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Clinical trials of fatty acid treatment in ADHD, dyslexia, dyspraxia and the autistic spectrum

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Abstract

Considerable clinical and experimental evidence now supports the idea that deficiencies or imbalances in certain highly unsaturated fatty acids may contribute to a range of common developmental disorders including ADHD, dyslexia, dyspraxia and autistic spectrum disorders (ASD). Definitive evidence of a causal contribution, however, can only come from intervention studies in the form of randomised, double-blind, placebo-controlled trials. Published studies of this kind are still fairly few in number, and mainly involve the diagnostic categories of ADHD and dyslexia, although other trials involving individuals with dyspraxia or ASD are in progress. The main findings to date from such studies are reviewed and evaluated here with the primary aim of guiding future research, although given that fatty acid supplementation for these conditions is already being adopted in many quarters, it is hoped that some of the information provided may also help to inform clinical practice.

1. Introduction

Omega-3 and omega-6 fatty acids are absolutely essential for normal brain development and function, but cannot be synthesised de novo in humans and must therefore be provided by dietary sources. The highly unsaturated fatty acids (HUFA) that are particularly important to the brain include arachidonic acid (AA) and di-homo-gamma-linolenic acid (DGLA) from the omega-6 series and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from the omega-3 series. If these are not provided directly by the diet, they must be manufactured via processes of desaturation and elongation from the simpler essential fatty acids: linoleic acid (LA) in the case of omega-6 or alpha-linolenic acid (ALA) in the case of omega-3.

Increasing evidence suggests that some common developmental disorders of childhood including ADHD, dyslexia, dyspraxia and autistic spectrum disorders (ASD) may involve functional deficiencies or imbalances in these fatty acids [1]. Thus physical signs of fatty acid deficiency are unusually common in individuals with ADHD, dyslexia or ASD when compared with matched controls [2–5]; blood biochemical studies have shown depletion—particularly of the omega-3 HUFA—in red cell membranes and/or plasma in children with ADHD or hyperactivity [2,3,6] or ASD [5,7]; and other evidence suggests abnormalities of cerebral membrane lipid turnover [8] and elevated cytosolic PLA2 enzymes in red cell membranes [9] in adults with dyslexia.

These observations have naturally led to the idea that treatment with fatty acids might be of benefit in these conditions. In the many years since a possible link between ADHD and fatty acid deficiency was first proposed by the UK Hyperactive Childrens' support group [10], plentiful anecdotal evidence has suggested that some individuals with this diagnosis can benefit from fatty acid supplementation. The same is true for dyslexia and dyspraxia, in which open studies have suggested possible benefits [11,12], and also in the autistic spectrum, for which the first published evidence of fatty acid anomalies is more recent [13].

The proper evaluation of potential treatment effects, however, requires careful and systematic investigation; and randomised, double-blind placebo-controlled trials have long been regarded as the 'gold standard' in this

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respect. Unfortunately, randomised controlled trials (RCTs) also have their limitations [14]. They are most suited to evaluating single treatments for physical medical conditions involving clear diagnostic criteria and homogeneous study populations. They are much less suited to multi-dimensional, behaviourally defined conditions such as ADHD, dyslexia, dyspraxia or the autistic spectrum, where the causes are almost inevitably complex and multi-factorial, and even the rigorous use of formal diagnostic criteria will usually identify a very heterogeneous population. Given this variability, it seems a priori unlikely that fatty acid abnormalities would be a pre-dominant cause of the behavioural and learning difficulties that define these conditions in more than a subset of cases. Nonetheless, the serious consequences of these common behavioural and learning disorders, together with the relative lack of proven interventions that are both safe and effective, make this issue an important one that clearly merits formal investigation.

