Essential fatty acids and attention-deficit–hyperactivity disorder: a systematic review

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LIST OF ABBREVIATIONS

ALA	α-Linolenic acid
DHA	Docosahexanoic acid
EFA	Essential fatty acid
EPA	Eicosapentanoic acid
LC-PUFA	Long-chain polyunsaturated fatty acid
MVM	Multivitamin/mineral
TOVA	Test of Variables of Attention

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AIM Essential fatty acids (EFAs), also known as omega-3 and omega-6 fatty acids, have been claimed to have beneficial effects as a treatment for attention-deficit–hyperactivity disorder (ADHD). Animal experiments have provided information about the role of EFA in the brain, and several mechanisms of EFA activity are well known. The current review provides an updated, systematic overview of the theory and use of EFA in ADHD.
METHOD Clinical studies and review papers of EFA blood levels and EFA supplementation trials in children with ADHD were researched in the Medline PubMed database. Additional studies were found from the references of these reports.
RESULTS Children with ADHD present lower levels of blood EFAs, and open-label EFA supplementation trials in ADHD raise EFA blood levels and improve symptoms of ADHD. Randomized controlled trials, however, have generally been unsuccessful in demonstrating any behavioural treatment effects.
INTERPRETATION Current findings do not support the use of EFA supplements as a primary or supplementary treatment for children with ADHD.

Essential fatty acids (EFAs) as a complementary or alternative treatment for attention-deficit–hyperactivity disorder (ADHD) have generated discussion in many countries. These fatty acids have been used as both a primary and an adjunctive treatment for ADHD. Therefore, the scientific evaluation of these supplements is highly important. Several review articles and reports have been published in this field, and the reader is encouraged to consult these in detail.[1–4] The purpose of the current review is to provide an updated, systematic overview of the theory and use of EFAs in ADHD.

Humans are unable to synthesize linoleic acid, an omega-6 fatty acid, and α-linolenic acid (ALA), an omega-3 fatty acid, de novo. The main dietary sources of linoleic acid are vegetable oils (such as corn, sunflower and cotton) and their seeds. ALA is found in vegetable oils (especially in soy, canola, flaxseed, and walnut oils), flaxseeds, and walnuts.[5]

Figure 1 shows a schematic representation of the main pathways of EFA in the human body. Linoleic acid and ALA can be further desaturated and elongated by a series of enzymes. The main EFAs that can be found after desaturation and elongation include arachidonic acid, an omega-6 fatty acid, and eicosapentanoic acid (EPA), an omega-3 acid. In this process, omega-3 and omega-6 use the same enzymes, from which δ-6-desaturase (D6D) is rate limiting. EPA is further metabolized into docosahexanoic acid (DHA), which can be converted back to EPA in vivo. DHA and EPA are obtained in the diet mainly from fatty fish and fish oils.

Arachidonic acid, EPA, and DHA are usually referred to as long-chain polyunsaturated fatty acids (LC-PUFAs). Synthesis of LC-PUFAs takes place mainly in the liver, brain, heart, and lungs. They are incorporated into phospholipids, and exist in very low amounts in triglycerides. LC-PUFAs are often hydrolysed by phospholipase A_2 and further oxidized by cyclooxygenase or lipooxygenase enzymes. This process creates a wide range of high-impact, short-lived metabolites, known as eicosanoids, with the preferred substrate being arachidonic acid. Each eicosanoid

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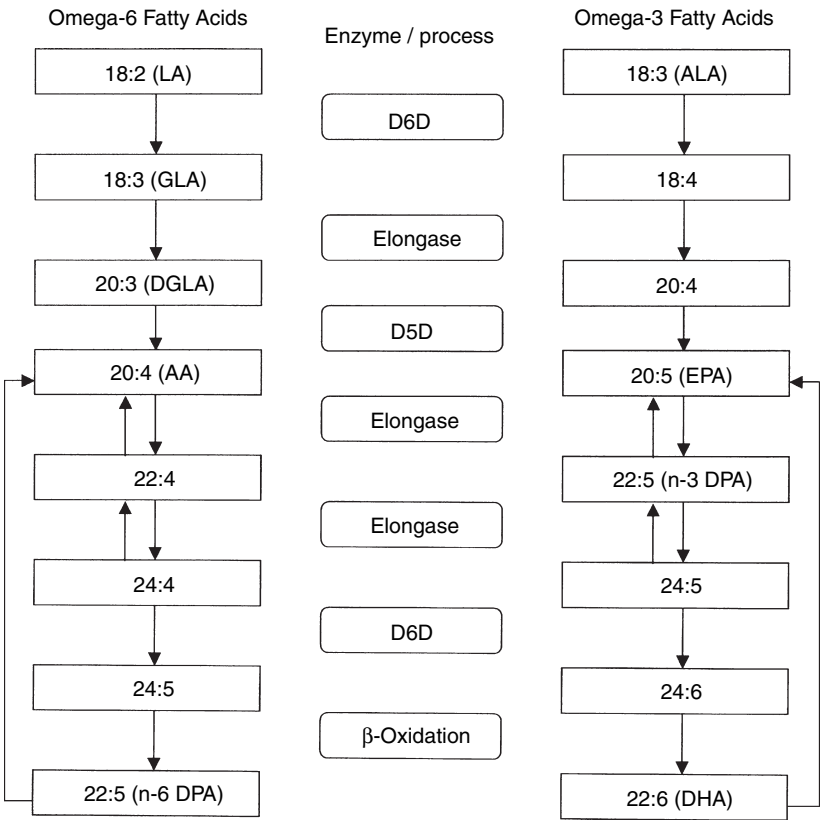

