-controlled trials in children, adolescents, and adults with ADHD suggested that a comprehensive vitamin and mineral supplement reduces aggression, hyperactivity, impulsivity, inattention, and depression with effects comparable to conventional pharmacology and with fewer side effects (Popper, 2017). Another recent double-blind, placebo-controlled trial in 80 adults by Rucklidge, et al provided further support for the efficacy and safety of broad-based nutrient supplements, reporting significant symptom reductions in 64% of treated participants (Rucklidge et al., 2017). Nevertheless, count orthomolecular treatments with targeted, high-dose micronutrients based on individual biomarkers encourage the use of more precise methods (Kaufman, 2007; Marx et al., 2017).

Zinc and Copper

Zinc deficiency represents one of the most-recognized micronutrient deficiencies linked to ADHD symptoms. With key roles in enzyme activation and neurotransmitter synthesis, zinc is critical for regulation of dopamine, norepinephrine, serotonin, and gamma aminobutyric acid (GABA). Globally, zinc deficiency is a significant concern; at least 17% of the world’s population is at risk, and research suggests that levels of zinc in the food supply may be inadequate to supply needs. Stunted childhood growth in developing countries is considered an epidemiological measure of zinc deficiency, with significant implications for brain development (Wessells & Brown, 2012). Neurotoxins also contribute to zinc deficiency, as byproducts of plastic degradation bind and deplete zinc stores (Greenblatt, 2017a).

Ample evidence confirms a direct correlation between ADHD symptom severity and low blood and hair levels of zinc. In the Slovak Republic, plasma zinc levels in 58 children age six to fourteen were significantly lower than health controls, and were associated with parent and teacher ratings of inattention (Viktorinova et al., 2016). Dietary and nutrient patterns of roughly 300 Chinese children with ADHD demonstrated a highly-significant dose-response relationship between blood zinc and risk of ADHD, suggesting zinc level as a reliable biomarker (Zhou et al., 2016). Supplemental zinc as monotherapy or adjunctive therapy has been shown to normalize brain waves and improve memory and information processing (Yorbik et al., 2008). Children given zinc supplements also show improvements in hyperactivity, impulsivity, and social engagement (Bilici et al., 2004). Furthermore, zinc supplements may increase the effectiveness of ADHD stimulant medications, lowering the necessary dose and reducing side effects (Arnold et al., 2017).

Zinc also plays an essential function in regulating copper levels. While trace amounts of copper are necessary for dopamine and norepinephrine synthesis, excess concentrations can lead to over-excitation by these neurotransmitters and contribute to hyperactive ADHD symptoms. The copper-to-zinc ratio is critical, and like zinc, is inversely correlated with risk of ADHD (Viktorinova et al., 2016). Excess copper and imbalanced copper-to-zinc ratios are linked to elevated levels in drinking water through leaching of copper pipes (Greenblatt, 2017). Neurotoxic levels of copper in plasma and hair samples from children and adults with ADHD reveal adverse effects on mood, attention, and memory (Kicinski et al., 2015; J. Rucklidge, Taylor, & Whitehead, 2011). In addition to inhibiting the beneficial properties of zinc, copper can also reduce antioxidant capabilities and reduce the effectiveness of conventional and supplemental ADHD treatments (Greenblatt, 2017a).

Magnesium

Possibly the most crucial micronutrient for optimal brain performance, magnesium participates in virtually all enzyme reactions, nerve signal conduction, and in the function of dopamine and serotonin receptors. Magnesium also plays a key role in the excitation status of nerves through inhibition of excitatory glutamate receptors and promotion of GABA reception (Greenblatt, 2017). Deficiency of magnesium is identified in almost all cases of ADHD, and is widespread even in healthy populations (Moshfegh, A. et al., 2009). Poor-quality diets and high consumption of processed foods that are stripped of nutrients contribute to inadequate magnesium intakes in many developed countries. Furthermore,

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the bioavailability of magnesium is limited to approximately 30-40% (Greenblatt, 2017). Globally, at least a third of the population is estimated to be deficient (Hruby & McKeown, 2016). Low magnesium is significantly correlated with IQ and all ADHD symptom domains in addition to comorbid anxiety and depression (Starobrat-Hermelin & Kozielec, 1997).

Abundant clinical evidence promotes magnesium supplements as safe and effective for improving ADHD symptoms. Magnesium depletion of the food supply and its limited bioavailability suggest that supplement doses greater than current FDA daily requirements are necessary to impact brain function and produce clinical results. Significant decreases in hyperactivity were produced in 50 children with ADHD treated with 200 mg of magnesium for six months; symptom improvements were also accompanied by beneficial effects on sleep and anxiety with implications for behavior (Case, 2016). Supplements also containing vitamin B_6 increase the absorption of magnesium and show the greatest promise for reducing ADHD symptoms (Mousain-Bosc et al., 2006). Like zinc, magnesium may also be a successful adjunct therapy to conventional pharmacology. El Baza, et al, demonstrated that magnesium supplements reduced ADHD symptoms greater than medication alone (El Baza et al., 2016). Abundant support for the use of magnesium in ADHD has led some researchers to conclude that it should be a required component of ADHD interventions (Mousain-Bosc, M. et al., 2006).