The few properly controlled trials of fatty acid treatment published to date have involved individuals with a primary diagnosis of either ADHD (or similar difficulties) or dyslexia. Unfortunately, these have mainly been small, researcher-led studies and have involved different methods of identifying study populations, different study designs and different outcome measures, while the compositions and dosages of fatty acid treatments (and placebos) used have also varied between them. This obviously makes either direct comparisons between studies, or a clear synthesis of their collective findings, somewhat difficult. Furthermore, few trials have included biochemical measures of fatty acid status, either in the selection of subjects, to monitor treatment compliance, to assess the physical effects of treatment on fatty acid status, or to investigate how this may relate to baseline characteristics or outcome measures; and this also limits the interpretation of current findings.

Here, the controlled trials to date will therefore simply be summarised by condition, and their main findings outlined and evaluated as far as possible in the light of current knowledge. The primary aim of this review is to guide future research in these areas, but it is hoped that some of the information provided may also be useful to clinicians and others interested in its potential practical applications.

2. ADHD

2.1. Omega-6 fatty acids

Two of the earliest RCTs of fatty acid treatment for ADHD-type difficulties [15,16] involved only omega-6 fatty acids in the form of evening primrose oil (EPO), a rich source of GLA. Subjects were not pre-selected in any way for low fatty acid status, and the treatment period in both studies was only four weeks. This is clearly less than optimal given that subsequent work has shown that dietary supplementation for at least three months is needed to restore key fatty acids in cerebral membranes to normal levels following chronic deficiency [17]. Both studies also employed a full crossover design, which the slow membrane turnover of HUFA would also argue against.

The first of these studies [15] involved 31 children. 26 were selected for marked inattention ($>$90th centile on standardised parent and teacher rating scales), but most also showed a similar degree of hyperactivity. The other five had a formal diagnosis of DSM III Attention Deficit Disorder (with or without hyperactivity). The active treatment of EPO supplied 270 mg GLA and 2160 mg LA per day while the placebo was castor oil. After four weeks there was a one-week washout period, followed by a full treatment crossover for a further 4 weeks.

Only minimal effects of active treatment over placebo were seen across a wide range of cognitive, motor, and standardised symptom ratings. Improvements were found on parent-rated, but not teacher-rated, symptoms of attention and motor excess; and significant changes were seen on two performance measures, only one of which (accuracy of short-term memory) could reliably be interpreted as an improvement. On statistical correction for multiple tests, only parent-rated improvements in attention remained significantly associated with EPO treatment.

Blood fatty acid measures showed increased concentrations of DGLA, but not AA, with active treatment. Post-treatment, DGLA concentrations were comparable with those of controls in a previous experimental study [6]. The unchanged AA concentrations were reported to be lower than those of the hyperactive children in the earlier study, which had in turn been significantly lower than control values. Baseline fatty acid concentrations appeared unrelated to treatment response, although children had not been pre-selected on these measures.

The second such study [16] involved three different treatments (dextroamphetamine, EPO or placebo) administered to just 18 ADHD boys aged 6–12 years (i.e. 6 subjects per treatment group) in a Latin-square double-crossover design. Each treatment was administered for one month, and ADHD-related symptoms were assessed at each of the four study time-points via standardised parent and teacher rating scales. Given the very slow turnover of HUFA in the brain compared with the almost instantaneous effects of stimulant medications, this was an unfortunate choice of study design.

Results again showed only minimal effects of fatty acid treatment. Teacher ratings indicated a trend for benefits from EPO compared with placebo, but this

reached conventional significance levels only on one scale (Conners' Hyperactivity factor), and did not match the improvements seen with dextroamphetamine. Possible effects of treatment sequence were noted, however, and the authors recommended that future studies should use a different design as well as exploring different fatty acid dosages.

An interesting subsequent report on this study suggested that zinc status may have influenced treatment effects, for both fatty acid treatment and stimulant medication [18]. This had been assessed via analysis of hair, red cells and urine, and these measures were used to classify subjects into zinc-adequate ($n = 5$), borderline zinc ($n = 5$), and zinc-deficient ($n = 8$). Re-analyses of the data for each zinc category revealed that placebo-controlled treatment effects for dextroamphetamine increased linearly with zinc status. For EPO, the relationship was U-shaped, in that treatment benefits were evident only in the group with borderline zinc status.