Figure 1: Main essential fatty acids pathways. Left: Omega-6 fatty acids. Right: Omega-3 fatty acids. Middle: enzyme/process. Fatty acids are written by the number of carbons and double bonds, e.g. 18:2, 18 carbons, 2 double bonds. EFA, Essential Fatty Acids, LA, Linoleic acid, GLA, Gamma-linolenic acid, DGLA, Di-homo gamma-linolenic acid, AA, Arachidonic acid, DPA, Docosapentanoic acid, D6D, Delta-6-desaturase, D5D, Delta-5-desaturase, ALA, Alpha-linolenic acid, EPA, Eicosapentanoic acid, DHA, Docosahexanoic acid.

acts through a specific superficial or intracellular receptor, modulating signal transduction pathways and gene transcription.[6]

THE IMPORTANCE OF EFA IN THE BRAIN

The brain is one of organs the richest in LC-PUFA. Lipids comprise around 50 to 60% of the dry weight of the adult human brain, and about one-third of this content is in the form of LC-PUFA, mainly arachidonic acid and DHA.[7–9] It is still to be revealed what is so unique about DHA, and why the brain maintains its special lipid content.

The essentiality of dietary DHA, however, is questionable. Many countries practice low fish consumption, and within these countries some individuals undoubtedly consume worthless amounts of DHA. Vegetarians and vegans, Buddhists, Hindu, Taoists, and other populations avoid consumption of fish (sometimes for several generations). Nevertheless, none of these populations are known for low brain volume, or high prevalence of neuropsychiatric problems.[10]

The most widespread technique used to study the role of EFA in the brain in laboratory animals is that of EFA deficiency. These studies usually compare a group of animals consuming a 'normal' laboratory diet with an EFA-deficient group. To create severe deficiency, the diet can even be maintained for two or three generations. These studies, most of which have been on rats, inform us about various biochemical and cognitive measures of the EFA-deficient animal.

Based on these studies it can be concluded that the brain adequately maintains its DHA content, and when this fails it uses a compensatory synthesis of the omega-6 docosapentanoic acid. In addition, the frontal cortex, which is typically rich in DHA, tends to be sensitive to dietary omega-3 deficiency, being the first to reduce DHA levels and the last to restore them.[11–13] Omega-3 deficiency influences anatomical parameters,[12,14–16] retinal function and visual capabilities,[15,17,18] learning and memory scores (reviewed in Fedorova and Salem),[19] highly important biochemical measures such as energy

consumption and Na^+, K^+-ATPase activity,[17,20] and electroencephalography powers.[21]

Pharmacological challenges revealed that animals deficient in omega-3 display significant elevations in amphetamine-induced locomotor activity, significant decrements in locomotor activity in response to scopolamine, and significant decrements in catalepsy induced by haloperidol.[12] In rats raised on normal diets, DHA fractions in phosphatidyl-ethanolamine were significantly correlated with nocturnal locomotor activity and the locomotor response to novelty (hyperactive individuals had less DHA than hypoactive ones). A similar correlation was not found with attention or impulsivity tests.[22]

The monoamine content of the brain is drastically affected by changes in dietary EFA, with the dopaminergic system and the frontal cortex being the most sensitive. Various brain regions and dopaminergic pathways seem to be influenced differentially. For example, in animals deficient in omega-3 the mesolimbic pathway seems to be hyperfunctional, whereas the mesocortical pathway seems to be hypofunctional.[21,23–26] These neurochemical changes (although not proven in humans) may be strongly involved in the altered cognitive, motivational, and even motor patterns seen in animals deficient in omega-3. In this context, it should be remembered that ADHD is strongly linked to prefrontal and striatal catecholamines, in both theoretical and practical terms.

MECHANISMS OF ACTION OF EFA IN THE BRAIN

Two main mechanisms were traditionally considered responsible for the effects of EFA: the alteration of biophysical properties of the cell membrane (especially fluidity) by DHA, and the control of EFA metabolites (mainly eicosanoids) by LC-PUFA. Other proposed mechanisms include EFA involvement in synapse and nerve growth processes, and modulation of different kinds of protein (such as enzymes and ion channels). The views about these two proposals have dramatically advanced over the past 10 years, and the current paper will only make references to these issues. A newer direction is that of gene regulation. These suggested mechanisms are related to each another. For example, membrane biophysical properties are assumed to affect the function of membrane proteins (such as ion channels and key enzymes involved in signal transduction), and eicosanoids have been proven to affect synapse and nerve growth.

Eicosanoids are involved in a wide range of crucial activities in the cell and its close environment, such as vasodilation, vasoconstriction, inflammation, pain, immunomodulation, platelet aggregation, and adhesion. In the brain, eicosanoids are involved in several physiological processes including synaptic plasticity, temporal summation, membrane excitability, neurotransmitter release, apoptosis, and ageing.[27–30] A schematic representation of the main EFA metabolites is presented in Figure 2. Although arachidonic acid is converted to the 2-series prostanoids and 4-series leukotrienes, EPA is converted to the 3-series prostanoids (e.g. PGE_3) and the 5-series leukotrienes (e.g. LTB_5). Di-homo-gamma-linolenic acid, an omega-6 acid, forms the 1-series prostanoids (e.g. PGE_1). Eicosanoids formed from EPA and di-homo-gamma-linolenic acid have a different activity and are generally less inflammatory than the arachidonic acid metabolites. Accordingly, adding EPA or di-homo-gamma-linolenic acid to the diet without increasing arachidonic acid amounts will result in a change in the composition of eicosanoids produced in the cells (owing to substrate competition), followed by physiological and sometimes clinical effects.[18,27,31] Several other LC-PUFA metabolites have been studied, some of which have only recently been discovered and seem to be of high importance.[29,32–34]

