

Clinical Trials of Fatty Acid Supplementation in Dyslexia and Dyspraxia

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INTRODUCTION

Developmental dyslexia is a complex syndrome showing overlaps and associations not only with many other developmental disorders of childhood such as dyspraxia, ADHD and autistic spectrum disorders, but also with certain adult psychiatric conditions – notably anxiety, depression and some conditions within the schizophrenia spectrum (Richardson and Ross, 2000). In Chapter 41 the associations of dyslexia with dyspraxia and schizotypy are discussed, and an overview is provided of the experimental evidence for fatty acid abnormalities in these conditions. This has provided an obvious rationale for investigations of the possible therapeutic role of fatty acids in their management. Clinical trials of fatty acid treatment in dyslexia and dyspraxia are the subject of this chapter, while similar research into ADHD is reviewed in Chapter 46. The role of fatty acids in other psychiatric disorders is amply covered elsewhere in this volume.

OVERVIEW

Summaries of three different randomised controlled trials involving children with dyslexia or dyspraxia are presented here. Each was designed to address a different question, but all employed a similar study design that involved two phases, i.e. a period of treatment in parallel groups (active treatment versus placebo) followed by a similar time period with one-way treatment crossover (from placebo to active treatment). A full crossover design is inappropriate for this type of treatment owing to the slow dynamics of membrane fatty acid turnover in the brain. Following chronic dietary deficiency, cerebral membrane levels of these fatty acids usually take more than ten weeks to return to normal levels once they are reintroduced into the diet (Bourre et al., 1989), so the minimum treatment period used in these studies was twelve weeks. In each trial the active treatments used involved a combination of n-3 and n-6 fatty acids from fish oil and evening primrose oil, weighted heavily in favour of n-3, while the placebo used in each case was olive oil.

The first of these trials was a pilot study (Richardson and Puri, 2002) involving 41 dyslexic children referred to a special school for one year for remediation of their reading difficulties. Children were eligible for this study if they also showed features of ADHD, although none had a formal ADHD diagnosis. 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 find out whether ADHD-related symptoms in these children would be reduced by treatment with n-3 and n-6 highly unsaturated fatty acids (HUFA). The duration of each treatment period was 12 weeks, and behavioural and learning problems related to ADHD were assessed at baseline, 12 and 24 weeks using standardised parent rating scales.

The second study involved 102 dyslexic children aged 8-12 years referred to a research clinic for investigation of their reading difficulties. The main aim in this case was to determine the effects of fatty acid treatment on reading progress, which is an acquired skill that depends on explicit instruction and learning. Children were therefore treated in parallel groups for a full six months in order to allow time for any changes in their reading achievement to become apparent. Reading ability was assessed at baseline and three-month intervals using a standardised single word reading test. Preliminary results only from the 6-month parallel group phase are reported here, because at the time of writing, the results of this study have not yet been fully analysed nor published in a peer-reviewed journal.

The third study involved 116 dyspraxic children aged 6-12 years, recruited from twelve different primary schools within the Local Education Authority of County Durham in Northern England. As for the first study, treatment duration was 12 weeks in parallel groups, followed by a one-way treatment crossover for a further 12 weeks. The aim was to find out whether fatty acid treatment could reduce dyspraxic symptoms; but these are quite diverse, reflecting the very high comorbidity between dyspraxia, dyslexia and ADHD, so key outcome measures were selected to represent each of these domains. These included standardised measures of visuomotor performance, reading and spelling, and ADHD-related symptoms as assessed by both parents and teachers. Again, results of this study are still awaiting peer-review and have not yet been fully analysed, so only a brief indication can be given here of the preliminary results.

STUDY 1 – ADHD-RELATED SYMPTOMS IN CHILDREN WITH DYSLEXIA

Hypothesis

The main hypothesis was that children receiving fatty acid supplementation would show reduced behavioral and cognitive problems after 12 weeks compared with those receiving placebo treatment. After the one-way treatment crossover, the hypothesis was that behavioral and cognitive problems would then improve in the group previously receiving placebo, while in the group continuing with active treatment, any earlier improvements would be maintained or increased.

Participants

The study population consisted of children aged 8-12 years attending a special school in Northern Ireland for remediation of their specific reading difficulties. All had been referred there by teachers in mainstream schools who had identified them as having unexpected problems in learning to read and write relative to their general ability. Our own psychometric assessments confirmed this, and showed that they also had the specific weaknesses in working memory and phonological processing that are characteristic of dyslexia. None of these children had received an official diagnosis of ADHD or any other psychiatric disorder.

Inclusion criteria were general ability within the normal range, reading achievements significantly below the level expected from this, English as a first language, and endorsement from the child's family doctor. Eligibility for this study also required the child's scores to be above the general population average for their age on three parent rating scales designed to assess ADHD-related symptoms according to DSM-IV criteria: the DSM Inattention, DSM Hyperactive-Impulsive, and DSM Combined-type ADHD global scales from the Conners Parent Rating Scales (CPRS-L) (Conners, 1997). Exclusion criteria included the use of fatty acid supplements within the previous six months, consumption of oily fish regularly more than twice a week, or a history of any other neurological or major psychiatric disorder or other significant medical problems.

Treatments, Assignment and Masking

For the first 12 weeks of the trial, children in the active treatment group received a supplement containing both n-3 and n-6 HUFAs, to provide 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. The placebo group

received identical-looking capsules containing olive oil. 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 subjects were individually randomized between the two groups. Initial allocation to parallel groups was double-blind, and determined by pre-randomized codes generated by computer. Coded treatments were allocated sequentially to subjects in strict order of their registration for the trial. After crossover the study was single-blind in that supervisors and research staff knew the design details, but care was taken to preserve double-blind conditions as far as possible for children and their parents and teachers. There was no direct contact at any stage between the generator and executors of the assignment.

