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OMEGA-3 FATTY ACID SUPPLEMENTATION FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENT: LITERATURE REVIEW

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ABSTRACT

Introduction and objective. Attention Deficit Hyperactivity Disorder affects 5.29% globally, with rising incidence, particularly in boys. The eleventh revision of the International Classification of Diseases defines ADHD by persistent patterns of inattention and/or hyperactivity-impulsivity. Stimulants (such as methylphenidate) and atomoxetine are effective but carry side effects. Omega-3 fatty acids show promise in influencing synaptic membrane structure and neurotransmitter activity. Studies suggest benefits for ADHD symptoms, making Omega-3 supplementation a potential adjunctive treatment. **Review methods.** PubMed database was used for the review. An electronic search was performed within publication years (2005–2024) using English search phrases such as "ADHD," "ADHD treatment," "Omega-3 supplementation," and "polyunsaturated fatty acids in ADHD." All retrieved articles, including original and randomized controlled studies, were analyzed. **Results.** The average Omega-3 intake in the U.S. falls below recommended levels. Western diets' Omega-6 dominance may exacerbate inflammation, while Omega-3 deficiencies could impact ADHD symptoms. Studies suggest Omega-3 supplementation may reduce impulsivity and improve attention. A Mexican trial found comparable efficacy between Omega-3/6 and methylphenidate (MPH). However, a French trial favored a placebo. Recent Italian research found limited benefits in mild ADHD cases. **Conclusions.** As ADHD rates rise, more research is needed to manage the disorder. Omega-3 supplementation shows mixed results in improving symptoms, highlighting the need for further investigation. For a final determination of this impact, it seems necessary to conduct studies with a long observation period, in which various doses and combinations of Omega-3 acids will be considered, as well as retrospective studies.

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INTRODUCTION.

ADHD – epidemiology, diagnosis, neurobiology, and treatment.

ADHD is a widely prevalent impairing condition, often co-occurring with other mental disorders (Posner et al., 2020). It is one of the most common neurodevelopmental disorders in child psychiatry, (Thapar & Cooper, 2016). The global prevalence of ADHD is 5,29%, it has shown an upward trend over the years and is more common in boys than girls (Polanczyk et al., 2007; Thapar & Cooper, 2016).

According to the new eleventh revision of the International Classification of Diseases (ICD-11) ADHD is characterized by a persistent pattern lasting at least 6 months, involving symptoms of inattention and/or hyperactivity-impulsivity, which significantly impair academic, occupational, or social functioning. These symptoms typically manifest before age 12, often in early to mid-childhood, although onset may occur later for some individuals. The severity of inattention and hyperactivity-impulsivity exceeds what is considered typical for age and cognitive ability. Inattention is marked by difficulty sustaining focus on tasks lacking

immediate rewards, along with distractibility and organizational challenges. Hyperactivity involves excessive motor activity and difficulty remaining still, particularly in structured situations requiring self-regulation. Impulsivity entails acting on immediate stimuli without forethought regarding risks or consequences. The relative balance and expression of these characteristics vary among individuals and may evolve over time. Diagnosis requires evidence of symptoms across diverse settings, such as home, school, or work, with variations influenced by environmental demands. Symptoms must not be better explained by another mental, behavioral, or neurodevelopmental disorder, nor attributable to substance or medication effects. (Organization, 2021)

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) delineates various manifestations of ADHD: predominantly inattentive (with 6 or more out of 11 symptoms present), predominantly hyperactive/impulsive (with 6 or more out of 9 symptoms present), and combined presentation (meeting both criteria), alongside a category for partial remission (Drechsler et al., 2020).

Diagnostic criteria outlined by the ICD and DSM enable a reliable balance of risks and benefits associated with assigning a diagnostic label and initiating treatment, which is not devoid of adverse effects (Thapar & Cooper, 2016).

Like other psychiatric disorders, ADHD demonstrates heterogeneity at clinical, etiological, and pathophysiological levels. Individuals with this condition vary in terms of symptom combinations, degree of impairment, co-occurring illnesses, and other environmental factors, significantly complicating diagnosis (Katzman et al., 2017).