Arachidonic acid and DHA modulate gene expression at the transcriptional level. DNA microarray studies of rodents raised on various diets (which differ in their EFA content) revealed that either ALA or EPA+DHA enrichment increased the expression of 55 genes (up to sevenfold), whereas the expression of 47 genes was decreased (up to minus five-fold). Among the modulated genes, one can find some that are related to serotonin, immunoglobulins, nuclear factor kappa B, synaptic plasticity, signal transduction, ion channel assembly, cytoskeleton, energetic metabolism, and protein regulation.[18,34] Microarray analysis in EFA-deficient rodents found a wide range of overexpressed transcripts, some of which code for several receptors, including that for glutamate, acetylcholine, gamma-aminobutyric acid, and dopamine.[35]

EFAs affect major signalling pathways and regulate the activity of voltage-gated K^+, L-type Ca^{2+}, and sodium channels, as well as Ca-ATPase in neuronal membranes and gap-junction intercellular communication.[36,37] The administration of DHA to rodent fetal brain enhanced its free-radical scavenging ability.[35] DHA was also shown to have neurotrophic properties during the perinatal period, promoting nerve growth factor, synaptogenesis, neuronal arborization, and differentiation.[12]

Adding these findings to the neurochemical effects found in animal experiments (e.g. monoamine alterations, discussed above), suggests that EFAs are actually involved in many cellular activities within the neuron, from gene expression, through cytoplasmic and membrane protein activities, to electrical and chemical conduction of the signal. The amount and complexity of the components influenced by EFAs and their cross-interactions currently prevent us from describing their exact effective pathways.

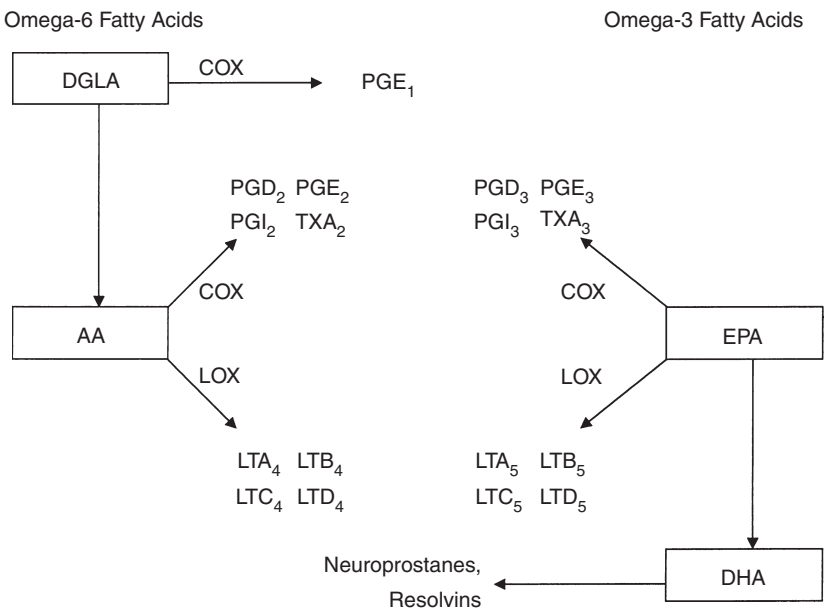

Figure 2: Main essential fatty acids metabolites. EFA, Essential Fatty Acids, DGLA, Di-homo gamma-linolenic acid, AA, Arachidonic acid, EPA, Eicosapentanoic acid, DHA, Docosahexanoic acid, COX, Cyclooxygenase, LOX, Lypooxygenase, PG, Prostaglandin, LT, Leukotriene, TX, Thromboxane.

WHICH DATA LINK EFA SUPPLEMENTATION TO ADHD?

EFA blood levels in children with ADHD

The association between EFA and hyperactivity was initially hypothesized in 1981.[38] This hypothesis is compatible with lower blood EFA fractions in children with ADHD compared with matched comparisons. Several studies have explored this issue (Table I).[39–46] Although the results are inconsistent, and most of these studies suffer from methodological shortcomings, some of the findings were replicated by several studies, and are considered more reliable. These include lower plasma fractions of arachidonic acid, DHA, and EPA, a similar picture for red blood cells, and a higher omega-6 to omega-3 ratio in the population with ADHD.

Several factors may contribute to the unusual EFA profile in ADHD.[47] One can hypothesize that an EFA blood profile simply reflects the dietary EFA composition. Consistent with this idea, Yang et al.[48] found that children with ADHD consume significantly lower amounts of linoleic acid and ALA. These results, however, contradict three other reports, finding either higher PUFA and fat intake by these children[41] or no difference in dietary intake, except for a higher consumption of energy or fat.[45,46]

Another hypothesis that links EFA to ADHD is that children with ADHD might suffer from slower conversion of linoleic acid and ALA to LC-PUFA. A recent genetic study supports this direction: Brookes et al.[49] scanned fatty-acid desaturase genes for associations between 45 single nucleotide polymorphisms and ADHD. They found a significant association of ADHD with the single nucleotide polymorphism rs498793 in the *FADS2* gene (odds ratio: 1.6, 95% confidence interval: 1.15–2.23). A different biochemical hypothesis is that children with ADHD may have enhanced non-enzymatic oxidation of EFAs; however, current antioxidant measurements and other findings do not support this hypothesis.[47]

Stevens et al.[50] examined children with and without behavioural difficulties, and divided them to three groups according to their plasma omega-3 levels. The group with lower omega-3 presented significantly worse behaviours on various scores, including conduct, anxiety, hyperactivity/impulsivity, temper tantrums, and sleep problems. Teacher evaluations of behaviour were not significantly different between the groups, except for scores in mathematics and overall academic skills, which were significantly lower in the group with low omega-3. A similar division for three groups, made by values of omega-6 plasma, resulted in no significant difference in any of the behavioural scores.