Overall, these two early RCTs using EPO in hyperactive or ADHD children thus showed little if any treatment benefits, although the study designs were not optimal in either case. Some positive trends were noted, suggesting that there may be some individuals who could benefit from supplementation with this source of GLA, but further investigation would be needed to confirm this.

More fundamentally, however, evidence accumulating since these early studies were conducted has indicated that omega-3 fatty acids may be more relevant than omega-6 in the management of behavioural and learning difficulties; and furthermore, these are also much more likely to be lacking from modern diets [19]. These factors have therefore influenced the choice of treatments used in subsequent studies.

2.2. Omega-3 fatty acids

The next RCT of fatty acid treatment in ADHD children was carried out at Purdue University, and involved four months of treatment in parallel groups with either an active supplement of fish oil and EPO—supplying mainly omega-3 fatty acids (80 mg EPA and 480 mg DHA daily) with some omega-6 (96 mg GLA and 40 mg AA)—or an olive oil placebo. In an attempt to reduce heterogeneity and provide a valid test of the fatty acid hypothesis, children were eligible only if they showed clinical signs consistent with fatty acid deficiency (such as excessive thirst and dry skin) as assessed using a simple checklist rating scale [2]. Although formal psychiatric diagnoses of ADHD were not obtained for this study, all participants were under the care of a clinician for ADHD according to parental report.

Fifty children were recruited, and an early preliminary report of findings indicated that active treatment led to blood fatty acid changes that were associated with reduced ADHD symptoms on some measures [20]. This study has only recently come to full publication at the time of writing, however [21], and as it included blood biochemical measures in addition to a wide range of outcome measures, the details deserve careful consideration.

Despite the selection criteria, pre-treatment concentrations of both AA and DHA in red cell membranes in this particular group of children were paradoxically *higher* than those of a reference group, contrary to earlier findings from experimental studies [2]. In plasma, the same fatty acids were significantly lower in the ADHD children than controls, however, which did replicate the earlier findings.

Active treatment led to a doubling of EPA and DHA in both plasma and red cell membranes, while AA concentrations in plasma increased by around 25%, but fell by a similar proportion in membranes along with concentrations of other longer-chain omega-6 fatty acids. Placebo treatment, however, was also followed by marked blood fatty acid changes. Plasma concentrations of the ALA (present in small quantities in olive oil) increased significantly over the 4-month treatment period, although EPA and DHA did not. AA concentrations in plasma increased to a similar extent as for active treatment, with a smaller reduction in RBC concentrations; thus for both treatment groups the direction of changes in AA in both compartments was the same. Particularly, surprising was that plasma concentrations of oleic acid fell in both treatment groups, despite the fact that the olive oil placebo provided 5 g per day of this fatty acid.

As the authors point out, however, the actual concentrations of individual blood fatty acids are probably far less significant in functional terms than their relative proportions. Active treatment led to dramatic reductions in the ratio of omega-6 to omega-3 fatty acids in both red cells and plasma, while these ratios did not change in either case following placebo treatment.

The physical symptoms of thirst and dry skin on which children had been selected improved in both treatment groups, with no significant advantage for active treatment over placebo. With respect to the behavioural outcome measures, intention-to-treat analyses showed significant benefits of active treatment over placebo on just two of sixteen outcomes—parent-rated conduct problems and teacher-rated attentional difficulties. Furthermore, with respect to conduct, oppositional defiant behaviour dropped from clinical to sub-clinical levels in significantly more children receiving active treatment. In the sample as a whole, changes in RBC concentrations of AA, EPA, DHA and alpha-tocopherol showed significant correlations with various measures of behavioural change. As some biochemical changes in

the placebo group were similar those induced by active treatment, this suggests that fatty acid changes (rather than conventional 'placebo effects') may have contributed to the behavioural improvements seen in these children. Thus although the overall advantage of active treatment in reducing behavioural symptoms was only modest, this study clearly suggests that further investigations of fatty acid treatment are warranted in children with ADHD-type difficulties.

