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Effect of Omega-3 as an Add-on Therapy in Reducing Inattention Symptoms in Children and Adolescents with Attention Deficit-Hyperactivity Disorder: An Evidence-Based Case Report

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ABSTRACT

Attention Deficit Hyperactivity Disorder (ADHD) is the most common neurodevelopmental disorder in childhood. It is mainly characterized by inattention and impulsivity or hyperactivity. The current medication used to manage ADHD is pharmacological stimulant, methylphenidate. The consumption of omega-3 was found to be beneficial in children development and neuropsychiatric disorders. However, the usage of omega-3 in ADHD is rather inconclusive. Investigating the benefit of omega-3 as an add-on therapy to reduce ADHD inattention symptoms in children and adolescents. Systematic literature search was done on PubMed, Cochrane, PsycINFO, and EMBASE database for relevant randomized control trials (RCT) and systematic review of RCT, resulting in 323 records identified. From there, a total of 265 articles were screened, which leads to 2 selected articles. Critical appraisal on eligible studies were conducted using Oxford CEBM critical appraisal tools, consisting of 3 components: validity, importance, and applicability. Both studies included were of high quality. One systematic review and one RCT were appraised in this report. The systematic review shows that omega-3 as adjunctive therapy is slightly superior compared to conventional therapy in reducing ADHD inattentive symptoms, but the result was not statistically significant. In contrast, the RCT found that reduction of ADHD scores is higher in the conventional therapy group, but the result was also statistically insignificant. There was no conclusive evidence that omega-3 as an add-on therapy is able to reduce the inattentive symptoms in children and adolescents with ADHD.

1. INTRODUCTION

1.1 ADHD

ADHD (Attention Deficit Hyperactivity Disorder) is a neurodevelopmental disorder that shows patterns of inappropriate levels of inattentiveness, impulsivity or hyperactivity. This condition is long believed to be affecting children's ability to function. Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder were once a different thing until the publication of The Diagnostic and Statistical Manual of Mental Disorder or DSM IV combined the two, into one diagnosis with three main presentations of predominantly hyperactive, predominantly inattentive or predominantly hyperactive-inattentive [1]. There is also a newer version of DSM V available already with some revisions in the diagnostic criteria of DSM IV, however it doesn't change the core ADHD symptoms domain (Inattentive and Hyperactivity) [2].

Pharmacological is the therapy of choice in managing ADHD. It is divided into stimulant and non-stimulant categories. Stimulants can be further categorized into methylphenidates and amphetamines. Stimulants are the main therapy in managing ADHD, they are effective in 70% of patients with NNT (number needed to treat) of 2. The side effects of stimulants include decreasing appetite and sleep, changes in blood pressure and risk of dependency. The non-stimulant categories are also divided into two types: antidepressant and alpha agonist. Atomoxetine is one example from the antidepressant types, though it is not as effective as stimulant, it is still known to be effective in many trials as ADHD treatment. It also has minimal anti-depressant effect and is often used for children who do not tolerate stimulants. Alpha agonist such as clonidine and guanfacine can be used to treat ADHD, however it is associated with multiple cardiovascular effect such as lowering blood pressure, dizziness, sedation and more [1].

1.2 Omega-3

Omega-3 fatty acid is one of the two major classes of polyunsaturated fatty acids (PUFAs). This group of fatty acids consists of several types, the most studied being alpha-linoleic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoid acid (DHA). ALA is frequently found from plant sources, such as flaxseed and canola oils. Meanwhile, marine sources like fish meat and fish oil are the primary source for DHA and EPA. It primarily functions as a constituent of the phospholipid bilayer [3]. Adequate consumption of a combination of omega-3 fatty acids were found to be beneficial to a wide range of conditions: proper neonatal development, cardiovascular diseases, and neuropsychiatric disorders [4]. In addition, a review by Young G and Conquer J has suggested a reduction in symptom severity in several neuropsychiatric disorders, such as attention deficit hyperactivity disorder (ADHD), Alzheimer's disease, schizophrenia, and depression [5]. In the case of ADHD, omega-3 supplementation by itself has shown to cause reduction of ADHD symptoms scoring results among children in comparison to placebo. In regards to the subscales of ADHD symptoms scoring results, evidence showed that there is a trend of positive effects toward inattention subscale, in comparison to hyperactivity/impulsivity subscale. However, the results of these studies are not always in agreement, some studies stated that the effects are statically significant, but there are some others that showed that the results are very small (not clinically significant) or even negative results [6- 9]. Hence, this review is conducted to investigate whether omega-3 supplementation, when paired as an add-on therapy to the standard treatment for ADHD, might reduce the inattention symptoms in children and adolescents with ADHD.