One should note that lower levels of EFA in the blood do not necessarily reflect lower levels of EFA in the brain, as demonstrated in rodents by Rioux et al.[51] This may be a consequence of several factors, one being the existence of

Table I: Summary of studies on blood essential fatty acid (EFA) status in children with attention-deficit–hyperactivity disorder (ADHD)

Reference	Participants	Significant findings (ADHD group compared with non ADHD group)	Comments
Mitchell et al.[39]	23 'maladaptive, hyperactive' children, 20 comparison children; age range 7.5–13y	No significant differences in red blood cell fatty-acid contents	No formal diagnosis
Mitchell et al.[40]	48 hyperactive children, 49 comparison children; age range 9.1, SD 2.3y	Lower serum DHA, DGLA, arachidonic acid	Some of the children were on special diets
Stevens et al.[41]	53 children with ADHD, 43 comparison children; age range 6–12y	Lower plasma arachidonic acid, EPA, DHA, total n-3 and red blood cell arachidonic acid, docosapentanoic acid, higher n-6/n-3 ratio	
Chen et al.[42]	58 children with ADHD, 52 comparison children; age range 4–12y	Higher plasma γ-linolenic acid, higher red blood cell oleic acid, lower red blood cell linoleic acid, arachidonic acid, DHA, nervonic acid	
Joshi et al.[43]	30 children with ADHD, 29 comparison children; age 8y (mean)	No significant differences in red blood cell fatty-acid contents	
Germano et al.[44]	16 children with ADHD, 31 comparison children; age range 3.5–16y	Higher arachidonic acid/EPA ratio	Specific EFA levels were not reported
Antalis et al.[45]	12 ADHD students, 12 comparison students	Higher total saturated fatty acids (plasma, red blood cell), higher oleic acid (plasma), lower total n-6 (plasma), higher arachidonic acid (red blood cell), lower EPA (plasma), DHA (plasma, red blood cell), higher n-6/n-3 and arachidonic acid/EPA ratios (plasma, red blood cell). DHA amounts negatively correlated with ADHD symptoms	Adult population
Colter et al.[46]	12 ADHD adolescents, 11 comparison adolescents; age range 13.6, SD 2.2y	Lower red blood cell DHA, DGLA, and total n-3, higher red blood cell linoleic acid and n-6/n-3 ratio	Major difference in sex ratio between the groups

DHA, docosahexanoic acid; DGLA, dihomo-γ-linolenic acid; EPA, eicosapentanoic acid.

the blood–brain barrier. The rate and mechanisms of penetration into the brain are not the same for all EFAs,[52–54] and evidence suggests that the blood–brain barrier plays a role in the conversion of linoleic acid and ALA to arachidonic acid and EPA.[55–57] In addition, the association between EFA blood status and ADHD symptoms is not sufficient to prove a causal relation. There are no reference levels of EFA blood levels required for normal health in humans, and the fact that some children have lower levels than others does not necessarily have clinical implications.

EFA deficiency signs in children with ADHD

Colquhoun and Bunday[38] observed excessive thirst, frequent urination, dry skin, and dry hair in their sample of children with ADHD. Mitchell et al.[40] found that his sample of 48 hyperactive children reported significantly more polydypsia and polyuria than the 49 in his comparison group, but there was no higher prevalence of asthma, eczema, or other allergies. Stevens et al.[41] found that the total score of seven EFA-deficiency signs was significantly higher in individuals with ADHD than in the comparison group. The same list of symptoms was used by Antalis et al.[45] who found that adults with ADHD also present significantly higher deficiency scores than matched comparisons.

Stevens et al.[41] went further on to examine the relation between EFA deficiency signs and actual EFA status in the blood. They found that children with ADHD presenting more EFA deficiency signs had significantly lower plasma concentrations of arachidonic acid and DHA than did children with ADHD with less EFA deficiency signs. The group with more deficiency signs demonstrated greater incidence of allergic rhinitis, temper tantrums, and problems getting to sleep. In terms of dietary intake, the only reported difference was increased fluid consumption.

However, the group of children with ADHD with deficiency signs did not demonstrate significantly different plasma EFA contents from that of the normal comparison group of children.

Further analyses revealed significant correlations; the total deficiency score was negatively correlated with arachidonic acid and DHA values, and positively correlated with behavioural evaluations by parents (i.e. increased deficiency signs were associated with ADHD behaviour).[41] DHA values were negatively correlated with the same behavioural estimations. The subsequent study by the same group found that individuals having lower levels of plasma omega-3 reported significantly increased deficiency symptoms. In the group with lower total omega-6 levels, a greater frequency of dry skin and dry hair was observed.[50]

CAN EFA SUPPLEMENTATION INFLUENCE ADHD SYMPTOMATOLOGY?