Treatment codes were held at a remote location by an independent third party until the trial was completed and all data collated, verified and archived. Sealed envelopes containing the treatment codes had been provided to the trial supervisor and were returned unbroken at study completion. The analyses were then carried out by the trial supervisor, who had minimal involvement in both administration of assessments and contact with participants. In order not to bias the statistical testing, analysis of the results was performed as described above using semi-unblinded codes that revealed group membership, but not the nature of the treatments. Full unblinding was undertaken only when these analyses had been carried out.

Assessments

At baseline, 12 weeks and 24 weeks the CPRS-L was used to assess a range of behavioral and learning problems associated with ADHD. This yields normalized, age-standardized scores (in the form of t-scores) for seven sub-scales assessing individual features of ADHD (Oppositional, Cognitive Problems, Hyperactivity, Anxious-Shy, Perfectionism, Social Problems, Psychosomatic) and seven global scales (Conners ADHD Index, Conners Restless-Impulsive, Conners Emotional Lability, Conners Global Index, DSM Inattention, DSM Hyperactive-Impulsive, DSM Global Total).

Statistical Analyses

Group comparisons were carried out at baseline, three and six months; and within-group paired comparisons were made for scores pre- and post-treatment for the 0-3 and 3-6 month time periods. The primary outcome measures were the group comparisons of change scores for the parallel group phase of the study, although these were also examined for the crossover period. Treatment effect sizes (mean change/baseline SD) were calculated for each group and time period; and change scores within the placebo-crossover group were compared between the two time periods. In many cases the data were not normally distributed, therefore non-parametric tests were used.

Recruitment and participant flow

Forty-one children (mean age 10.25 years (SD=0.74 years)) were recruited into the study. Their mean intelligence quotient pro-rated was 101.2 (SD 12.2), but their measured reading achievement was almost three years behind chronological age, and they also showed the expected deficits in auditory working memory and phonological skills. Of these children, 22 received the HUFA supplement, while 19 received the placebo during the first 12 weeks. The mean age of the active group (10.30 (SD=0.73) years) did not

differ significantly from that of the placebo group (10.19 (SD=0.77) years; $t=0.44$, $df=39$, $p=0.66$); nor did the sex ratio (active: 18 males: 4 females; placebo: 17 males: 2 females; Fisher's exact probability test, $p=0.41$).

Of the 41 children who started the trial, nine (5 active, 4 placebo) withdrew before the end of the 12-week period and were not available for re-assessment. The reasons given did not differ between groups. Parent CPRS-L ratings at 12 weeks were not available for a further three children (2 active, 1 placebo), so per-protocol analyses involved 29 children (15 active, 14 placebo); these two groups did not differ significantly with respect to age or sex. Treatment compliance at follow-up was calculated from counts of capsules returned, and did not differ between groups (mean (SD): active 90.4% (10.1%), placebo 86.6% (16.4%)).

Results

Baseline comparisons

At baseline, scores for the two groups (15 active, 14 placebo) did not differ significantly on any of the 14 CPRS-L scales, as shown in Table 1.

TABLE 1. Baseline Scores (Age-Standardized with Respect to General Population Norms, in the Form of t-Scores (Mean 50, SD 10)) on CPRS_L Scales for Both Active and Placebo Groups

CPRS_L scale	HUFA Supplementation (N=15)		Placebo (N=14)		z	p
	Mean	SD	Mean	SD		
<i>ADHD subscales</i>						
Anxious/Shy	61.1	13.1	61.9	13.6	0.13	0.90
Cognitive Problems	62.1	9.6	63.4	7.6	0.44	0.66
Hyperactivity	66.4	11.4	64.4	10.2	0.44	0.66
Opposition	60.9	12.4	57.5	9.0	0.70	0.48
Perfectionism	56.3	15.3	57.0	10.2	0.75	0.46
Psychosomatic	64.9	16.8	64.9	15.0	0.18	0.86
Social Problems	63.0	16.3	57.9	10.3	0.62	0.54
<i>ADHD global scales</i>						
Conners' Index	59.9	11.3	60.1	6.4	0.44	0.66
Restless-Impulsive	63.5	10.0	65.1	9.2	0.46	0.65
Emotional Lability	64.5	13.1	61.4	15.5	0.68	0.49
Conners' Total	64.9	10.2	65.1	10.7	0.13	0.90
DSM Inattention	61.6	10.3	64.7	8.3	1.16	0.25
DSM Hyperactivity	67.5	10.6	67.9	9.5	0.28	0.78
DSM Total	65.7	10.3	67.2	7.7	0.74	0.46

Three month analyses

The scores for the two groups after three months are shown in Table 2. It can be seen that the active treatment group now had significantly lower scores than the placebo group on two global scales - Conners' Index and DSM Inattention, and a trend towards lower scores on three sub-scales - Psychosomatic, Cognitive Problems and Anxious/Shy - as well as the global scale Conners' Restless-Impulsive.