Vitamin B_6

In addition to supporting magnesium metabolism, pyridoxine (vitamin B_6), as pyridoxal phosphate (PLP), has independently essential roles in the nervous system, energy production, neurotransmitter synthesis, heme production, and is critical for strong immune function and the inflammatory response (Ho et al., 2016; Rucklidge et al., 2017; Ueland et al., 2017). Often assessed by measuring tryptophan degradation, reduced activity of PLP-dependent enzymes reflects genetic errors involving vitamin B_6 and subsequent impairments in amino acid metabolism. In children with ADHD, reduced conversion of tryptophan to serotonin results in greater impulsive and hyperactive behaviors. Deficiencies of vitamin B_6, particularly during pregnancy, can significantly compromise brain development, nerve conductivity, and neurotransmitter regulation. In 2016, a Canadian study showed that at least 12% of healthy multi-ethnic women of child-bearing age had low PLP activity and B_6 status (Ho et al., 2016). The British Journal of Psychiatry recently reported that inadequate levels of B_6 predominate in adults with ADHD and were inversely associated with symptom severity (Landaas et al., 2016). Low vitamin B_6 status also predicts cognitive decline in older adults, emphasizing the vital need for this micronutrient throughout the lifespan (Moore et al., 2017; Porter et al., 2016).

Use of fortified foods and vitamin supplements containing vitamin B_6 is directly related to plasma levels, and food sources alone appear to be inadequate at supplying sufficient amounts of B6 and other B-vitamins (Moore et al., 2017). Supplemental pyridoxine in hyperactive children has demonstrated its ability to normalize serotonin and reduce disruptive behavior (Bhagavan et al., 1975; Coleman, M. et al., 1979). In combination with magnesium, Vitamin B6 supplements help to normalize red blood cell magnesium and therefore facilitate and moderate neurotransmission. The addition of magnesium may also lessen any potential adverse effects from pyridoxine supplements (Mousain-Bosc, M. et al., 2006). Importantly, vitamin B_6 also works synergistically with zinc to produce serotonin, recommending its incorporation in most ADHD treatment regimens in combination with zinc and magnesium (Zhou et al., 2016).

Iron

At appropriate concentrations, iron is another essential cofactor in the enzymatic production of serotonin, norepinephrine, and dopamine (Rucklidge et al., 2017). Most reliably assessed by serum ferritin, low iron status is a significant but heterogeneous risk factor for ADHD, independent of anemia diagnosis (Konofal et al., 2008). Iron stores are depleted with insufficient dietary intake as well as heightened inflammation (Wang et al., 2017). In individuals with insufficient serum ferritin, iron supplements show beneficial effects on ADHD symptoms without adverse side effects. Progressive improvements in ADHD symptoms similar to those achieved by stimulants were measured in children with low serum ferritin taking 80 mg of oral iron over 12 weeks (Konofal et al., 2008).

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Insufficient iron impacts cognitive, social, and emotional health as well as motor function through its role in neural signaling. Children in Uruguay with low iron status showed problems with cognition, attention, learning, and socialization (Barg et al., 2017). Evaluation of serum ferritin in 200 Turkish children and adolescents with ADHD, demonstrated that iron deficiency is most strongly related to hyperactivity symptoms (Percinel et al., 2016). A recent study by Demirci, et al, showed that approximately 20% of adult women with iron deficiency anemia met criteria for adult ADHD diagnosis (Demırci et al., 2017). A systematic review of 10 studies, including over 1600 individuals from the US, Europe, Egypt, Asia, and Brazil, revealed consistently low iron status in children with ADHD when assessed by serum ferritin. However, results varied significantly across studies, suggesting that individual genetics and environment may have a dominant influence (Wang et al., 2017).

Vitamin C

Vitamin C is a critical component of the antioxidant system. Heightened oxidative stress caused by chronic inflammation, heavy metal or other environmental exposures, and hyperexcited neurons place heavy demands on the brain's antioxidant system. Stimulant medications used for ADHD are also implicated in oxidative damage to the brain (Lopresti, 2015). In the nervous system, vitamin C is also an essential factor in collagen synthesis, promoting the integrity of myelin sheaths and enhancing neural signaling. Much of the world's population may be at risk for vitamin C deficiency despite its ubiquity in many foods. Easily oxidized and vulnerable to damage by air, heat, and metal, unfortified levels of vitamin C in fresh foods are highly overestimated. Hoffer and Pauling strongly believed that "no one" receives adequate Vitamin C from food alone (Hoffer, 2008). As one of the most familiar micronutrients, vitamin C is underappreciated in its sacrificial and protective roles, but its deficiency has profound implications for mental wellness.