Regardless of the role that EFA deficiency plays in the aetiology of ADHD, a practical question was raised: can EFA supplementation improve symptoms of ADHD? The list of published EFA intervention trials in ADHD (or ADHD-like populations) so far, with some key characteristics, can be found in Tables II (open-label trials) and III (randomized controlled trials).

Open-label EFA supplementation trials in ADHD

Harding et al.[58] compared 10 children receiving EFA plus food supplement complex with 10 other children receiving methylphenidate (5–15mg two or three times daily) for 4 weeks. The assignment of the children to the two groups was done by parental choice, lacking randomization or blindness. Both groups significantly improved their behaviour, and there was no significant between-group difference at the completion of the study.

Thirty diagnosed, non-medicated children with ADHD were recruited to an open-label, uncontrolled study of supplementation with flax oil and vitamin C for 13 weeks (Joshi et al.).[43] Plasma EPA and DHA significantly increased from baseline, whereas plasma arachidonic acid level significantly decreased. All reported behavioural measures (comprising parental rating scales of restlessness, inattention, impulsivity, self-control, social problems, and learning problems, based on the DSM-IV significantly improved from baseline. This study demonstrated the ability of ALA supplementation to cause significant changes in the plasma EFA status, elevating DHA and EPA and reducing arachidonic acid, thus decreasing the ratio of omega-6 to omega-3.

Germano et al.[44] presented an open-label trial of 31 non-medicated children with ADHD. Each of the children consumed 2.5g/day of fish oil (52% EPA, 28% DHA) per 10kg of body weight, for a period of 8 weeks. Nineteen children completed the study, but three of them reported consuming fish oil before the study and were therefore excluded from behavioural analyses (effective dropout rate 43%). Both inattention and hyperactivity scores (assessed by parents) significantly improved. Other behavioural measures were not reported. Besides the low sample size and high dropout rate, the only questionnaire used was the abbreviated version of the Conners' Rating Scales.

Sorgi et al.[59] tested nine children diagnosed with ADHD, before and after 8 weeks of supplementation with up to 16.2g/day of EPA plus DHA. All ADHD-related behavioural assessments demonstrated significant improvements. This clinical improvement was correlated with the

Table II: Summary of open-label essential fatty acid (EFA) supplementation trials in children with attention-deficit–hyperactivity disorder (ADHD)

Reference	Participants	Supplements (daily amounts)	Period (wks)	Significant findings	Comments
Harding et al.[58]	20 children with ADHD; age range 7–12y	Either 180mg EPA+120mg DHA+food supplements (*n*=10), or MPH (*n*=10)	4	Improved behavioural ratings in both groups	Group assignment made by parents
Joshi et al.[43]	30 children with ADHD; age 8y (mean)	Flax oil (400mg ALA)+vitamin C	13	Improved behavioural ratings	
Germano et al.[44]	16 children with ADHD; age range 3.5–16y	2.5g fish oil (52% EPA, 28% DHA) per 10kg of body weight	8	Clinical improvement	
Sorgi et al.[59]	9 children with ADHD; age range 8–16y	Up to 16.2g/d EPA+DHA	8	Improved behavioural ratings	Children were instructed about healthy diet at baseline

MPH, methylphenidate; ALA, α-linolenic acid.

Table III: Summary of randomized controlled essential fatty acid (EFA) intervention trials in attention-deficit–hyperactivity disorder (ADHD)

Reference	Participants	EFA supplements (daily amounts)	Placebo (daily amounts)	Period (wks)	Significant treatment effects	Dropout rate (%)	Comments
Aman et al.[61]	31 children	3g Efamol (240mg γ-linolenic acid+2.1g linoleic acid)		4	Improvement in only 2 of 42 variables		No diagnosis: children with some ADHD symptoms, double-crossover
Arnold et al.[62]	18 children; age range 6–12y	4g Efamol (320mg γ-linolenic acid+2.8g linoleic acid)	Mineral oil or dextroamphetamine	4	No improvements (after statistical corrections)		Many details are missing, Latin-square
Voigt et al.[63]	63 children; age range 6–12y	345mg DHA	Not reported	17.5	No improvements	14	All children were medicated
Brue et al.[64]	60 children; age range 4–12y	2g flaxseed+supplement cocktail	Slippery elm supplement	12	Improvements in 1 of 4 scales for the medicated children	15	Half of the children in each group were medicated
Stevens et al.[65]	50 children; age range 6–13y	480mg DHA, 80mg EPA, 40mg arachidonic acid, 96mg γ-linolenic acid	6.4 g olive oil	17.5	Improvement in only 2 of 16 target measures	34	All children present EFA deficiency signs, most children were medicated
Hirayama et al.[66]	40 children; age range 6–12y	~500mg DHA+100mg EPA (added to foods)	Indistinguishable control foods	8.5	Better results for placebo (no difference when excluding undiagnosed children)		Six children were not diagnosed, most children not medicated
Richardson and Puri[67]	41 children; age range 8–12y	186mg EPA, 480mg DHA, 96mg γ-linolenic acid, 864mg LA, 42mg arachidonic acid, 8mg thyme oil	Olive oil	12	Improvement in some of the scales	29	Non-ADHD children (learning difficulties)
Richardson and Montgomery (phase 1)[68]	117 children; age range 5–12y	558mg EPA, 174mg DHA, 60mg γ-linolenic acid	Olive oil	13	Improvement in all ADHD-related scales (inattention, hyperactivity–impulsivity), assessment by teachers	6	Non-ADHD children (developmental coordination disorder)
Sinn and Bryan (phase 1)[69]	167 children; age range 7–12y	558mg EPA, 174mg DHA, 60mg γ-linolenic acid, with or without additional supplements	Palm oil	15	Improvement in most ADHD scales in parents reports, no improvement in teacher reports	37	No ADHD diagnosis (reported ADHD symptoms)
Johnson et al. (phase 1)[71]	75 children; age range 8–18y	558mg EPA, 174mg DHA, 60mg γ-linolenic acid	Olive oil	13	No improvements in most ADHD scales, improvement only in clinical impression	22	
Raz et al.[72]	73 children; age range 7–13y	480mg linoleic acid+120mg ALA	Vitamin C	7	No improvements	14	

