An updated systematic review on the effects of n-3 long-chain polyunsaturated fatty acids on autistic spectrum disorder

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\textbf{A B S T R A C T}

Objective: It has been suggested that omega-3 fatty acids deficiency could play a role in the pathogenesis of several psychiatric disorders, especially autism spectrum disorder (ASD). This systematic review of all available studies was conducted to assess the efficacy of omega-3 fatty acid supplementations on the core features of ASD.

Methods: To find the relevant articles, databases including MEDLINE, EMBASE, PsycINFO, PubMed, Scopus and Cochrane between 1966 and December 2016 were searched. The criteria of selecting studies were English language; oral administration of n-3 fatty acids supplements; clinical trials involving human patients with autism; and relationships between omega-3 fatty acids, DHA or EPA supplementation, as well as fish oil, and autism-related clinical- and social-related outcomes.

Results: We identified 337 articles in the systematic search, nine articles were finally chosen to be included in the review. Most studies have shown that omega-3 fatty acid supplementation can reduce hyperactivity and social problems in individuals diagnosed with autism. However, no significant association has been reported between omega-3 fatty acid supplementation as compared to placebo in behavioral abnormalities in most of the studies.

Conclusion: Based on the available literature, omega-3 fatty acids can act as an effective supplement in individuals with autism.


**Keywords:** Autism, Behavior, Omega-3 fatty acids, Hyperactivity, Social problems

\textbf{Introduction}

Autism spectrum disorder (ASD) is a neurological disorder, usually with an onset in early childhood, with symptoms such as problems in social interactions, delay in language skills and restricted behavior patterns. In addition to these core symptoms, children with autism might have serious behavioral problems such as self-injurious behaviors, aggression or tantrums. Although psychopharmacological therapies for autism have been studied for more than 50 years, only two drugs have recently been approved by the Food and Drug Administration (FDA) for the treatment of ASD symptoms (risperidone and aripiprazole for the treatment of irritability) [1]. Complementary and alternative treatments such as administering omega-3 fatty acid supplements, digestive enzymes and high doses of vitamins

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Omega-3 fatty acids and autism

have been used widely despite lack of enough evidence for their effectiveness or safety [2]. Recently, assessing the effectiveness of omega-3 fatty acid supplementation in improving and treatment of autism symptoms has received the attention of many investigators [3]. Several studies have shown that lipids play an essential role in neuronal processes and immune modulating — both involved in ASD. Polyunsaturated fatty acids, especially docosahexaenoic acid (DHA), are important in growth and maturation of the brain. Some recent evidence suggests that the metabolism of essential fatty acids may change due to genetic defects and imbalances in ASD [4]. Based on the available evidence, the ratio of omega-6 to omega-3 fatty acids is higher in the blood of children with ASD, while the long-chain polyunsaturated fatty acid (LCPUFA) group concentration in their blood is lower [5].

Mothers of the autistic children usually are not willing to have their sick children treated by drugs, so they look for alternative and effective treatments due to their negligible side effects. Nutritional interventions for children with autism are safer, more holistic and “natural” [6].

Parents who give fish oil supplements to their autistic children have reported improvements in their general health, sleep patterns, cognitive and motor skills, concentration, eye contact and sociability, as well as reduced irritability, aggression and hyperactivity [7].

A review in 2011 found no evidence for the efficacy of omega-3 fatty acids in improving social interaction, communication, stereotypy, or hyperactivity in children with ASD, but a trend towards improved hyperactivity [8].

The results of studies on the benefits of n-3 LCPUFAS for the treatment of ASD are contradictory and with no decisive conclusion. This literature review was conducted to evaluate the effects of omega-3 fatty acids in the improvement and treatment of behavioral symptoms of autism.