These positive results are in stark contrast with those of another RCT involving children with a formal DSM-IV diagnosis of ADHD, which showed no benefits at all from supplementation with DHA alone [22]. Subjects were 63 ADHD children aged between 6 and 12 years, who received four months of treatment with either 345 mg/day of pure DHA (from an algal source) or placebo, in addition to their maintenance stimulant medication. Outcome measures included computerised measures of inattention and impulsivity as well as parent-rated ADHD symptoms. Blood biochemical measures were included, but although plasma phospholipid concentrations of DHA increased significantly on active treatment, reaching 2.6 times those of the placebo group at the four-month point, this was not matched by any improvements in behaviour. In fact, although no group differences reached conventional levels of statistical significance, the effects of treatment appeared to be worse for DHA than placebo on almost every outcome measure.

This important negative finding is consistent with other evidence that EPA, rather than DHA, is likely to be the more important omega-3 fatty acid for the treatment of functional disturbances of attention, cognition or mood [23,24], but the apparent contrast with results from the Purdue study might also reflect differences in subject selection. In the latter, children were selected on the basis of physical signs consistent with fatty acid deficiency, while no such indices were used in this study by Voigt and colleagues. Instead, they applied extremely strict exclusion criteria, ruling out any comorbidity and ensuring that their sample consisted of children with 'pure' ADHD. Population studies suggest that this procedure would rule out almost 90% of children eligible for the ADHD diagnosis [25]. Furthermore, given that omega-3 fatty acids (but particularly EPA) have shown benefits in the treatment of both depression [26,27] and bipolar disorder [28], and might therefore be expected to be particularly beneficial to those ADHD individuals with a comorbid mood disorder, it is at least possible that these researchers inadvertently 'threw out the baby with the bathwater'.

The idea that DHA alone is indeed ineffective for these purposes is reinforced, however, by the results of a further recent RCT that has not yet come to full publication [29]. This involved 40 ADHD children aged between six and twelve years, who received either foods fortified with DHA (at a dosage of approximately 0.5 g/day) or indistinguishable control foods for 2 months. Measures taken pre- and post-treatment included: ADHD symptoms according to DSM-IV criteria, parent and teacher ratings of aggression, measures of visual and auditory perception, working memory and visual-motor integration, and a continuous performance test. The only significant difference found between treatment groups was an improvement of visual and auditory memory for placebo relative to DHA-fortified foods. Proper evaluation of other aspects of this study must await its full publication, and biochemical measures were not available; but this appears to have been a carefully conducted RCT, as was also the case with the study by Voigt and colleagues.

3. Dyslexia

The first RCT of fatty acid treatment in dyslexia was a pilot study designed to assess whether supplementation with fish oil and EPO (providing mainly omega-3 but some omega-6 HUFA) could reduce behavioural and learning difficulties in dyslexic children who also showed features of ADHD [30]. Given the high comorbidity between dyslexia and ADHD, and previous research implicating fatty acid deficiencies in both conditions, it was thought that benefits from fatty acid treatment might be particularly evident in a group of children showing features of both conditions. The aim was to therefore find out whether ADHD-related symptoms in these children could be reduced by fatty acid treatment.

Subjects were 41 dyslexic children referred to a special school for one year for remediation of their reading difficulties. Children were eligible if, in addition to a confirmed dyslexic profile on psychometric testing, they showed above-average scores on all three global ADHD scales from the Conners Parent Rating Scales (CPRS-L) [31]—viz. Inattention, Hyperactivity and Combined-Type, modelled on DSM-IV criteria for ADHD. In practice this yielded a group with mean scores around one SD above population means on these scales. No child in this study had been formally assessed for ADHD by a psychiatrist, and case histories and clinical impressions suggested that no more than a few would have met full diagnostic criteria for DSM-IV ADHD.