TABLE 2. Scores (Age-Standardized with Respect to General Population Norms, in the Form of t-Scores (Mean 50, SD 10)) at Three Months on CPRS_L Scales for Both Active and Placebo Groups

CPRS_L scale	HUFA Supplementation (N=15)		Placebo (N=14)		z	p
	Mean	SD	Mean	SD		
<i>ADHD subscales</i>						
Anxious/Shy	53.9	14.6	62.1	11.8	1.74	0.08
Cognitive Problems	57.0	10.4	63.5	9.3	1.79	0.07
Hyperactivity	62.0	12.2	62.3	12.3	0.13	0.90
Opposition	59.7	9.9	59.8	10.4	0.09	0.93
Perfectionism	53.2	12.8	56.1	13.7	0.70	0.48
Psychosomatic	53.4	8.9	61.5	12.2	1.93	0.05
Social Problems	62.1	17.2	60.6	10.1	0.22	0.83
<i>ADHD global scales</i>						
Conners' Index	57.6	6.64	64.2	8.42	2.21	0.03
Restless-Impulsive	58.3	5.22	64.0	8.71	1.69	0.09
Emotional Lability	59.7	9.62	63.7	15.99	0.79	0.43
Conners' Total	59.7	6.90	65.2	10.51	1.34	0.18
DSM Inattention	55.9	9.79	63.6	9.95	1.95	0.05
DSM Hyperactivity	64.5	11.20	65.9	11.21	0.50	0.61
DSM Total	60.5	9.17	65.7	10.16	1.25	0.21

Within the placebo group there were no improvements on any scale at 3 months relative to baseline levels (Wilcoxon signed rank test), and for one global scale, Conners' Index, there was a significant deterioration ($z=2.14$, $p=0.03$).

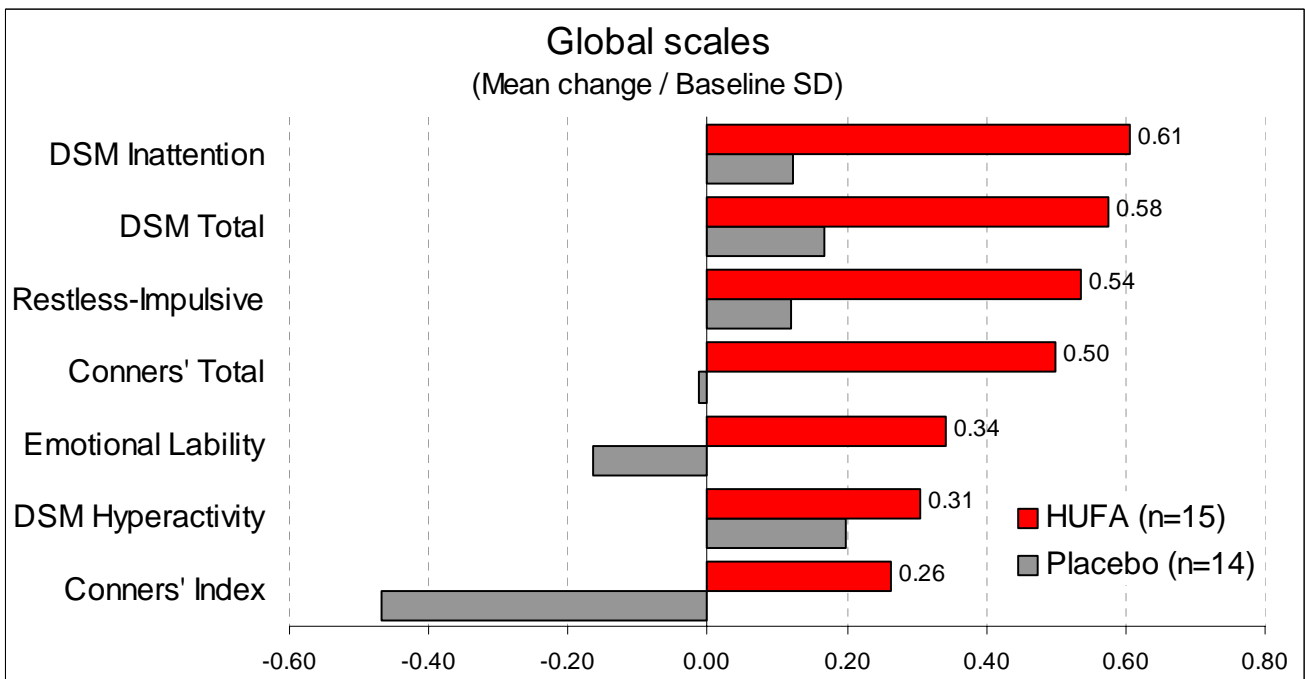
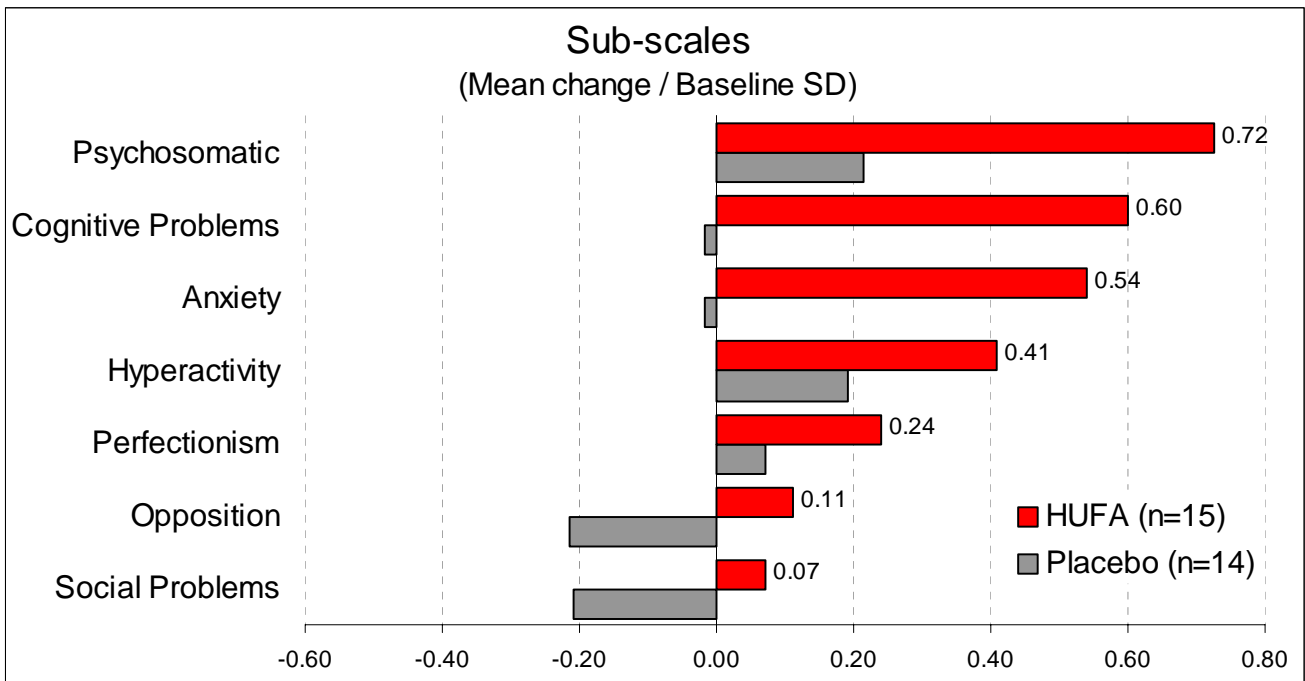
In contrast, within the active treatment group significant symptom reductions from baseline were found for three of the seven ADHD sub-scales: Psychosomatic complaints ($z=2.51$, $p=0.01$), Anxious/Shy ($z=2.34$, $p=0.02$) and Cognitive Problems ($z=2.29$, $p=0.02$) and four of the seven global scales: DSM Inattention ($z=2.59$, $p=0.01$), DSM Total ($z=2.45$, $p=0.01$), Conners' Total ($z=1.95$, $p=0.05$) and DSM Hyperactive-Impulsive ($z=1.97$, $p=0.05$), as well as trend-level improvement in two further global scales, Conners' Emotional Lability ($z=1.77$, $p=0.08$) and Conners' Restless-Impulsive ($z=1.68$, $p=0.09$).

