Combined \(\omega 3\) and \(\omega 6\) Supplementation in Children With Attention-Deficit Hyperactivity Disorder (ADHD) Refractory to Methylphenidate Treatment: A Double-Blind, Placebo-Controlled Study

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Abstract

Children (6-12 years) with attention-deficit hyperactivity disorder (ADHD) being treated with methylphenidate and standard behavior therapy for more than 6 months, whose parents reported no improvement in behavior and academic learning, were randomly assigned to receive supplementation with a combined \(\omega 3\) and \(\omega 6\) preparation or a placebo. Outcome was measured at 3 and 6 months after treatment using a self-assessment checklist completed by the parents. Statistically significant improvement was found in the treatment group compared with the placebo group (\(P < .01\)) in the following measures: restlessness, aggression, completing work, and academic performance. Statistically significant improvement was not found at 3 months of treatment between groups but was evident at 6 months of treatment (\(P < .05\)) with inattention, impulsiveness, and cooperation with parents and teachers. Distractibility failed to show improvement. Effect sizes ranged from 0.3 to 1.1 at 3 months and 0.2 to 1.4 at 6 months for individual symptom variables.

Keywords

ADHD, comorbidity, \(\omega 3\) and \(\omega 6\), behavior problems, learning difficulties

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Problems in behavior and learning (risk of accident and injury, aggression, and educational failure) in attention-deficit hyperactivity disorder (ADHD) are directly attributed to its symptoms.\(^1-3\) Methylphenidate, although ameliorating some comorbidities,\(^4-6\) is effective in eliminating symptoms only in 45% to 50% of cases.\(^7-9\) High rates of multi-agent treatment in ADHD also suggest that suboptimal stimulant response is common.\(^10-12\) Additional agents (antipsychotics and mood stabilizers) are often used as adjunct to stimulant medication.\(^11-15\) Among such agents studied are \(\omega 3\) and \(\omega 6\). Their deficiency is implicated in the pathogenesis of neurodevelopmental disorders such as ADHD, dyslexia, dyspraxia, and autism.\(^16-19\) Their potential role in the treatment of these disorders has not been established because of inconsistent claims of efficacy.\(^20-22\) Although dietary supplementation with \(\omega 3\) and \(\omega 6\) was found to be a safe and effective option in the treatment of children with educational and behavior problems,\(^23\) reviews on open and control trials do not support the use of these agents as primary or supplementary treatment for ADHD.\(^24-27\) No studies have yet investigated the effectiveness of \(\omega 3\) and \(\omega 6\) as supplementary treatment in children with ADHD with behavioral and educational problems that are refractory to stimulant medication alone.

The objective of this study was to assess the effectiveness of combined \(\omega 3\) and \(\omega 6\) supplementation in children with ADHD whose parents reported no improvement in behavior and academic learning with methylphenidate and standard behavior therapy for 6 months or more.

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Patients and Methods

Participants

Participants for the study were children 6 to 12 years of age, selected from an outpatient treatment program for ADHD. All children in the program were clinically diagnosed (according to criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition), supported by positive scores in Swanson, Nolan and Pelham version IV (SNAP) parent and teacher evaluation. The associated behavior problems and difficulties in academic learning were made on clinical history and teacher report (based on age-related academic standards set for Sri Lankan children by the Institute of Education, Sri Lanka). All children were prescribed a total daily dose of methylphenidate (0.7-1 mg/kg body weight) and standard behavioral intervention.
The ADHD treatment program had 422 registered children. Ninety-five were excluded for being registered for less than 6 months. Eleven children whose hyperactivity was primarily related to intellectual impairment, brain injury, and insult were also excluded. Another 141 were excluded for satisfactory outcome in ADHD symptoms, behavior, and school-based learning, evidenced from clinical records for 3 consecutive months or more. A further 77 were excluded for missed follow-up appointments and medication refills as they could not be counted as definitively “refractory to treatment.” Ninety-eight children were eligible for inclusion in the study.

The 98 selected for the study received consistent treatment for 6 months or more. The parents’ reports of persistent ADHD-related symptoms were confirmed using the parent version of SNAP IV (mean combined score 2.62; range, 1.89-4.00; SD 0.51). Comparison, Swanson, Nolan and Pelham version IV (SNAP) scores were also obtained from a random sample of 78 from among the 141 children who were excluded for satisfactory outcome (mean combined score 1.52; range, 0.11-1.56; SD 0.80). Persistence of behavior problems was identified at a clinical interview and from the entry in clinical records for the previous 3 consecutive months and learning problems from examination of school workbooks. Behavior and learning problems included comorbid oppositional defiant disorder, conduct disorder, specific learning disorder, and tic disorder. The parents gave informed written consent for inclusion in the trial. The eligible children were randomly assigned in a 1:1 ratio to receive active treatment or placebo, which were labeled in code. The researchers and the patients were masked to group allocation, carried out by an independent third person. The true identity of the codes was revealed in the presence of authorized persons independent of the study, after all data were collected, verified, and analyzed.