DHA, docosahexanoic acid; EPA, eicosapentanoic acid; ALA, alpha-linilenic acid.

changes in the plasma phospholipid ratio of arachidonic acid to EPA.

In summary, open-label EFA trials in ADHD clearly demonstrate that several weeks of EFA supplementation (whether in the form of LC-PUFA or short-chain EFA) can easily normalize EFA blood levels (see also Young et al.).[60] We can also conclude that ADHD symptoms are responsive to EFA supplementation, when given in an open-label form. These studies, however, cannot separate the biological effects from the placebo effects on behavioural endpoints.

Randomized controlled EFA supplementation trials in ADHD

Aman et al.[61] gave 31 children who were 'selected for marked inattention and overactivity' either evening primrose oil or placebo, in a double-crossover design, with 4 weeks of supplementation for each condition. The study's results were disappointing. Although supplementation significantly improved parental ratings of attention and hyperactivity, such effects were not demonstrated by a variety of eight other psychomotor performance tests, nor by teacher rating scales. Overall, significant improvement was seen only in 2 out of 42 outcome variables. Baseline blood EFA concentrations were found to be unrelated to treatment effects. The trial suffered from two main methodological shortcomings: unclear inclusion/exclusion criteria and a double-crossover design. The half-lives of EFAs in the brain are much too long to switch directly from EFA supplementation to placebo and consider the period after the crossover free from the influence of EFA.

Evening primrose oil was tested again in a higher dose on 18 children with ADHD by Arnold et al.[62] This study compared the supplement with placebo and with dextroamphetamine, in a double-crossover Latin-square design. EFA proved better than placebo only in the parent-assessed hyperactivity scores, whereas all other measures, including ratings by teachers, did not show significant treatment effects. Important details, such as dropout rate and the full list of measures taken, were not reported. The small sample size and Latin-square design make it difficult to draw conclusions from this study. When examining only the results of the first month (i.e. no crossover), no significant treatment effect was found.

Voigt et al.[63] recruited 63 stimulant-medicated children with ADHD to a randomized, double-blind study comparing DHA supplementation with identical-appearance placebo (contents not specified) for 4 months. Outcome measures included variables produced by the computerized Test of Variables of Attention (TOVA), as measured after 24 hours without medication, behavioural variables assessed by the parental Child Behavior Checklist and parental Conners' Rating Scales, and the Children's Color Trails Test. Fifty-four children completed the trial (dropout rate 14%). Plasma DHA increased by an average of 260% from baseline for the DHA group, whereas plasma arachidonic acid and EPA decreased by 12.5% and 30% respectively. The placebo group did not demonstrate significant changes in plasma EFA profile. Despite the elevated plasma DHA levels, there was no significant difference between the groups in any of the outcome measures. Looking at treatment effects within the groups, TOVA errors of omission (considered to reflect inattention) worsened significantly in the DHA group but not in the placebo group, and TOVA errors of commission (considered to reflect impulsivity) improved significantly in the placebo group but not in the DHA group. In other words, the placebo group actually did better than the control group, although this between-groups difference did not reach statistical significance. In addition, there was no significant correlation between initial plasma DHA and initial or final scores on any component, or between the change in plasma DHA and the change in scores on any component.

Brue et al.[64] conducted a trial with 30 unmedicated and 30 medicated (receiving methylphenidate) children with ADHD. Each group included 15 children receiving either flaxseed (rich in ALA) plus a supplement cocktail, or placebo plus the same supplement cocktail, for 12 weeks. Fifty-one children completed the study (dropout rate 15%). In the two groups of medicated children, flaxseed proved significantly better than placebo on the teacher-assessed inattention scale, but other assessments (parental assessments of inattention, teacher and parental assessments of hyperactivity/impulsivity) did not demonstrate a between-groups effect. In the two groups of non-medicated children, scales of inattention did not show any treatment effect. The hyperactivity/impulsivity factor did show significantly better improvement for the EFA group on teacher assessment, but the opposite was observed for parental ratings. The main shortcomings of this research were low sample size and the use of the supplement complex. Because of the inconsistent results, one can hardly draw a clear conclusion from this study.

Stevens et al.[65] compared 50 children with diagnosed ADHD and reported thirst and skin problems, who received either an EFA complex or placebo for 4 months, in a double-blind randomized trial. Eighteen children from the EFA group and 15 from the placebo group completed the study (dropout rate 34%). Significant treatment effects were seen only for 2 out of 16 target measures (conduct, rated by parents, and attention, rated by teachers). The increase in red blood cell EPA was significantly and negatively correlated with parental assessments of disruptive

behaviour. Similar results were obtained for red blood cell EPA and DHA, and teacher-assessed attention ratings. This study is interesting because of the inclusion criteria of EFA deficiency symptoms. Despite this condition, the study failed to turn up with a clear, positive benefit for EFA over placebo. In addition, the final sample size was small, as a result of the high dropout rate.