Group comparisons of the changes in scores between baseline and 12 weeks showed that improvements were significantly greater for active treatment over placebo (Mann-Whitney test, 2-tailed) for the sub-scales Cognitive Problems ($z=2.45$, $p=0.01$) and Anxious/Shy ($z=2.02$, $p=0.04$) as well as the global scale Conners' Index ($z=2.25$, $p=0.02$), measuring a broader range of behavioral problems. There was also a trend for improvement on Conners' Emotional Lability ($z=1.74$, $p=0.08$) to be better on active treatment.

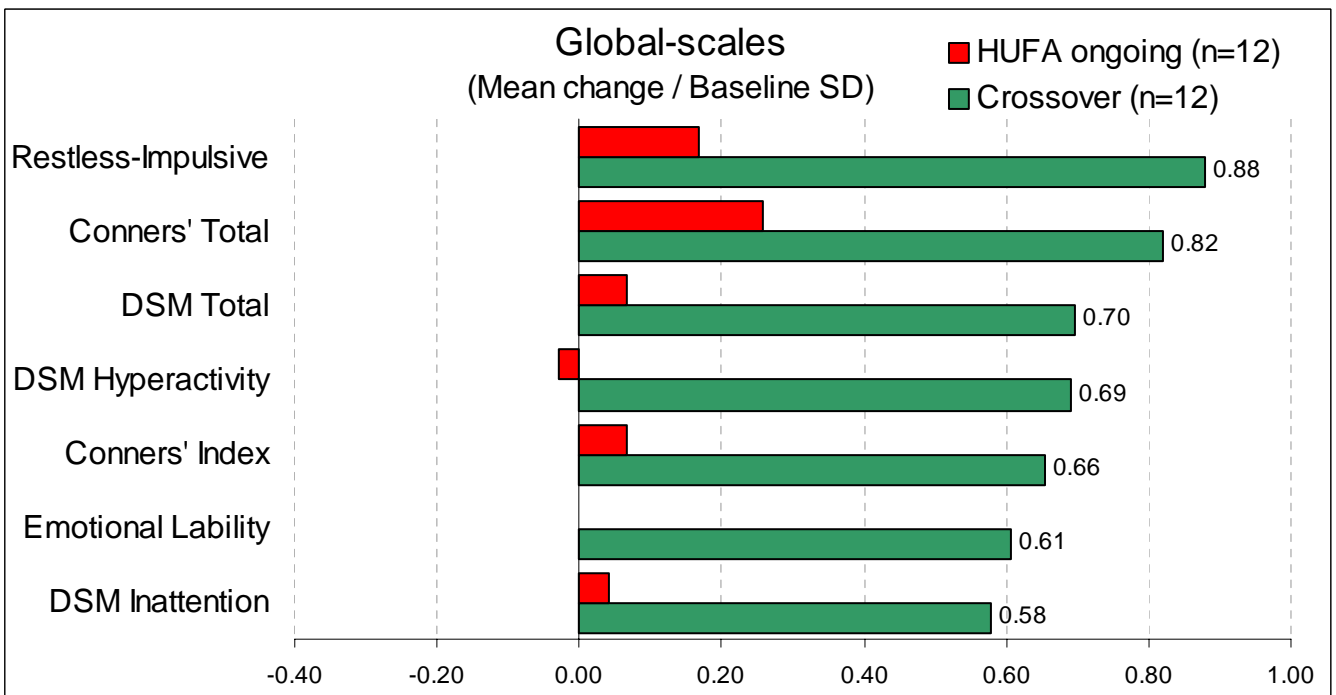
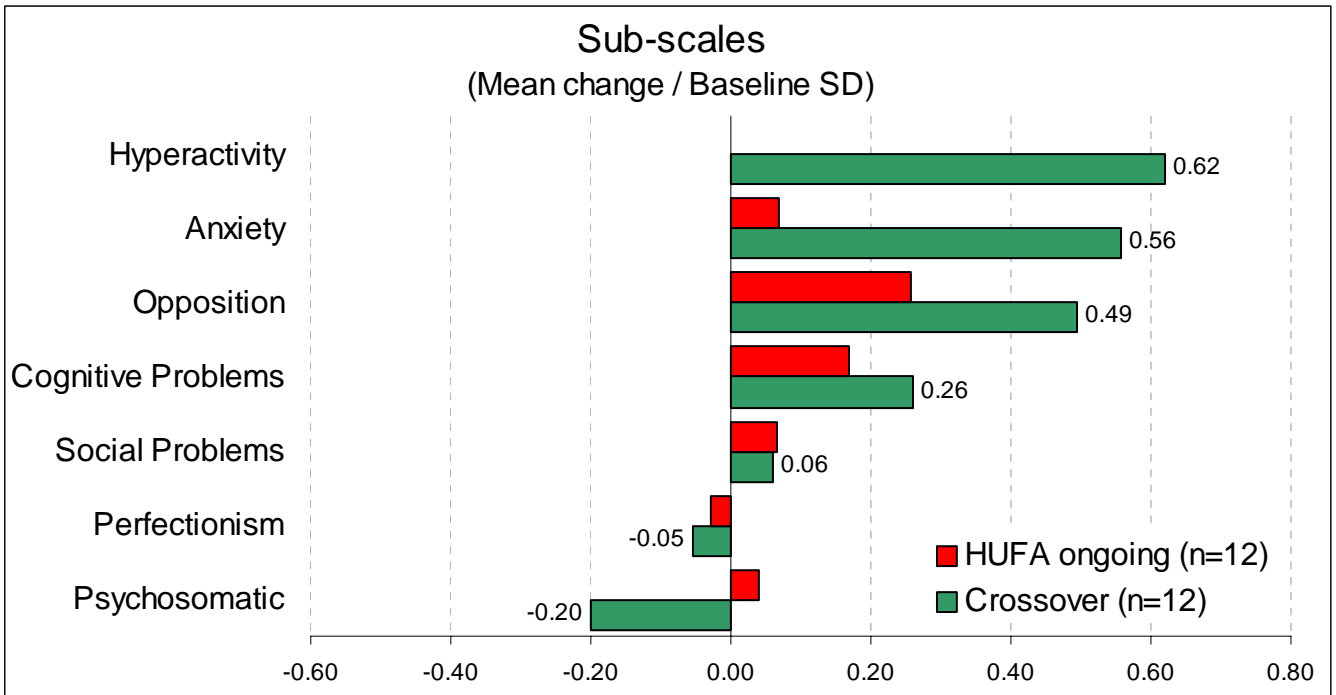
Treatment effect sizes for each group are shown in Figure 1(a). For all scales, the changes observed were more favorable for HUFA treatment than placebo.

Figure 1 Treatment effect sizes for each treatment group during the two treatment periods: (a) 0-3 months - parallel groups (HUFA vs placebo) (b) 3-6 months following one-way crossover (placebo to HUFA).

(a) Treatment effect sizes 0-3 months (parallel groups)



(b) Treatment effect sizes 3-6 months following one-way crossover (placebo to HUFA)



Six month analyses