2. CLINICAL SCENARIO

P, an eight years old boy came with his parents for regular consultation in a clinic for his ADHD condition. He has been given medication for ADHD with methylphenidate and behavior therapy along with parental psychoeducation about his problems for 6 months. Although his hyperactivity symptoms have improved, he still has problems with his attention thus sometimes failing to finish his school tasks. Abbreviated teacher/parent rating scale showed a decreasing score from 24 to 12 in 3 months and to 10 in 6 months. His parents read in a magazine that omega-3 in fish oil may benefit children with ADHD. His parents asked the

clinician, if additional supplementation of omega-3 is needed for their child.

3. CLINICAL SCENARIO

The proposed question in this is study is "Does omega-3 as an add-on therapy reduce the inattention symptoms of ADHD in children and adolescents?"

4. METHODS

4.1 Search Strategy

Several large databases were accessed on 25th October 2020 to search for relevant articles. The databases used include MEDLINE, Cochrane, PsycINFO and Embase (Figure 1). Keywords used were children and adolescents, ADHD and omega-3, as well as its synonyms and related terms. Boolean OR and AND were used to increase sensitivity and specificity of article searching.

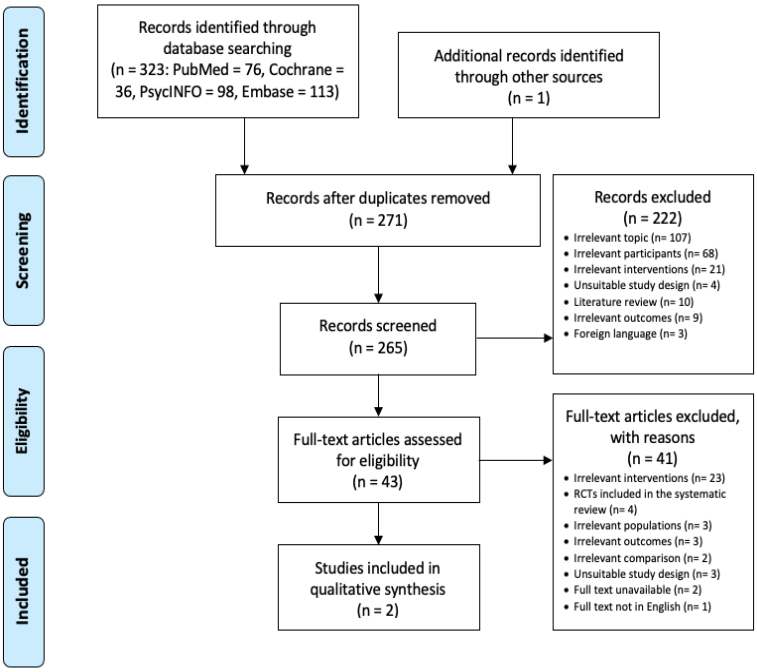

Figure 1. PRISMA flow diagram

4.2 Critical Appraisal

Critical appraisals of the articles evaluate components of Validity, Importance and Applicability (VIA). The critical appraisal tools used were selected according to the study design of the article, either systematic reviews or randomized controlled trials. Systematic reviews were critically appraised using FAITH tools. Randomized controlled trials were critically appraised using the critical appraisal tools constructed by Centre for Evidence-Based Medicine (CEBM), University of Oxford (https://www.cebm.ox.ac.uk/resources/ebm-tools/critical-appraisal-tools). The critical appraisal for each study was conducted independently by two different evaluators. Should there be any differences in opinion, the two evaluators discuss to reach an agreement. A third evaluator may be involved if the first two evaluators did not reach a conclusion.

4.3 Eligibility Criteria

To determine which studies were eligible for qualitative analysis, a set of eligibility criteria was generated. These inclusion and exclusion criteria were used as parameters when conducting article screening (Table 1).