Hirayama et al.[66] conducted a blind randomization of 40 children with ADHD (34 of whom were properly diagnosed and the rest only 'suspected') to 2 months of either DHA plus EPA or placebo, both consumed through supplemented foods. All children (n=20 in each group) completed the study. The changes in most measures taken were not significantly different between the groups. Significant changes that did occur between the groups (improvements in visual short-term memory and errors of commission on the continuous performance test) displayed better outcomes for the placebo group.

Richardson and Puri[67] tested 41 children with specific learning difficulties and symptoms of ADHD in a randomized double-blind study. Each child received either an EFA complex or placebo for 12 weeks. Twenty-nine children completed the study (15 EFA, 14 placebo, dropout rate 29%) including full parental assessment at the final stage. Behavioural improvements were significantly better for the EFA group over placebo, for scales of cognitive problems, anxiety/shyness, and the Conners' index, so measuring a broader range of behavioural problems. The main methodological limitations of the study were the small sample size and the high dropout rate. The applicability of the study to children with ADHD is highly questionable; the children were not diagnosed, and the authors state that most of them showed subclinical levels of ADHD symptoms.

A follow-up randomized, double-blind, one-way crossover trial was published 3 years later (Richardson and Montgomery).[68] The first phase of the study included 117 unmedicated children having a diagnosis of developmental coordination disorder. The treatment group received an EFA complex whereas the placebo group received placebo for 3 months. No child had a formal ADHD diagnosis, but the average score of ADHD symptoms (for both groups) was higher than the average in the general population.

The first phase was completed by 110 children (dropout rate 6%). ADHD symptoms were assessed by teachers only, with significantly better treatment effects for the EFA group in two out of six subscales and seven out of seven global scales, including those of inattention and hyperactivity/impulsivity. One hundred children completed the second phase of the study (a one-way crossover, placebo to EFA), which lasted an additional 3 months (dropout rate for the second phase was 9%). Moving from placebo to EFA supplementation resulted in similar outcomes to those shown in the first phase for the EFA group. The children from the original EFA group continued to improve on all measures.

This study corrected some of the methodological difficulties that appeared in Richardson and Puri.[67] Sample size and dropout rates were addressed and improved. As to the blind phase, behavioural improvements, especially in ADHD-related rating scales, were impressive, and constitute better results than the previous study. In terms of interpretation, the open-label phase should be considered as a separate, uncontrolled study, and its effects cannot be distinguished from the placebo effect. Owing to the inclusion of children without ADHD, the applicability of this trial to ADHD is questionable.

Sinn and Bryan[69] performed another follow-up study, sharing the same design and a similar supplement. This study recruited 167 non-medicated children who presented scores of at least two standard deviations above the population mean in the Conners' Abbreviated ADHD Index. For the first 15 weeks of the trial (phase 1), the children were randomized to the following three groups: EFA, EFA plus multivitamin/mineral (MVM), and placebo. The second phase of the study (wks 16–30) was single-blind: all participants were given EFA plus MVM, a condition that was known to the researchers only.

One hundred and thirty-two participants completed the first phase, but complete data for analysis were available for 104 only (dropout rate 37%). There was no significant difference in treatment effects in the EFA plus MVM group compared with the EFA group. These two groups were combined and compared together with the placebo group. This comparison yielded significant improvements in the EFA groups (combined) compared with the placebo group on the following parental rating scales: cognitive problems/inattention, Conners' ADHD Index, restless–impulsive (Conners' Global Index), oppositional behaviour, and DSM-IV symptom subscales of inattention and hyperactivity–impulsivity. Improvements for emotional lability, anxious/shy, perfectionism, social problems, and psychosomatic scales were not significantly different in this comparison. No significant difference between groups was found for any assessments by teachers.

One hundred and nine children completed the second phase of the study, but complete data were available for only 87 participants (dropout rate 34%). The placebo group significantly improved on cognitive problems/inattention, hyperactivity, Conners' ADHD Index, restless–impulsive (Conners' Global Index), and both DSM-IV symptoms subscales inattentive and hyperactive–impulsive, as well as on the perfectionism and social problems subscales. Both PUFA groups continued to improve on

cognitive problems/inattention, Conners' ADHD Index, restless–impulsive (Conners' Global Index), both DSM-IV symptom subscales inattentive and hyperactive–impulsive, and on the hyperactivity subscale. Assessments by teachers were again found to be insensitive to treatment in all groups.

The study had several methodological problems, which are discussed in more detail in Busch[3] and subsequently in Sinn.[70] The participants were assumed to reach the clinical threshold of ADHD symptoms, but this was based on an abbreviated parental questionnaire only, and a definite diagnosis was not established. Another issue was the problematic blindness management, because the EFA plus MVM group took a daily MVM tablet, in addition to the six daily EFA capsules, whereas the placebo group took only six daily placebo capsules. No assessment of blindness was reported. Very high dropout rates are another potential bias. The use of the MVM tablets and the inclusion of the MVM plus EFA group in a combined group for comparison with placebo, without a separate comparison between EFA only and placebo, is also problematic. Taken together, these shortcomings make the interpretation of the first phase of the study difficult, despite its positive results from parental questionnaires. The second phase, being single-blind and uncontrolled, is very similar to an open-label study, with all the additional considerations that follow the interpretation of such study design.