Table 3 shows the scores for the two groups at six months, following one-way crossover. There were no longer any significant differences between the groups; the scores for children switching from placebo to HUFA supplementation had now fallen to match

those of the children treated with HUFA supplementation from the start. Scores for both groups were now within the normal range for almost all ADHD measures.

TABLE 3. Scores (Age-Standardized with Respect to General Population Norms, in the Form of t-Scores (Mean 50, SD 10)) at Six Months on CPRS-L Scales for Both Groups Following One-Way Crossover

CPRS-L scale	HUFA Supplementation (N=12)		Crossover (placebo to HUFA) (N=12)		z	p
	Mean	SD	Mean	SD		
<i>ADHD subscales</i>						
Anxious/Shy	52.3	10.8	53.5	11.1	0.26	0.79
Cognitive Problems	54.4	8.5	59.5	7.8	1.62	0.11
Hyperactivity	59.0	9.7	56.0	7.8	0.78	0.43
Opposition	55.7	9.2	57.3	11.9	0.06	0.95
Perfectionism	54.7	17.0	58.3	12.1	1.16	0.25
Psychosomatic	54.4	9.4	64.2	18.8	1.04	0.30
Social Problems	58.1	15.0	60.1	11.9	0.99	0.32
<i>ADHD global scales</i>						
Conners' Index	54.6	8.0	58.6	7.0	1.25	0.21
Restless-Impulsive	57.7	9.6	58.6	7.8	0.53	0.60
Emotional Lability	59.3	10.1	58.3	13.1	0.35	0.73
Conners' Total	58.8	8.4	59.3	9.0	0.26	0.79
DSM Inattention	52.8	8.4	56.6	7.0	1.45	0.15
DSM Hyperactivity	58.9	7.9	59.4	7.5	0.23	0.82
DSM Total	55.8	8.4	58.8	6.6	0.90	0.37