Children were randomly allocated to 12 weeks of treatment in parallel groups with either a fatty acid supplement providing the following daily doses: EPA 186 mg, DHA 480 mg, gamma linolenic acid 96 mg, vitamin E (as dl-α tocopherol) 60 IU, *cis*-linoleic acid 864 mg, AA 42 mg and thyme oil 8 mg.) or an identical-looking olive oil placebo. At 12 weeks there was a one-way crossover (placebo to active treatment) so that both groups received the HUFA supplement for a further 12 weeks. The primary outcome measure was scores on the

Conners' Parent Rating Scales [31], which were completed at the pre-treatment baseline and repeated at 12 and 24 weeks. Biochemical measures could not be included in this study for practical reasons.

The groups did not differ before treatment, but after 12 weeks scores for anxiety, attentional difficulties and general behaviour problems were significantly lower for active treatment ($n = 15$) than placebo ($n = 14$). Paired t-tests showed significant improvements from baseline on 6/14 scales for active treatment, none for placebo. Group differences in change scores all favoured active treatment, although only three reached conventional significance levels: 'cognitive problems', indexing difficulties with attention, concentration and working memory; 'anxious-shy', tapping tendencies to fearful overarousal and social withdrawal; and 'Conners' Index', measuring a broader range of behavioural problems. By 24 weeks the crossover group showed significant improvements on 9/14 scales, in stark contrast to their earlier lack of improvement on placebo, while children continuing with the fatty acid treatment maintained or improved upon earlier symptom reductions [32]. Study numbers in this pilot study were small, hence statistical power was very limited, and results were significant only on per protocol analysis. The treatment effects obtained, however, were quite substantial—and clinically meaningful—indicating that further investigations of this kind are warranted.

The second RCT of fatty acid treatment in dyslexia involved 102 children aged 8–12 years referred to a research clinic for investigation of their reading difficulties. Results have not yet been fully analysed or submitted for peer-reviewed publication, hence only an outline can be given here. The treatments used were the same as for the pilot study just described, but the main aim of this study was to determine the effects of fatty acid treatment on reading progress, so children were treated in parallel groups for a full six months in order to allow time for any changes in their reading achievement to become apparent. The primary outcome measure was changes in reading age as assessed via standardised tests of single word reading. Blood samples were collected from a subset of participants, but unexpected changes at collaborating laboratories have unfortunately precluded proper analysis of these.

Preliminary results indicated that improvements in reading age were significantly greater for active treatment than placebo, although there was considerable individual variation within both groups. Further exploration suggested that placebo-controlled benefits from fatty acid treatment were greater in children with high pre-treatment scores on simple checklist ratings of either minor physical signs of fatty acid deficiency and/or visual symptoms when reading (which were inter-correlated), suggesting that these features might prove useful in pre-selecting subjects for similar studies in future.

4. Dyspraxia

At the time of writing, there appear to be no published RCTs of fatty acid treatment in dyspraxia. One such study has now been completed, and is briefly considered here. Again, however, preliminary findings only can be provided, as results have not yet been subjected to full peer review.

This study involved 116 dyspraxic children aged 6–12 years. The aim was to find out whether fatty acid treatment could reduce dyspraxic symptoms; but as these are quite diverse, reflecting the high comorbidity between dyspraxia, dyslexia and ADHD, key outcome measures were selected for each of these domains. These included standardised measures of visuomotor performance, reading, spelling and working memory; and ADHD-related symptoms as assessed by parent and teacher ratings.

Active treatment was a supplement containing 80% fish oil and 20% EPO, at a daily dosage supplying 558 mg EPA, 174 mg DHA and 60 mg GLA plus 9.6 mg Vitamin E (as alpha-tocopherol). The placebo contained olive oil, carefully matched with the active treatment for both colour and flavour. Treatment duration was 12 weeks in parallel groups, followed by a one-way treatment crossover for a further 12 weeks. The primary outcome measures were changes in standardised measures of visuomotor control, reading and spelling, working memory and ADHD-related symptoms.