Johnson et al.[71] tested the same EFA supplement in a similar research design. In this study, children diagnosed with ADHD were randomized to either an EFA supplement or placebo for 3 months. The first phase, which ended with a dropout rate of 22%, demonstrated significant treatment effects in the Clinical Global Impression scores, but not in ADHD Rating Scales. These measures were filled by the investigators, based on interviews with the parents. Similar results were obtained for the second (open-label) phase of the study. The authors concluded the study results to be essentially negative, not supporting superiority for EFA over placebo. This study tried to replicate the success demonstrated by earlier studies that used the same supplement, while improving the methodology: lower dropout rates, careful diagnosis, and blindness management. Unfortunately, most of the benefits shown by previous studies diminished, and the positive findings (i.e. improved Clinical Global Impression scores) were justifiably judged by the authors as negligible, given the failure of the more detailed and structured scales to show similar improvements.

Raz et al.[72] randomized children diagnosed with ADHD to either short-chain EFA supplementation or placebo groups, for a period of 7 weeks. The study used teacher and parental questionnaires, as well as an objective continuous performance test (TOVA). With a dropout rate of 14%, the study failed to demonstrate a benefit for EFA supplementation over placebo in any of the measures taken.

In summary, despite successful open-label trials, randomized controlled trials of EFA in ADHD have generally been unsuccessful in demonstrating treatment effects, and some of them even displayed better results for the placebo group.[63,66,72] This response probably demonstrates a strong placebo effect for this treatment and diagnosis, and emphasises the need for strict blinding during clinical trials. Three trials with partial positive results[67–69] represent a small minority, and two of them have several methodological limitations. In addition, the applicability of these three studies to children with ADHD is questionable because none of them used children diagnosed with the disorder.

Subgroup analyses of EFA supplementation trials

Although the hypothesis that EFA can ameliorate symptoms of ADHD in most children with the disorder is not supported by current evidence, a milder version of this hypothesis suggests that some subgroups of children with ADHD, with certain characteristics, may benefit from EFA supplementation. In this context, the ability of EFA blood levels or EFA deficiency signs to predict the behavioural response to EFA supplementation was tested in some of the trials reviewed above. Unfortunately, these parameters did not predict the response to supplementation. Sinn[73] reported that baseline levels of EFA deficiency signs were actually negatively correlated with some ADHD-related behavioural parameters, although in small magnitude. Moreover, as repeatedly demonstrated, EFA supplementation does not improve EFA deficiency signs significantly more than placebo.[72,73]

Raz et al.[72] tested other possible subgroups, based on age, sex, comorbidities, ADHD severity, and several blood biomarkers. None of these was found to be relevant. A similar analysis[71] suggests that the following subgroups may have a better response to the treatment: male sex, age 13 to 18 years, inattentive ADHD type, and the existence of a reading or writing disorder. One should note, however, that the sample size on which this analysis was based is inadequate.

Adverse effects of EFA supplements in children

Adverse effects of EFA are generally underreported or completely missing and overlooked in the reports reviewed above, because many researchers did not explicitly ask their participants about this issue. However, some of the trials did report adverse effects, and these data help to evaluate the safety and tolerability of EFA supplements. Complaints of gastrointestinal side effects are most

common, and usually include diarrhoea, nausea, fishy aftertaste, belching, irritable bowel, indigestion, or other symptoms of digestive upsets. These events seem to be mild, transient, and infrequent, and most of them appear in the placebo groups as well, particularly when the placebo was oily material. EFA supplements in amounts of up to 1g/day seem to be well tolerated in children, at least for a limited period of several months, and no severe side effect was reported. We recommend, however, that possible interaction with medications that prolong bleeding time should be considered in clinical settings. Additional information about safety and tolerability of EFA can be found in the Agency for Healthcare Research and Quality report.[1]

SUMMARY AND CONCLUSIONS

There is a biological rationale for supplementation trials of EFA in children with ADHD, which includes evidence from animal models, information about possible mechanisms, and a few data from cross-sectional studies. In addition, open-label studies are efficacious in elevating circulating EFA levels and demonstrate clinical improvements. However, in the era of evidence-based medicine, more than this is needed for a positive recommendation of a biological intervention.

Current findings from randomized clinical trials of EFA supplements in children with ADHD, reviewed above, are very disappointing. Most randomized trials have clearly demonstrated lack of superiority or arbitrary findings (which may be a result of multiple analyses without appropriate statistical correction) compared with placebo. The real picture might even be worse, because of publication bias. Moreover, the studies that showed positive findings did not use children properly diagnosed with ADHD, and none of them was able to demonstrate clinical improvement in more than one setting.[67–69] For example, Sinn and Bryan[69] demonstrated significant improvements in parental assessments, but this effect was totally missing from teacher reports of the same participants. Similar inconsistencies were seen in three other studies.[62,64,65] This delineation is not compatible with a robust, valid, clinical effect, and does not support the use of EFA supplements as a treatment for children with ADHD.

To change this conclusion and support the use of EFA supplements in children with ADHD, future studies will have to demonstrate consistently positive clinical effects on ADHD symptoms. These studies are also expected to be rigorous for methodological issues such as proper ADHD diagnosis, blinded control (which is problematic with fish oil supplements), adequate sample size, and behavioural assessment in more than one setting.

We are aware that it is not easy to conduct clinical trials of food supplements, but EFA supplements have passed the evidence level required for medical indication in other conditions, such as hypertension or secondary prevention after myocardial infarction. On the other hand, despite the hope that EFA supplements may offer a 'natural' intervention for ADHD, free of serious side effects and perhaps even beneficial for other body systems, researchers in this field should also be unprejudiced to accept the possibility that this intervention might simply be inefficient for this particular condition.

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