### Intervention

The active treatment (commercially marketed as Vegepa) was a capsule containing ω3 and ω6 (fish oil and cold-pressed evening primrose oil in the ratio 1.6:1; ω3 = 296.37 mg, ω6 = 180.75 mg). A capsule of identical appearance containing sunflower oil was used as the placebo. The dose throughout the study was 2 capsules per day in 2 doses, administered by mothers. All participants were supplied with capsules for 30 days at a time. At the end of each 30 days participants were reviewed by the authors, who assessed for any adverse effects, encouraged compliance, and provided another supply of capsules. This process was repeated for 6 months. All participants continued taking methylphenidate (immediate-release preparation 0.7-1 mg/kg/d) and continued the home- and classroom-based behavioral interventions throughout the study period. (Immediate-release methylphenidate is the only preparation available in Sri Lanka.) In addition, both groups were administered micronutrients in recommended doses for age as tablets to avoid any confounding effect from deficiency states. Any other medication the child was already taking was continued. None were introduced to new medications during the study.

### Outcome Measures

The outcome of intervention was assessed by using an 11-item checklist, written in local language, which was self-administered by the parents. The items on the checklist assessed symptoms of ADHD and associated behavioral problems and learning difficulties. Each item was scored on a 3-point scale of “better,” “same as before,” and “worse than before” as 1, 2, and 3, respectively. Accordingly, at baseline each child had a total score of 22 and at outcome a score ranging from 11 to 33. This checklist was used in a previous study to obtain parents’ feedback on the outcome of ADHD treatment and was found to be reliable and valid28 (test–retest reliability 96.1% and content validity using Delphi technique +1). Mothers responded to the checklist by comparing the current status of the child with that at the commencement of the study, and measures were taken at 3 months and 6 months. Tolerability and side effects of medication were checked at each monthly review. Sociodemographic data and nonverbal intelligence were obtained from the clinical records of participants.

### Statistical Analysis

Comparison between the groups receiving active treatment and placebo was made using independent t test. P ≤ .05 was considered statistically significant. An additional measure of effect size was calculated using the formula:

\[
\text{Effect Size} = \frac{\text{Mean of Experimental Group} - \text{Mean of Control Group}}{\text{Standard Deviation Pooled}}
\]

Analysis was made on the intention-to-treat sample.

### Results

From a total of 98 children recruited to the study, 1 from the active treatment group and 2 from the placebo group were discontinued for refusal to take the supplement. One child from the placebo group dropped out of the study. All 4 left before the first outcome measure was made at 3 months. The total number who completed the study was 94 (48 and 46 receiving active...
Table 3. Frequency Distribution of Outcome Variables at 3 and 6 Months With Active Treatment and Placebo, n (%)

<table>
<thead>
<tr>
<th>Symptom Variable</th>
<th>Outcome at 3 Months</th>
<th>Outcome at 6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active Treatment, n = 48</td>
<td>Placebo, n = 46</td>
</tr>
<tr>
<td>Improved</td>
<td>Same</td>
<td>Worse</td>
</tr>
<tr>
<td>Aggressiveness</td>
<td>38 (79.2)</td>
<td>9 (18.8)</td>
</tr>
<tr>
<td>Restlessness</td>
<td>34 (70.8)</td>
<td>14 (29.2)</td>
</tr>
<tr>
<td>Inattention</td>
<td>24 (50.0)</td>
<td>20 (41.7)</td>
</tr>
<tr>
<td>Distractibility</td>
<td>15 (31.2)</td>
<td>31 (64.6)</td>
</tr>
<tr>
<td>Easy anger</td>
<td>26 (54.2)</td>
<td>21 (43.8)</td>
</tr>
<tr>
<td>Impulsiveness</td>
<td>15 (31.2)</td>
<td>32 (66.7)</td>
</tr>
<tr>
<td>Fighting</td>
<td>26 (54.2)</td>
<td>22 (45.8)</td>
</tr>
<tr>
<td>Cooperation</td>
<td>31 (64.6)</td>
<td>16 (33.3)</td>
</tr>
<tr>
<td>Completing work</td>
<td>19 (39.6)</td>
<td>29 (60.4)</td>
</tr>
<tr>
<td>Wait for turn</td>
<td>18 (37.5)</td>
<td>26 (54.2)</td>
</tr>
<tr>
<td>Academic performance</td>
<td>39 (81.2)</td>
<td>5 (10.4)</td>
</tr>
</tbody>
</table>
treatment and placebo, respectively). Figure 1 gives the flow of participants through the study.