Within the crossover group significant improvements were found on eight of the 14 scales relative to their scores at the 3-month point (Wilcoxon signed rank test): sub-scales Hyperactivity ($z=2.58$, $p=0.01$) and Anxious/Shy ($z=2.20$, $p=0.03$), and the global scales: DSM Hyperactive-Impulsive ($z=2.68$, $p=0.01$), Conners' Emotional Lability ($z=2.53$, $p=0.01$), DSM Total ($z=2.41$, $p=0.02$), Conners' Total ($z=2.40$, $p=0.02$) Conners' Index ($z=2.32$, $p=0.02$) and DSM Inattention ($z=2.09$, $p=0.04$). Trend-level improvements were also found for the Oppositional sub-scale ($z=1.81$, $p=0.07$) and the global scale Conners' Restless-Impulsive ($z=1.73$, $p=0.08$).

Within the group continuing on active treatment, no significant changes from the 3-month point were seen following this second treatment period, but their earlier improvements were sustained. Treatment effect sizes on all scales for each group are shown in Figure 1(b).

Finally, comparisons of change scores for the crossover group between the 0-3 month (placebo) and 3-6 month (active treatment) periods revealed significant differences for three scales: Conners' Index ($z=2.47$, $p=0.01$), Conners' Emotional Lability ($z=2.44$, $p=0.01$), and Oppositional ($z=2.43$, $p=0.01$), as well as a trend-level difference for Conners' Global Total ($z=1.88$, $p=0.06$). In all cases, improvements were greater for active treatment than placebo.

Discussion

Under double-blind conditions, HUFA supplementation was found to be significantly better than placebo in reducing a wide range of ADHD symptoms in children

with specific learning difficulties. A strong crossover effect occurred when the placebo group switched to HUFA supplementation, thus reinforcing the results of the parallel group study. The advantage for HUFA treatment appeared to be remarkably clear-cut, and no adverse side-effects were associated with this treatment.

STUDY 2 – READING PROGRESS IN CHILDREN WITH DYSLEXIA

Hypothesis

The main hypothesis was that children receiving active treatment would show better reading progress over the six month period than those receiving placebo treatment. After the one-way treatment crossover, the hypothesis was that reading progress would then improve in the group previously receiving placebo, while in those continuing with active treatment, any earlier gains would be maintained or increased.

Participants

The study population consisted of children aged 8-12 years referred to a specialist research clinic for investigation of their specific reading difficulties. Eligibility criteria were: general ability within the normal range as assessed via the Similarities and Matrices subtests from the British Ability Scales (BAS) (Elliot, 1983); reading achievements (BAS word reading) more than two standard deviations below the level expected from this; English as a first language; case history and psychometric profile consistent with dyslexia; and endorsement from the child's family doctor. Exclusion criteria included the use of fatty acid supplements within the previous six months, consumption of oily fish regularly more than twice a week, or a history of any other neurological or major psychiatric disorder or other significant medical problems.

Treatments, Assignment and Masking

These were exactly the same as for Study 1, but the duration of treatment was six months in parallel groups, followed by a further six month period following the one-way treatment crossover.

Assessments

Psychometric assessments at the pre-treatment baseline included the standardised measures of general ability, reading and spelling from the BAS as well as working memory and phonological skills in order to confirm dyslexic status. Word reading and spelling were reassessed at three, six, nine and twelve months from the initiation of treatment. As described elsewhere (Richardson et al., 1999, Richardson et al., 2000), checklist measures of both dyslexic symptoms and fatty acid deficiency signs were also administered at each of these study time-points.

Statistical Analyses

These followed the same format as for study 1, involving group comparisons at each timepoint and within-group paired comparisons for each time period. The primary analyses, however, involved group comparisons of changes in reading age over the six

months of treatment in parallel groups. For many of the variables, the data were not normally distributed, so non-parametric statistics were used for most of these analyses.

Results

Preliminary results for the parallel groups phase only are reported here, and these should be regarded as such, because the data from this study have not yet been fully analysed, nor the results subjected to peer review.

102 children were initially recruited into the study (76 male, 26 female). Their mean age was 119.4 months (SD=16.8), reading age 93.2 months (SD=12.3) and spelling age 93.9 months (SD 11.2), hence these lagged behind their chronological age by over two years, despite the fact that the general ability of this sample was almost one standard deviation above the population average (BAS IQ pro-rated: mean 113.7, SD=12.4).

51 children were randomised into each treatment group (active: 37 male, 14 female; placebo: 39 male, 12 female), and the two groups did not differ significantly with respect to age, general ability, or baseline reading and spelling abilities. 78 of these children (35 active, 43 placebo) were followed up to the six-month point. The number who dropped out, and the reasons for this, did not differ significantly between treatment groups.

At baseline these two groups did not differ on general ability, reading or spelling. After six months, the mean increase in reading age for the sample as a whole was 7.1 months (SD =7.1). In the active treatment group the mean increase was 8.3 months (SD=7.6), while in the placebo group it was 6.2 months (SD=6.6). As is usual, reading age gains over this period correlated significantly with initial reading age, both in the sample as a whole and within each treatment group. Group comparisons of the changes in reading age, controlling for initial reading ability, showed a significant advantage for active treatment over placebo ($p < 0.03$). There was considerable individual variation in reading age gains, but on preliminary exploration, the benefits of HUFA supplementation appeared to be greater in children with high pre-treatment scores on simple checklist ratings of either minor physical signs of fatty acid deficiency, or visual symptoms when reading.