Another challenge is that diagnosis relies solely on reported symptoms—currently, there are no available biological tests to establish a diagnosis. This implies that despite clearly defined diagnostic criteria, there is a potential risk of overdiagnosis and underdiagnosis (Thapar & Cooper, 2016).

ADHD exhibits high comorbidity with other neurodevelopmental disorders, namely: autism spectrum disorder, dyslexia, developmental coordination disorder, intellectual disability, and tic disorders. Additionally, a more frequent co-occurrence of ADHD with oppositional defiant disorder and conduct disorder has been observed. The presence of disruptive behavior disorders is an indicator of a poorer prognosis in children with ADHD (Thapar & Cooper, 2016).

The heritability of ADHD is high, with most estimates ranging between 70 to 80%. Studies based on whole genome sequencing have identified 12 susceptibility loci for ADHD risk. However, these associations only account for approximately 22% of the heritability of this disorder. Other studies have demonstrated an increased number of copies of certain genes in individuals with ADHD, but these findings require further confirmation (Faraone et al., 2005; Posner et al., 2020).

Numerous environmental factors have been associated with ADHD and are considered potential risk factors. However, due to the complexity of the underlying causes, including correlations between genetic susceptibility and environmental factors, as well as the observational nature of research projects, the majority of these associations have yet to be conclusively proven. Potential risk factors for developing ADHD include prematurity, low birth weight, prenatal exposure to stress, tobacco smoke, and medications (e.g., paracetamol). Environmental toxins, particularly prenatal or early childhood exposure to lead, as well as organophosphate pesticides and polychlorinated biphenyls, are indicated as potential risk factors for ADHD. Nutritional deficiencies (e.g., zinc, magnesium, and polyunsaturated fatty acids), as well as excesses (e.g., sugar and artificial food colorings), and abnormal IgG (immunoglobulin G) levels in the diet have not been linked convincingly to ADHD and are currently considered correlates. Psychosocial risks such as low income, family difficulties, harsh or hostile parenting, while strongly causal for some mental disorders, are more likely correlates than proven causes of ADHD (Dark et al., 2018; Posner et al., 2020).

Functional magnetic resonance imaging (fMRI) studies have revealed abnormalities in the functioning of multiple neuronal networks in response to cognitive tasks in patients with ADHD. Meta-analyses of structural MRI studies indicate changes in the basal ganglia and limbic areas, occurring more frequently in individuals diagnosed with ADHD. Reduced overall gray matter volume and altered volumes of the basal ganglia appear to be associated with familial occurrence of ADHD (Thapar & Cooper, 2016). The network activity between these areas is maintained by neurotransmitters such as dopamine (DA) and norepinephrine (NE). What is important in case of the treatment of ADHD, several studies have shown that the DA receptor density in several brain regions of ADHD patients is lower than normal (Sharma & Couture, 2014).

As per international protocols, treatment is structured around a multimodal strategy incorporating both behavioral and pharmacological interventions (Carucci et al., 2022). Most organizations recommend initiating treatment with psychoeducation and behavioral interventions, especially in individuals with mild symptoms. American guidelines suggest considering pharmacological treatment as the first-line approach, not excluding the use of pharmacotherapy in preschool-aged children and those with mild ADHD. Conversely, the National Institute for Health and Care Excellence (NICE) guidelines suggest that initiating pharmacotherapy in children under 5 years of age should only be considered after attempting parent training and obtaining a second opinion from a specialist in pediatric ADHD (Posner et al., 2020; Thapar & Cooper, 2016).

Stimulants such as methylphenidate (MPH) and dextroamphetamine are the first-line treatment for ADHD, while atomoxetine, a norepinephrine reuptake inhibitor, is considered second-line treatment. Each of these medications increases the bioavailability of catecholamines. Despite their demonstrated efficacy in reducing ADHD symptoms in meta-analyses, these medications have many adverse effects. The most reported adverse effects include decreased appetite, delayed growth, insomnia, nausea, psychostimulant dependence, dose-dependent increases in blood pressure and heart rate (Cortese et al., 2013). Although current pharmacotherapies can improve ADHD symptoms, there is still about 20–40% of patients with ADHD who do not benefit from these medications (Chang et al., 2018). The course of the disease is not aided by low adherence to pharmacological recommendations, which may stem from developing tolerance to treatment, as well as the stigma associated with the condition and societal resistance to pharmacotherapy (Culpepper & Mattingly, 2010).