Preliminary results indicate highly significant group differences in favour of active treatment for changes in reading, spelling and working memory after 12 weeks of treatment in parallel groups, as well as significant reductions in ADHD-related symptoms. Only minimal group differences were observed, however, on objective measures of visuomotor function. At 24 weeks, clear crossover effects were apparent on almost all measures in the group switching from placebo to active treatment, while those continuing with active treatment maintained or increased their earlier improvements.

With regard to ADHD symptoms, results from this study thus appear to replicate and extend those from the pilot study of dyslexic children [30]. The apparent benefits to reading and spelling progress appear stronger than those found in children with a primary diagnosis of dyslexia in the study mentioned earlier. This may reflect the fact that the dyspraxia diagnosis (which usually shows a 50% mutual overlap with dyslexia) particularly captures those whose difficulties reflect attentional and visual-perceptual rather than auditory-linguistic difficulties. However, there were also differences in the supplements used in the two studies: both involved an 80:20 ratio of fish oil to EPO, but the fish oil used in the dyspraxia study had an unusually high ratio of EPA to DHA, while that used in the earlier dyslexia studies was the reverse.

5. Autistic spectrum disorders

To date, no controlled trials of fatty acid treatment in ASD have yet been reported, although such studies are now underway.

6. Discussion

Clinical and experimental evidence has provided a strong rationale for investigating the use of omega-3 and/or omega-6 fatty acids in the treatment of several common and overlapping childhood disorders of behaviour and learning, including ADHD, dyslexia, dyspraxia and ASD [1]. Although RCTs still remain few in number, the available evidence does indicate that fatty acid treatment may benefit some individuals with these conditions, at least in the short-term. Further research is still needed, however, to establish this with certainty, to assess the durability of such treatment effects, to determine optimal treatment compositions and dosages (which may of course vary between conditions or individuals), and to develop reliable ways to identify those individuals most likely to benefit from this kind of treatment approach.

6.1. Study populations

Future treatment trials clearly need to be designed with careful attention to the characteristics of the subjects studied. Clinically, the heterogeneity and comorbidity inherent in current diagnostic classifications for these conditions is a major complication, and unless features of all relevant conditions are carefully assessed, many subjects are likely to meet criteria for more than one of the numerous overlapping developmental or psychiatric disorders in which fatty acids have now been implicated [33]. The selection of 'pure' cases of any one disorder is unlikely to be the best solution, as this will almost inevitably lead to a highly unrepresentative sample [25]. It may even be the case that fatty acid treatment will prove most effective in those individuals showing features of more than one 'phospholipid spectrum disorder'. The one study of ADHD children in which comorbidity was rigorously ruled out yielded wholly negative results [22], which would be consistent with this idea (although the use of pure DHA in this study may have been an important factor here, as discussed further below). In any case, future studies might do well to focus on specific subgroups identified via dimensional measures of specific traits or features, even if these may cut across conventional diagnostic categories.

The use of objective diagnostic measures might seem a better way to proceed than via any of the essentially descriptive, behavioural measures currently used in psychological and psychiatric diagnosis, but blood samples are not usually easy to collect from these kinds of populations. In most of the studies reviewed here, subjects were not pre-selected in any way for low fatty acid status, a fact that would be expected to weaken any treatment effects. The exception is the Purdue study of children with ADHD-type difficulties, in which subjects were selected for physical signs consistent with fatty acid deficiency—but in this case, objective biochemical measures pre-treatment then unexpectedly revealed that despite low plasma concentrations in red cell membranes, their red cell concentrations of the same fatty acids were in fact higher than those of an appropriately matched reference group. Too little is currently known of how such biochemical measures may relate to clinical symptom profiles, but where possible, objective assessment of fatty acid status should help to improve this state of affairs and to clarify the results obtained. Other aspects of nutritional status are also likely to be relevant, as illustrated by the post-hoc finding in one early study that zinc status in ADHD children appeared to predict responses to treatment with either EPO or stimulant medication [18].