Table 1. Eligibility criteria

Inclusion criteria	Exclusion criteria
Children and adolescents (age 4-18)	Presence of comorbidities (depression, anxiety, OCD, language disabilities, learning disabilities, fine and gross motor difficulties, another psychological or neurological problem)
Subjects were diagnosed with ADHD according to DSM-IV or DSM-V criteria	Intervention arm were given combination therapy of omega-3 with any substances other than conventional therapy
Intervention arm were given omega-3 (fish oil capsule, fish or fortified food) as an add-on to conventional therapy (methylphenidate or other medication)	No measurable outcomes on inattention symptoms
Control arm were given conventional treatment only (methylphenidate or other medication)	Preclinical studies
Systematic review or meta-analysis of RCTs and RCTs	
Text in English or Bahasa Indonesia	
Full-text article available	
Original article	

5. RESULTS

After literature search and selection, one randomized controlled trial (RCT) and on systematic review of RCTs was included for review. A total of 160 patients were evaluated within the studies included in this EBCR. Patient group in the studies range from 4-18 years old, all of which were diagnosed with ADHD according to DSM-IV criteria. Severity of the ADHD symptoms were measured using Parental Child Behvaior Checklist (CBCL), ADHD Rating Scale (ADHD-RS) and/or Conner's Rating Scale (CPRS). Systematic reviews were critically appraised using FAITH tools (Table 2). Randomized controlled trials were critically appraised using the critical appraisal tools constructed by Centre for Evidence-Based Medicine (CEBM), University of Oxford (https://www.cebm.ox.ac.uk/resources/ebm-tools/critical-appraisal-tools) (Table 3). Level of evidence was determined according to the criteria by Oxford Centre for Evidence-Based Medicine 2011.

Table 2. Critical appraisal of systematic review: validity, importance, applicability and level of evidence

	Validity	Importance	Applicability	Level of Evidence

es	PICO	Question	Find	Appraise	Include	Total Up	Heterogeneity		Similarities of study subject to clinical subject	Appropriateness to patients values and preferences	Feasibility in clinical setting	
	+	+	-	±	±	+	-	Out of two studies in this systematic review that are relevant to our clinical question, both studies showed positive results, although statistically insignificant	+	+	+	I

Table 3. Critical appraisal of RCT: validity, importance, applicability and level of evidence

cles	Validity							Importance	Applicability			Level o Eviden
	Randomization	Allocation concealment	Similar baseline characteristics	Standardized treatment	Follow-up	Blinding	Intention-to-treat Analysis		Similarities of study subject to clinical subject	Appropriateness to patients values and preferences	Feasibility in clinical setting	
	+	±	+	+	+	+	-	Insignificant within-group comparison (F= 0.79; p ≥ 0.48) and between-group comparison (F= 0.32; p ≥ 0.86). There was 55.22% and 59.55% decrease in the ADHD inattention score in omega-3 group and placebo group, respectively	+	+	+	II

+ = Yes
- = No
± = Unclear

A systematic review of RCTs by [10] included two RCTs (n=94) that investigated the efficacy of omega-3 PUFAs as an add-on therapy for methylphenidate or atomoxetine on ADHD inattention symptoms. The first RCT by [12] shows that children receiving omega-3 as add-on therapy have a mean reduction of 3.8 of CBCL-T result, which is a 5.6% reduction. Meanwhile, those without had a mean reduction of 3.4 CBCL-T result, which is a 5.3% reduction [12]. This scoring was observed for 4 months from baseline [12]. An RCT by [13]

shows that inattention score in children receiving omega-3 supplementation reduces from a mean of 18 ±3 in the first visit to 6±5 in the 10th week (65% change compared to the baseline). This does not differ compared to the control group ($p = 0.691$) in which ADHD-RS score decreases from 18±4 to 7±4 [13]. Therefore, both of these studies that were included in the systematic review showed positive results, although without statistical significance [10]. The systematic review concluded that the evidence of the benefit of omega-3 was difficult to be concluded due to heterogeneity of the methods across studies, such as an variation in sample size, study duration, type and dosage of omega-3 supplementation [10].

An RCT by [11] measured the reduction of inattention symptom according to Parent ADHD Rating Scale (ADHD-RS) in 66 children aged 6-2 years old that were diagnosed with ADHD according to DSM-IV-TR. The results of this study concluded that there was no significant difference between two groups for within comparison ($F= 0.79$; $p \geq 0.48$) and between-group comparison ($F= 0.32$; $p \geq 0.86$) in the inattention subscale [11]. However, the inattention subscale mean score have decreased between week 0 (omega-3 vs. placebo; 21.86 ± 3.98 vs. 22.25 ± 2.82) and week 8 (omega-3 vs. placebo vs.; 9.79 ± 4.81 vs. 9.00 ± 4.74) [11]. There was 55.22% decrease in the omega-3 group and 59.55% decrease in the placebo group [11].