Methods

Search strategy and data extraction

In order to find the relevant articles (with no restriction as regards language of publications), six databases including MEDLINE, EMBASE, PsycINFO, PubMed, Scopus and Cochrane between 1966 and December 2016 were searched. The following keywords were used: n-3 PUFA, fish oil, “essential fatty acid”, EFA, “ω-3”, “omega-3”, ALA, ”Eicosapentaenoic Acid”, EPA, ”Docosahexaenoic Acids”, DHA, and “liver oil”. They were combined with the following search terms for autism: ”Child Development Disorders”, Asperger, “Autistic Spectrum Disorder”, ASDs, autism, ”Social Behavior Disorders”, ”pervasive development disorder” and ”autism spectrum disorder”, so that finally a total of 337 articles were selected.

Study selection

Two researchers inspected the titles and abstracts independently. The studies with the following criteria were selected: English language; oral administration of n-3 fatty acids supplements; clinical trials involving human patients with autism, and evaluating the relationships between omega-3 fatty acids, DHA or EPA supplementation or fish oil and autism-related clinical- and social-related outcomes. We excluded any other type of documents such as letters, comments, reviews, or ecological and animal studies.

The data extracted by the researchers included full names of authors, country, year of publication, the number of patients included, intervention dose, and changes in clinical- and social-related outcomes.
Publication bias was minimized by using multiple online databases in combination with manual reference searches.

**Quality Assessment**

Two authors independently assessed the quality of each study by the Jadad scale. The Jadad score is calculated based on the following three criteria: methods of blinding, randomization, and reporting of dropouts and withdrawals.

**Results**

**Description of included studies**

In the electronic literature search, finally 337 articles were identified, from which some were excluded for reasons such as duplication and lack of relevance, as shown in Figure 1; two studies were excluded due to combining omega-3 fatty acids with other supplements. Finally, nine articles met all the inclusion criteria. The characteristics of the included studies are shown in Table 1.

The studies had been carried out in the United States [9-11], Singapore [12], Canada [13], Japan [14], Israel [3], Italy [15] and Austria [7]. One study included adults [15] and others children. The number of children with autism enrolled in the trials varied widely from eight [3] to fifty-seven [9], and the ages in the studies ranged between 2 and 40 years. And, finally, the omega-3 fatty acids and DHA doses ranged between 0.93 to 2 gram/day.

**Social Function**

One of the most common problems in patients with autism is a pervasive social function [16]. Ooi et al. in an open-label pilot study [12] assessed the effects of omega-3 supplementations on 41 children and adolescents with ASD for 12 weeks. The results showed significant improvements in the ASD-related symptoms such as social awareness, cognition, communication, motivation and attention problems. Concomitant with the results of this study, in another study significant improvements were observed in the withdrawal scores (P <0.01) and the social responsiveness scale (SRS) communication subscale scores (P <0.05) in the omega-3 fatty acid supplementation compared to the placebo group [14]. Also, in another open-label pilot study [17] 1 gram daily, for 12 weeks, of omega-3 fatty acids in ten children 4 to 7 years old with ASD led to improvements in social skills. However, in two studies no significant difference was observed between omega-3 fatty acid supplementation and placebo groups as regards social functions [10, 13].

**Hyperactivity**

Bent et al. [9] conducted an internet-based randomized controlled trial to determine the effects of omega-3 fatty acid supplementation on hyperactivity in patients with autism and showed that 1.3 gram/day omega-3 fatty acids for six weeks did not result in any significant improvement in hyperactivity compared to placebo (omega-3 group improvement = 1.9 points higher than placebo, 95% CI, −2.2 to 5.2, p = 0.38). Similar conclusions were drawn in three other studies [10, 11, 17]. However, in a pilot study in 2006, researchers showed that 6 weeks of supplementation with 1.5g/day of omega-3 fatty acids in 13 children 5-17 years old resulted in significant reductions in hyperactivity and stereotypy [7].