STUDY 3 – FATTY ACID TREATMENT IN CHILDREN WITH DYSPRAXIA

At the time of writing, there appear to be no randomised controlled trials of fatty acid treatment in dyspraxia in the literature. One small open study of dyspraxic children has been reported, involving supplementation for three months with both omega-3 and omega-6 HUFA from a combination of fish oil and evening primrose oil (Stordy, 2000). Reductions were found in both motor difficulties, as assessed via parental report and objective measures, and ADHD-related symptoms as assessed by the Conners Parent Rating Scales (Conners, 1997). However, without a placebo control group it is not possible to ascribe these changes to the treatment itself, as expectations can always play a very significant role. A controlled trial of HUFA treatment in dyspraxic children has now been completed, and its broad design is described here. As with Study 2, however, preliminary findings only can be outlined at this stage, as analyses of the data have not yet been fully completed.

The primary outcome measures were changes in age-adjusted measures of visuomotor control, reading and spelling, working memory and ADHD-related symptoms,

and the main hypothesis was that children on active treatment would show improvements on these measures compared with placebo-treated controls.

All children between 5 and 12 years of age from primary schools within Durham Local Education Authority who met DSM-IV criteria for DCD and were not currently receiving any treatment for this condition were eligible to take part with permission from their parents and family doctor, provided that they were not receiving medical treatment or supervision for a major physical or mental health condition.

A total of 116 children were recruited into the study, and measures of visuomotor function, reading and spelling and ratings of ADHD-related features were assessed using standardised measures before and after treatment for 12 weeks with either a fatty acid supplement or placebo. The active treatment was a supplement containing 80% fish oil and 20% evening primrose oil, supplying the following fatty acids: EPA (558mg), DHA (174 mg) and GLA (60 mg) plus 9.6mg of Vitamin E (natural form, alpha-tocopherol). The placebo treatment contained olive oil, and was carefully matched with the active treatment for both colour and flavour.

At the 12-week point, only 6 children were lost to follow-up. Preliminary results indicate highly significant group differences in favour of active treatment for changes in reading, spelling and measures of working memory. Similarly, fatty acid treatment was associated with very significant reductions in ADHD-related symptoms on both teacher and parent ratings. 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.

SUMMARY

Three controlled trials of fatty acid supplementation in dyslexic and dyspraxic children are described here. Results from two of them have not yet been published in peer-reviewed journals at the time of writing, hence only a preliminary overview of the findings can be given.

The first study showed that treatment with a combination of n-3 and n-6 fatty acids can reduce parent-rated ADHD-related symptoms in children with a primary diagnosis of dyslexia (Richardson and Puri, 2002). 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 than placebo. 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, with two reaching conventional significance levels. 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. Study numbers in this pilot study were small, hence statistical power was very limited. The treatment effects obtained, however, were quite substantial – and clinically meaningful - so the results strongly indicate that further investigations of this kind are warranted.

The second, larger trial involved clinic-referred dyslexic children, and the primary aim was to investigate effects on reading progress. Preliminary results suggest that compared with placebo, fatty acid treatment led to greater increases in reading achievement over a six-month period, but no significant differences were observed for spelling. Within each treatment group there was considerable variation in reading age change over this time period. Although further studies would be need to confirm the

predictive value of these measures, the effects of treatment on reading appeared to be particularly pronounced in children who showed either physical signs of fatty acid deficiency or visual symptoms before treatment.

The third study was also relatively large, involving 116 children with dyspraxia / developmental coordination disorder. Formal details of the results are not yet available at the time of writing, but significant improvements were found for active treatment over placebo with respect to a number of different measures, including reading and spelling progress, working memory, ADHD-related symptoms and some measures of visuomotor performance.

These are the first studies of their kind in children with specific learning difficulties such as dyslexia and dyspraxia. Similar studies of ADHD children are reviewed in Chapter 46, but in summary, two double-blind trials have now found no benefits from DHA supplementation (Voigt et al., 2001); Hirayama et al., 2002) while another (Burgess, 1998) indicated some benefits from a supplement containing both EPA and DHA as well as n-6 HUFA, as was used in the trials reported here. Earlier studies of n-6 supplementation in ADHD gave broadly negative results (Aman et al., 1987, Arnold et al., 1989), so the current balance of evidence raises the possibility that the n-3 fatty acid EPA may be the important component in reducing ADHD symptoms. In schizophrenia and depression, treatment with EPA on its own has been found to be efficacious, while supplementation with DHA has not (Peet et al., 2001), as discussed elsewhere in this volume. Further studies of developmental conditions such as dyslexia, dyspraxia and ADHD may therefore do well to explore this possibility.

The choice of placebo is also important in clinical trials of essential fatty acids. The use of olive oil as a placebo in these studies is not ideal (Puri and Richardson, 2000), because olive oil is a rich source of oleic acid, from which the psychoactive lipid oleamide can be biosynthesized in mammals (Sugiura et al., 1996). Oleamide has a number of important psychoactive actions, such as the induction of sleep and modulation of receptor-mediated signalling via serotonin and other neurotransmitters (Cravatt et al., 1995, Boger et al., 1998, Huitron-Resendiz et al., 2001, Fedorova et al., 2001). The acceptability and tolerability of olive oil in these study populations is excellent, however, and its properties also allow for good matching against fatty acid supplements of this kind. Placebo effects were not evident in the first trial reported here, and although they did feature to some extent in the other two studies, these could equally be attributable to other factors. Nonetheless, the use of an inert placebo in future studies might be expected to result in more significant findings.