Considering the above, there is currently a growing need to explore alternative approaches to ADHD treatment, as medications may not always yield the desired effects, according to therapists' observations (Carucci et al., 2022).

Omega-3 fatty acids – general characteristics.

Omega-3 fatty acids (also known as n-3 fatty acids or ω-3 fatty acids) are polyunsaturated fatty acids (PUFAs), where the last double bond in the carbon chain is located at the third carbon atom from the end. This group includes various ω-3 polyunsaturated fatty acids that play an important role in human nutrition such as: alpha-linolenic acid (ALA), stearidonic acid (SDA), docosapentaenoic acid (DPA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) (Decandia et al., 2022).

The crucial yet limited subset of fatty acids for human health comprises essential fatty acids (EFAs). These EFAs are indispensable for maintaining homeostasis, as they cannot be synthesized adequately by the body and thus must be obtained through dietary intake. While some authors classify all PUFAs as essential fatty acids, others identify linoleic acid (LA) and alpha-linolenic acid (ALA) as the most significant, often referring to them as "parent essential fatty acids" (Cholewski et al., 2018).

They play crucial roles as constituents of phospholipids and cholesterol esters within the neuronal cell membrane, particularly in dendritic and synaptic membranes. The justification for employing these novel agents in psychiatric conditions arose from their fundamental role in altering synaptic membrane structure. Indeed, they regulate and participate in brain cell signaling processes, including the regulation of monoamines, modification of receptor characteristics, and activation of receptor-mediated signal transduction pathways (Bozzatello et al., 2016).

Purpose of the work.

The objective of this paper is to conduct a comprehensive literature review encompassing studies and trials, with a specific focus on elucidating the role of Omega-3 fatty acid supplementation in the management of ADHD.

MATERIALS AND METHODS.

The authors extensively explored the PubMed electronic database, employing pertinent keywords and combinations like "Omega-3," "Omega-3 deficiency," "ADHD treatment," "supplementation". Studies focusing on the impact of Omega-3 supplementation on individuals with ADHD were incorporated. These selected studies underwent thorough critical analysis to evaluate the effects of supplementation on behavioral patterns and overall enhancement in ADHD individuals. The foundational research for this article was conducted between February and April 2024.

RESULTS.

Causes of nutrient deficiencies in patients with ADHD.

Between 2003 and 2008, the average dietary intake of long-chain Omega-3 fatty acids (including DHA, EPA, and EPA equivalents) among individuals in the United States stood at 0.17 g/day, falling below the recommended daily intake of 0.5 g/day. The proportion of Omega-3 fatty acids in one's diet is predominantly influenced by the availability of fish, as they serve as the primary source of EPA and DHA for human consumption (Cholewski et al., 2018).

In the Western diet, there is a notable predominance of Omega-6 fatty acids or their precursors (such as linoleic acid) compared to Omega-3 fatty acids or their precursors (such as alpha-linolenic acid) (Bloch & Mulqueen, 2014). Omega-6 fatty acids (such as gamma-linolenic acid [GLA]), like Omega-3 fatty acids, belong to the category of PUFAs, distinguished by a double bond in the 6th position of their carbon chain. These fatty acids are recognized for their potential to induce inflammatory responses within the body. Conversely, Omega-3 fatty acids are acknowledged for their anti-inflammatory properties (Abdullah et al., 2019).

Furthermore, it has been demonstrated that children diagnosed with ADHD exhibit more pronounced symptoms of essential fatty acid (EFA) deficiency. This clinical syndrome is characterized by inadequate levels of fatty acids and manifests symptoms including dry and scaly skin, eczema, and dry eyes. Some studies have described an association between unhealthy dietary patterns and ADHD (Chang et al., 2018).

Impact of Omega 3.

A research analysis revealed diminished levels of Omega-3 fatty acids in individuals with ADHD who exhibited heightened behavioral symptoms alongside reduced plasma concentrations. Consequently, it was proposed that a deficiency in fatty acids might worsen ADHD symptoms (Abdullah et al., 2019).