| Table 1: Characteristics of the studies included in the review |
|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Authors          | Country          | Design           | Jadad score | No. of patients | Intervention (N) | Received placebo |
| Bent et al.      | USA              | RCT              | 5           | 25               | 13               | 12               | 1.3             | 12               |
| Mankad et al.    | Canada           | RCT              | 4           | 37               | 19               | 18               | 1.5             | 24               |
| Amminger et al.  | Australia        | RCT              | 4           | 12               | 7                | 5                | 1.5             | 6                |
| Meiri et al.     | Israel           | open-label       | 0           | 8                | 8                | -                | 1               | 12               |
| Bent et al.      | USA              | RCT              | 5           | 57               | 29               | 28               | 1.3             | 6                |
| Ooi et al.       | Singapore        | open-label       | 0           | 41               | 41               | -                | 2               | 12               |
| Politi et al.    | Italy            | open-label       | 0           | 19               | 19               | -                | 1.86            | 6                |
| Voigt et al.     | USA              | RCT              | 5           | 48               | 24               | 24               | 0.2 (DHA)       | 24               |
| Yui, et al.      | Japan            | RCT              | 5           | 13               | 7                | 6                | 0.24 (DHA)      | 16               |

RCT: Randomized clinical trial
Behavioral problems
In most of the studies reviewed no significant changes were observed in behavioral problems due to omega 3 fatty acid supplementation in children with ASD compared to placebo [9, 10, 13, 18], while one study suggested that such supplementation in patients with autism led to a greater remission of irritability [7].

Discussion
Based on the evidence summarized above, omega-3 fatty acid supplementation may bring about some protective effects on autism-related problems such as hyperactivity or communication problems, but no effect on behavioral problems.

According to population-based studies, among subjects with a lower intake of food sources of omega-3 fatty acids such as walnuts, flaxseeds, fish, seafood and fish oils, the rates of psychiatric disorders specially depression and bipolar disorder were higher [19, 20]. N-3 fatty acids, especially DHA, are involved in brain cortical maturation and synaptic signal transduction [21]. Also, in animal studies, it has been shown that perinatal deficits in brain DHA can influence behavioral and neurocognitive processes due to disruption in hippocampus-dependent spatial learning and, finally, lead to some behavioral abnormalities such as anxiety, aggression, and depression [22, 23]. Based on neuroanatomical analyses, autism disorder can be mediated by damage to medial-temporal lobe (hippocampus and amygdala) and the cerebellum. These areas of the brain are prone to damage due to deficiencies of nutrients, specially n-3 polyunsaturated fatty acids [24, 25]. No significant association has been reported between omega-3 intake and behavioral problems in the papers reviewed, except in one open-label study [7], which indicated that omega-3 supplementation can decrease severity of irritability in children with autism. In this systematic review we tried to assess the efficacy of omega-3 fatty acid supplementation in patients with autism based on clinical trial studies. The studies reviewed provide interesting, hypothesis-generating information about omega-3 fatty acid efficacy in autism-related disorders. The strength of this systematic review was the use of rigorous search and methodology. However, some of the studies reviewed had several limitations, which might have influenced their overall conclusions. In three of the studies [12, 15, 17] with an open-label design no effective randomization procedures were used, and the number of samples in some studies [14, 17] was low. Also, in different studies different types of questionnaires were used for assessment of autism-related problems.

Some of the conclusions drawn in our review are in line with those of the Cochrane review [8], although the number of studies included in our review was higher. Furthermore, our study shows that omega-3 fatty acid supplementation in children with autism can decrease the severity of some problems such as hyperactivity and social abnormalities. Finally, we found no adverse events associated with n-3 fatty acids supplementation.

It seems that studies with higher sample sizes are essential to be able to draw more definite conclusions about effective doses of omega-3 fatty acids for individuals with ASD.

Conclusion
Based on this review, there is evidence to support the theory that omega-3 fatty acids supplementation can act as a protective or treatment agent against some problems in individuals with ASD.

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Conflict of Interests
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