Environmental pollution from industrial and agricultural processes and transportation is a foremost concern world-wide. Contamination of heavy metals in food and water are unavoidable and can confer alarming effects during growth and development. When adequately equipped, the body's detoxification system provides considerable protection; yet, in the modern toxic environment, promoting antioxidant activity through higher-than-average nutrient doses may be required for certain individuals (OMNS, 2007). Vitamin C participates in metabolic reactions that aid the brain in its ability to remove neurotoxins and reduce oxidative damage by excessive levels of copper, iron, and lead. Additionally, research supports adjunctive vitamin C with both conventional ADHD medications and nutritional supplements, particularly Omega-3 fatty acids, for antioxidant protection and enhanced efficacy (Joshi et al., 2006). The inclusion of Vitamin C in any ADHD treatment intervention is overwhelmingly supported by its safety record, clinical research evidence, and case reports from orthomolecular practitioners (Abbey, 2003; OMNS, 2007).

Lead

The 2014 crisis in Flint, Michigan, involving alarming levels of heavy metals in drinking water brought renewed attention to lead as a primary risk factor for ADHD, especially in children. However, water is not the only significant source of lead. Although use of lead paint ceased in the mid to late 20th century, the persistence of lead in the environment continues to be reflected in elevated blood levels all over the world. Data suggests that any measurable concentration of lead in the blood has cumulative detrimental effects on brain structure and function, affecting intelligence, behavior, and mood (Hong, 2015; Nigg et al., 2016). Multiple studies show direct correlations between high blood lead levels and ADHD, suggesting a four-fold increase in risk (Braun et al., 2006). The ability of lead to easily cross the blood-brain-barrier and other tissues increases its damaging impact during maternal, prenatal, and postnatal neurodevelopment (Nigg et al., 2016). Imaging studies reinforce evidence that reduced cortical grey matter in adulthood results from toxic lead exposure during these critical periods, matching data showing lower executive function and behavioral control (Cecil et al., 2008).

Lead toxicity exhibits heterogeneous effects between individuals, reflecting varying detoxification capabilities. A 5-year birth cohort study investigating lead levels in 578 Mexican children demonstrated a non-linear relationship between blood lead and ADHD symptoms. The study authors concluded that ADHD subtypes may be related to variations in lead detoxification (Huang et al., 2015). Research shows a relationship between genetic determinants of iron status and

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lead metabolism, implying that some individuals may be more susceptible to lead's neurotoxic effects. Carriers of the HFE gene variants show increased iron uptake, exacerbating oxidative stress and increasing vulnerability to developmental damage from lead (Nigg et al., 2016). However, Hong, et al, reported significant inverse relationship between blood lead and all ADHD symptom domains in a thousand Korean children, independent of confounds such as other toxin exposures (Hong, 2015). Still, both studies confirmed pronounced associations between elevated lead and symptoms of hyperactivity and impulsivity, supporting the hypothesis of oxidative damage to dopaminergic systems (Hong, 2015; Huang et al., 2015).

While attempts can and should be made to reduce exposures to lead and other environmental toxins, protecting the brain from their detrimental effects is also achievable from a nutritional perspective. Ensuring adequate macronutrients from food and boosting intakes of brain-enhancing vitamins, minerals, and antioxidants can better equip the body's natural ability to combat inflammation and oxidative stress. Zinc, magnesium, iron, and Vitamin C augment neural integrity and function and regulate neurotransmitter balance, and have proven benefits for ADHD symptoms in all age groups (Sinn, 2008). These micronutrients also aid in reducing the potential neurotoxic effects of copper, lead and stimulant medications.

Personalized, Integrative Treatments for ADHD

Widespread recognition of diet as a modifiable factor in the midst of numerous, un-modifiable risks, highlight nutritional interventions as first-line strategies for treating ADHD (Marx et al., 2017). In addition to promoting other preventive health behaviors such as physical activity, adequate sleep, and smoking cessation, approaching psychiatry from a nutritional standpoint is no longer optional. Strong associations between dietary quality and mental health risk are consistent across diverse demographics, nationalities, and cultures, encouraging use of a new integrative care model (Jacka, 2017).

While several common nutritional deficiencies have emerged among individuals with ADHD, orthomolecular approaches to treatment remain contingent upon biochemical individuality to tailor interventions on a case-by-case basis. Nutritional psychiatric practice should begin with full genetic and biochemical assessments, including food sensitivity analyses, to identify specific imbalances that require correction (Jackson et al., 1998). Comprehensive panels can also recognize individual variations in metabolism and digestion that inform the correct selection and dose of vitamin and mineral supplements (Kaufman, 2007). Unique ADHD symptom types may require substantially different approaches to restore a homeostatic balance of neurotransmitters in the brain (Benton, 1992).

Although global dietary patterns and practices vary, the basic building blocks of the human diet needed for optimal health and mental wellness are similar across time and culture. As research continues to elucidate the intricate biochemical roles of micronutrients, healthcare practices must take advantage of this knowledge to restore, maintain, and sustain health and wellness throughout the body and mind (Logan & Jacka, 2014). Neglecting evidence for the use of safe, affordable, naturally occurring and readily available micronutrient supplements for children and adults with ADHD is unjustifiable personally, socially, and economically (Marx et al., 2017; Sarris et al., 2015).

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