Scientists from Research Centers in Nutrition and Health, Madrid, Spain conducted a randomized clinical trial that included 76 children aged 6 to 16 years, of either sex with a diagnosis of ADHD, from the Pediatrics Department at Hospital El Escorial in Madrid (Spain)

who were recruited between 2017 and 2018. 60 of these children completed the intervention. The inclusion and exclusion criteria were strict. This study assesses the progression of impulsive behavior in children with ADHD after an 8-week dietary intervention with Mediterranean and/or Omega-3 fatty acid supplementation. The subjects were split into four groups, comprising a single control group and three groups receiving interventions. To evaluate impulsiveness, the study used the BIS-11c scale (Barratt Impulsiveness Scale), it assesses 3 subscales: motor impulsiveness, cognitive impulsiveness, and lack of planning. Patients with ADHD receiving Omega-3 supplementation presented less impulsive behavior than controls (San Mauro Martin et al., 2022).

Another intriguing study is a double-blind randomized placebo-controlled trial conducted by researchers at the University Medical Center in Utrecht. This research aimed to explore the impact of dietary Omega-3 fatty acid supplementation on ADHD symptoms and cognitive control in young boys, both with and without ADHD. The study team recruited a total of 40 boys with ADHD, aged 8–14 years, and 39 matched typically developing controls. They participated in a 16-week trial, in which participants consumed 10 g of margarine each day, enriched with either 650 mg of EPA/DHA each or placebo. Follow-up and baseline assessments addressed ADHD symptoms, fMRI of cognitive control, urine homovanillic acid and cheek cell phospholipid sampling. Supplementing with EPA/DHA improved attention ratings by parents in both ADHD and typically developing children. Children who received EPA/DHA supplements had higher phospholipid DHA levels at follow-up compared to those on placebo. However, EPA/DHA supplementation did not affect cognitive control or brain activity measured by fMRI. Overall, this study indicates that Omega-3 fatty acid supplementation can alleviate ADHD symptoms in both affected individuals and typically developing children. While cognitive control systems in the brain do not seem to mediate this effect, the study suggests that Omega-3 supplementation could complement pharmacological treatments for ADHD (Bos et al., 2015).

In 2017, an article was published comparing the efficacy of Omega-3/6 fatty acids with MPH and combined MPH + Omega-3/6 in children with ADHD. The experiment took place at the Neurology Department of Mexico's National Health Institute for Children as a randomized pilot study. The evaluation period lasted for 12 months. Participants were children aged between 6 and 12 years with newly diagnosed ADHD. Exclusion criteria included neurological disorders such as epilepsy, brain damage, mental retardation, autism, developmental disorders, previous pharmacological treatment for ADHD, known hypersensitivity to any of the interventions used, ongoing chronic conditions, or medications for those. Ninety patients met the inclusion and exclusion criteria and were randomly divided into three treatment arms: MPH; Omega-3/6 (558 mg EPA, 174 mg DHA, and 60 mg GLA each daily); Omega-3/6 + MPH. Clinical assessments were made at five time points using the Spanish version of the ADHD Rating Scale. The findings of this preliminary inquiry suggest that the specific combination of Omega-3/6 fatty acids under examination in this trial, while demonstrating a slightly diminished efficacy compared to MPH, emerges as a viable and well-tolerated therapeutic option for children afflicted with ADHD when employed as a monotherapy. Interestingly, the combination of Omega-3/6 with MPH offers no efficacy benefit over MPH monotherapy but did permit lower doses of MPH, suggesting that the combination therapy may lead to improved treatment adherence compared with MPH monotherapy. Control and reduction of symptoms were slower in the Omega-3/6 and MPH + Omega-3/6 arms compared with MPH monotherapy (Barragán et al., 2017).

An example of the role of Omega-3 fatty acid supplementation in the management of ADHD was also described in a 2021 research. Preschool children at risk for ADHD were recruited from kindergartens in Cologne and Mannheim, as well as families seeking assistance from various psychiatric and therapeutic departments at the University Hospital of Cologne and

the Central Institute of Mental Health, University of Heidelberg, Mannheim. The criteria for inclusion and exclusion were strict. The Study analyses 4-month treatment phase. It was a double-blind placebo-controlled trial, where children were assigned to either verum group, who received a treatment with Omega-3/6 fatty acids (daily dose of 372 mg EPA, 116 mg DHA, and 40 mg GLA), or placebo group. The primary outcome variables were parent- and teacher-rated ADHD symptoms rated on the ADHD Parent and Teacher Rating Scale for Preschool Children. Outcome measures were finalized for 16 children in the verum group and for 15 children in the placebo group. Intention-to-treat analyses suggest potential positive effects of Omega-3/6 fatty acids, particularly regarding teacher-rated inattention symptoms, internalizing problems, emotional reactivity symptoms, and anxious/depressed symptoms.