6. DISCUSSION

Omega-3 polyunsaturated fatty acids were thought to play a beneficial role in psychiatric disorders by modifying the synaptic membrane, thus facilitating the neuron signalling and activation of signal transduction [14]. Although the efficacy of omega-3 supplementation were reputable in many childhood psychiatric disorders, the effectivity of this intervention remains conflicting in ADHD. This was shown in the systematic review by [10] which included two RCTs investigating the efficacy of omega-3 as an add-on therapy on improving ADHD inattentive symptoms. The first RCT by [12] shows that omega-3 supplementation resulted in the mean reduction of 3.8 for CBCL-T score compared to a mean reduction of 3.4 for those receiving conventional therapy only. The second RCT by [13] shows that inattention score using ADHD-RS was reduced from 18±3 to 6±5 after 10 weeks in the experimental group and 18±4 to 7±4 in the control group. Both studies showed that omega-3 supplementation is better than placebo in reducing inattentive symptoms, however the differences between the two groups does not differ much. Thus, its clinical significance is doubted [12], [13]. Moreover, [13] study did not show a statistically significant difference between those who receive and do not receive omega-3 supplementation. This could be due to the small sample size of the study (n=40) [13]. Considering the result of the systematic review, heterogeneity between studies was the main issue of the weak associations [10]. There were variabilities in the type, dosage and duration of omega-3 treatment regimen, hence it is difficult to compare results between studies. Although detailed eligibility criterias for RCTs included were described on [10] systematic review, a concerning limitation was the lack of information on the level of quality of the studies included. It is unknown whether the quality of RCTs included were sufficiently high or not, hence could also affect the conclusion drawn by the systematic review [10].

The second study is an eight-week period RCT by [11]. This study failed to show the efficacy of omega-3 in reducing the attention-deficit symptom of ADHD patients [11]. The experimental group in this study reduced the ADHD-RS attention-deficit subscale scores from 21.86 ± 3.98 in week 0 (baseline) to 9.79 ± 4.81 in week 8 (55.22% decrease), while the control group score were decreased from 22.25 ± 2.82 in week 0 to 9.00 ± 4.74 in week 8 (59.55% decrease) [11]. However, this result showed no significant difference between the 2 groups ($F= 0.79$, $p \geq 0.48$). In other words, based on the result of this study, it can be concluded that there was no difference between the effect of methylphenidate in combination with omega-3 and methylphenidate with placebo on reducing the inattention symptoms of ADHD patients [11]. The results of this study were negative probably due to some of the study's limitations. Firstly, the sample size is limited and there is an

imbalance of children's weight between two groups (p <0.006). Secondly, the duration of this study was 8 weeks, which was not that long [11]. A systematic review by [15] concluded that follow up should be beyond three months and preferably longer to see the effect of omega-3. Third, higher doses of omega-3 supplementation may lead to different results. The experimental group patients in this study were given omega-3 supplementation twice a day, which consist of 180mg EPA and 120mg DHA [11]. Since omega-3 supplementation is easily tolerated, it seems logical to consider higher dosage, which plausibly increases the supplement efficacy. This is because fatty acids turnover in the brain is lower in younger children (6-12 years old), hence a longer duration and higher dosage of supplementation might be required to alter change the nervous system fatty acid content [16]. An RCT by [17] stated that the consumption of 650mg EPA and 650mg DHA per day for 16-weeks in male children age 8 and 14 years are still safe and well tolerated.

The strength of this EBCR includes the high relevance of the systematic review and RCT that were appraised with the clinical questions (PICO), these studies have similar population, intervention and outcomes as our patient's. Moreover, this EBCR only included systematic review of RCTs and RCTs, which ensured lesser study bias and were more reliable in assessing the effectiveness of medical treatments. On the other hand, the limitation in this EBCR is that we did not search for unpublished and ongoing studies, hence there is a possibility that some evidence was missed and not being reviewed.

In conclusion, based on the findings of the two evidences appraised in this EBCR, we could not recommend the addition of omega-3 PUFAs in the treatment of children with ADHD because there was no conclusive evidence on the benefit of this substance to reduce inattention symptoms. For our patient, P, we would recommend the continuation of the use of conventional therapy to further reduce the symptoms of ADHD. Nonetheless, given the importance of omega-3 in brain function, as well as the lack of consistent findings among included studies, it is important that future studies should continue to investigate the benefit of this substance.

Conflicts of Interest
None declared.

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