6.2. Treatments

With respect to treatments, a variety of different supplements have been used in the studies to date. Since these have included varying proportions of EPA, DHA, GLA and AA (as well as LA and other fatty acids), it is not known which fatty acids may be most important in contributing to the effects observed. However, there is little doubt that omega-3 fatty acids are more likely to be lacking from modern diets [19], and detailed consideration of the pattern of results from the existing RCTs offers some other possible clues.

In ADHD, two double-blind trials have now found no benefits from DHA supplementation [22,29], while another has found benefits from a supplement providing both EPA and DHA from fish oils as well as some GLA, AA (and LA) from EPO [21]. Similar omega-3/omega-6 formulations—all weighted in favour of omega-3—have yielded positive results in one pilot study of dyslexic children with ADHD-type features [30] as well as two further studies of dyslexic and dyspraxic children that are still awaiting full peer review [32]. Earlier studies of omega-6 supplementation in ADHD gave essentially negative results [15,16], so the current balance of evidence suggests that the omega-3 fatty acid EPA might well be the most important component. This certainly appears to be the case in adult psychiatric disorders such as schizophrenia and depression, for which treatment with EPA alone has repeatedly been found effective [23,26,27,34,35], while DHA alone has not [23,24]. Further studies of developmental conditions such as dyslexia, dyspraxia and ADHD may therefore

do well to explore this possibility, and a high-EPA marine oil with no EPO added is now under investigation in ongoing studies. However, it seems a priori likely that the fatty acid combinations usually found in the foods on which human beings evolved may prove more effective than large doses of any single nutrient in isolation.

Most specialist supplements take the precaution of including Vitamin E or other anti-oxidants, and this too may be relevant to any treatment effects [21]. Another issue is that no trials concerning the childhood developmental conditions have yet been sufficiently large-scale to allow an investigation of dose–response relationships, so this should also be a priority in future studies.

The choice of placebo is another potentially important factor. The acceptability and tolerability of olive oil in these study populations is excellent and its properties also allow for good masking against fatty acid supplements; but although frequently used, olive oil is not ideal for these purposes [36] because it is a rich source of oleic acid, from which oleamide can easily be synthesized [37]. Oleamide has important psychoactive effects, including the induction of sleep and the modulation of receptor-mediated signalling via serotonin and other neurotransmitters [38–41]. In the Purdue study of children with ADHD-type difficulties [21], olive oil was clearly an 'active' placebo in that it did not leave fatty acid profiles unchanged, giving good reason to suspect that this may have contributed to the positive behavioural effects of placebo treatment in that study. The latter have not been evident in all studies using olive oil as placebo [30], but the use of a truly inert placebo in future studies would enhance both the likelihood and significance of any positive treatment effects.

7. Conclusions

In summary, the current evidence from a series of small, researcher-led studies suggests that omega-3 fatty acids—and particularly EPA—may be of benefit in the management of common neurodevelopmental conditions such as dyslexia, dyspraxia and ADHD. A similar rationale exists for fatty acid treatment in ASD, and the first such trials are now underway, although none have yet been published. There is no clear evidence that omega-6 fatty acids alone may be helpful in these conditions, but positive results have been found in studies of both ADHD and dyslexia using omega-3/omega-6 combinations, so a possible contribution from the omega-6 component cannot yet be ruled out. Both the composition and the optimal dosage of fatty acid treatments for these purposes now require further systematic investigation. Larger trials are strongly indicated, and these should ideally include both different doses of the treatment under investigation, and a more inert placebo than olive oil. Further work is also needed to establish the specificity and durability of the treatment effects observed, and to develop methods of identifying those children most likely to benefit from HUFA supplementation.

The essentiality of these fatty acids for so many aspects of brain development and function means that the number of potential mechanisms by which they could be operating to affect behaviour, learning or mood is vast, so this remains an area for speculation, theorising and future investigation. Nonetheless, the general safety and tolerability of this kind of simple nutritional treatment means that the clinical use of fatty acid supplementation—under appropriate medical and other professional guidance—may already be considered as a possible option for those seeking an alternative or an adjunct to conventional treatment options.

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