One should approach the credibility assessment of this study with a degree of skepticism for several reasons. Among them, compliance was not systematically verified; adherence to the recommended intervention was solely the responsibility of the parents. Originally, the study was supposed to consist of two phases; however, due to recruitment issues, a high dropout rate, and a small sample size, only the first phase took place (Döpfner et al., 2021).

Between 2009 and 2011, 162 children from five French child psychiatry centers, aged 6–15 years with established diagnosis of ADHD were randomized 1:1 to receive either supplements containing DHA and EPA or a placebo for 3 months. It was a double-blind, placebo-controlled clinical trial. Exclusion criteria were taken under consideration. Primary outcome was the change in the ADHD-RS-IV (Attention-Deficit Hyperactivity Disorder Rating Scale version 4), Alouette test, KiTAP (Test of Attentional Performance for Children), CPRS-R (Conners Parent Rating Scale-Revised) and CDI (Children's Depression Inventory).

This randomized trial found an improvement from baseline ADHD-RS-IV score in favor of the placebo group compared to Omega-3 supplementation, and the size of the benefit was statistically significant. There was no biological explanation for greater effect in the placebo group, compared with the active group, the authors suggest that the result could be incidental (Cornu et al., 2018).

In 2021 a randomized, double-blind, placebo-controlled efficacy study was published. The Italian researchers assessed the effectiveness of an Omega-3/6 dietary supplement containing 2 capsules daily, each with 279 mg EPA, 87 mg DHA, and 30 mg GLA, in improving inattentive symptoms in children aged 6–12 with inattentive-type ADHD and a baseline ADHD-RS-Inattention score of 12 or higher. Additionally, the study examined alterations in overall functioning, illness severity, symptoms of depression and anxiety, learning disorders, and levels of fatty acids in the blood. The trial lasted for 12 months (6 months of double-blind evaluation and 6 month-open-label treatment on all patients), 160 patients in total were included in the analysis. The primary outcome revealed no superiority of the Omega-3/6 supplement over placebo, with only a small reduction observed in the Omega-3/6 ratio in blood levels within the active treatment group. In Phase II, a mild statistical improvement was noted in the ADHD-RS-total score for the Omega-3/6 group, though this improvement was not deemed clinically significant. Specifically, no improvement was observed in the ADHD-RS Inattention score. In conclusion, this study indicates that Omega-3/6 supplementation does not provide clinical benefits, suggesting a limited role for this treatment in children with mild ADHD-I (ADHD inattentive subtype) (Carucci et al., 2022).

DISCUSSION.

As the prevalence of ADHD continues to rise, it is imperative that we invest in further research to gain a deeper understanding of the etiology and potential management strategies for this disorder. With increased knowledge, we can offer greater comfort and tools to support children, adolescents, and therapists dealing with ADHD patients.

As one can see, clinical studies do not allow for definitive conclusions regarding the efficacy of Omega-3 supplementation in reducing ADHD symptoms. Some of the studies mentioned above suggest their impact on reducing impulsivity symptoms and improving attention in patients treated this way (Bos et al., 2015; San Mauro Martin et al., 2022). Others, however, refute this claim, indicating a lack of clinically significant effect of this intervention, and some even negate its potential existence (Carucci et al., 2022; Cornu et al., 2018).

CONCLUSIONS.

Based on this review, it can be inferred that Omega-3 fatty acids might offer advantages in addressing ADHD symptoms. Nevertheless, more extensive research is warranted. This should encompass not only larger-scale clinical trials with a long observation period, during which various doses and combinations of Omega-3 acids will be considered, but also retrospective studies involving mothers, with a particular emphasis on pregnancy and potential nutrient deficiencies during this period. Considering the evidence, the incorporation of supplementation and dietary adjustments is recommended for individuals with ADHD.

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Author's contribution.

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