Blood fatty acid measures would clearly be useful as objective measures of fatty acid status, and without them no inferences can be drawn concerning any biochemical changes underlying the improvements observed following fatty acid treatment. In each of these studies, however, subjects were not pre-selected in any way for low fatty acid status, a fact that would be expected to weaken any treatment effects. Future studies would do well to assess fatty acids if possible (and other aspects of nutritional status) as well as to investigate possible mechanisms. Further work is also needed to establish the specificity and durability of these treatment effects, and to develop simple methods of identifying those children most likely to benefit from HUFA supplementation.

In conclusion, HUFA supplementation appears to be of benefit in alleviating many ADHD-related symptoms in dyslexic and dyspraxic children, and preliminary results indicate that it may also help to improve progress in reading and spelling in these populations. Larger trials are strongly indicated, which should include an inert placebo and objective measures of fatty acid deficiency. The relative contribution of the n-3 fatty acid EPA to these effects would also appear to merit specific investigation.

REFERENCES

- Aman MG, Mitchell EA and Turbott SH. The effects of essential fatty acid supplementation by Efamol in hyperactive children. *J Abnorm Child Psychol* 1987; 15: 75-90.
- Arnold LE, Kleykamp D, Votolato NA, Taylor WA, Kontras SB and Tobin K. Gamma-linolenic acid for attention-deficit hyperactivity disorder: placebo-controlled comparison to D-amphetamine. *Biol Psychiatry* 1989; 25: 222-228.
- Boger DL, Henriksen SJ and Cravatt BF. Oleamide: an endogenous sleep-inducing lipid and prototypical member of a new class of biological signaling molecules. *Curr Pharm Des* 1998; 4: 303-314.
- Bourre JM, Durand G, Pascal G and Youyou A. Brain cell and tissue recovery in rats made deficient in n-3 fatty acids by alteration of dietary fat. *J Nutr* 1989; 119: 15-22.
- Burgess JR. Attention deficit hyperactivity disorder. Observational and intervention studies. NIH workshop on omega-3 essential fatty acids and psychiatric disorders, National Institutes of Health, Bethesda 1-3 September, 1998.
- Conners CK. *Conners' Parent Rating Scales - Revised*. Multi-Health Systems Inc., New York, 1997.
- Cravatt BF, Prospero-Garcia O, Siuzdak G, Gilula NB, Henriksen SJ, Boger DL and Lerner RA. Chemical characterization of a family of brain lipids that induce sleep. *Science* 1995; 268: 1506-1509.
- Fedorova I, Hashimoto A, Fecik RA, Hedrick MP, Hanus LO, Boger DL, Rice KC and Basile AS. Behavioral evidence for the interaction of oleamide with multiple neurotransmitter systems. *J Pharmacol Exp Ther* 2001; 299: 332-342.
- Hirayama S, Hamazaki T and Terasawa K. The effect of foods containing DHA on symptoms of attention-deficit hyperactivity disorder: a randomised controlled trial. *ISSFAL International Conference, Montreal, 6-12 May 2002*.
- Huitron-Resendiz S, Gombart L, Cravatt BF and Henriksen SJ. Effect of oleamide on sleep and its relationship to blood pressure, body temperature, and locomotor activity in rats. *Exp Neurol* 2001; 172: 235-243.
- Peet M, Brind J, Ramchand CN, Shah S and Vankar GK. Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia. *Schizophr Res* 2001; 49: 243-251.
- Puri BK and Richardson AJ. The effects of olive oil on omega3 fatty acids and mood disorders. *Arch Gen Psychiatry* 2000; 57: 715.
- Richardson AJ, Calvin CM, Clisby C, Schoenheimer DR, Montgomery P, Hall JA, Hebb G, Westwood E, Talcott JB and Stein JF. Fatty acid deficiency signs predict the severity of reading and related difficulties in dyslexic children. *Prostaglandins Leukot Essent Fatty Acids* 2000; 63: 69-74.
- Richardson AJ, Easton T, McDaid AM, Hall JA, Montgomery P, Clisby C and Puri BK. Essential fatty acids in dyslexia: theory, experimental evidence and clinical trials. In: Peet M, Glen I and Horrobin DF, eds. *Phospholipid Spectrum Disorder in Psychiatry*. Carnforth: Marius Press, 1999: 225-241.
- Richardson AJ and Puri BK. A randomized double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties. *Prog Neuropsychopharmacol Biol Psychiatry* 2002; 26: 233-239.
- Richardson AJ and Ross MA. Fatty acid metabolism in neurodevelopmental disorder: a new perspective on associations between attention-deficit/hyperactivity disorder, dyslexia, dyspraxia and the autistic spectrum. *Prostaglandins Leukot Essent Fatty Acids* 2000; 63: 1-9.
- Stordy BJ. Dark adaptation, motor skills, docosahexaenoic acid, and dyslexia. *Am J Clin Nutr* 2000; 71: 323S-326S.
- Sugiura T, Kondo S, Kodaka T, Tonegawa T, Nakane S, Yamashita A, Ishima Y and Waku K. Enzymatic synthesis of oleamide (cis-9, 10-octadecenoamide), an endogenous sleep-inducing lipid, by rat brain microsomes. *Biochem Mol Biol Int* 1996; 40: 931-938.
- Voigt RG, Llorente AM, Jensen CL, Fraley JK, Berretta MC and Heird WC. A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. *J Pediatr* 2001; 139: 189-196.