The basic characteristics of the treatment and placebo groups are compared in Table 1.

Mean age of the total sample was 9.3 ± 1.5 years (mode, 9 years). Sex distribution was 2.5:1, with 69 (73.4%) male. The mean duration of treatment prior to entry to the study was 16.5 ± 1.8 months. Other regular medications were for bronchial asthma and epilepsy, with 3 subjects (3.2%) taking anticonvulsants (all seizure-free for >12 months). There was no statistically significant difference between the active treatment and placebo groups in the educational achievement of mothers (P = .242) or that of fathers (P = .558). All participants attended mainstream education.

### Discussion

The results of this study suggest that compared with a placebo, the combined ω3 and ω6 were effective in reducing the symptoms of behavioral and learning difficulties that were refractory to methylphenidate and behavioral treatment alone. The effectiveness was shown in terms of statistically significant results on comparison of mean outcome scores (Table 2), reduction in frequency of individual symptom variables and statistically significant difference in individual symptom scores (Tables 2, 3, and 4), and the large effect size (Table 4). Improvement of symptoms at 6 months was significantly better than at 3 months overall (Table 2) and for most symptom variables (Table 3) and in showing increased effect sizes (Table 4). The only symptom that failed to show a statistically significant improvement was “distractibility” (Table 4). Highest effect sizes were recorded for change in “restlessness” and “aggression” variables (Table 4).

This study is the first to evaluate the effectiveness of ω3 and ω6 supplementation on behavioral and learning difficulties associated with ADHD that was refractory to standard interventions. It replicates findings of a study in children with developmental coordination difficulties that reported a beneficial effect of ω3 and ω6 on behavior, reading, and spelling in children.23 In contrast, however, in a placebo-controlled crossover trial in children and adolescents with ADHD, the majority failed to show a response.20 Nevertheless, in keeping with our results, a subgroup of 26% responded with more than 25% reduction of symptoms at 3 months and 47% at 6 months, where the responders had inattentive subtype of ADHD and comorbidities.20 A positive effect of ω3 and ω6 in reducing impulsivity and aggression has also been reported in other studies.19,20

### Limitations

Including a crossover component was not possible as the trial was confined to a period of 6 months. The turnover of fatty acids in neural membrane is slow and needs a longer trial to make a crossover design appropriate.18 Small sample sizes as well as the relatively short period of intervention are also limitations. The study did not use a standardized schedule and relied on relatively subjective information from parents, although this information was clinically verified. Lack of a culturally valid tool that fulfilled the study requirements was a barrier. Baseline dietary information and social background are potentially confounding factors that were not considered in this study. Also, the implications of anthropometric and developmental factors in influencing the results cannot be interpreted as these issues were not considered in the randomization process.

### Generalizability

The ω3:ω6 ratio in the preparation used in this study was 1.6:1 in a dose of 1 capsule twice a day. An equivalent ratio used in a similar study was 4:1.20 Hence, the optimal preparation and the dose cannot be arrived at. Supplementation with ω3 and ω6 was beneficial, but it cannot be inferred that a correction of a dietary deficiency played a role in improving behavior and learning. The low dropout rate seen in this study could be related to the attention given to the participants of a clinical trial but may not be seen in routine clinical outpatient care. As the study was carried out on a specific ethnic and racial population, the outcome cannot be generalized to other population groups.

### Table 4. Comparison of Outcome Variables as Effect Size at 3 Months and 6 Months Between Active Treatment and Placebo

<table>
<thead>
<tr>
<th>Outcome at 3 Months</th>
<th>Effect Size</th>
<th>95% CI</th>
<th>Outcome at 6 Months</th>
<th>Effect Size</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggressiveness</td>
<td>0.9861</td>
<td>0.8513 - 1.1209</td>
<td>1.4180</td>
<td>1.2832 - 1.5528</td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td>1.1104</td>
<td>0.9805 - 1.2404</td>
<td>1.3635</td>
<td>1.4983 - 1.4934</td>
<td></td>
</tr>
<tr>
<td>Inattention</td>
<td>0.4667</td>
<td>0.3124 - 0.6210</td>
<td>0.5877</td>
<td>0.4334 - 0.7420</td>
<td></td>
</tr>
<tr>
<td>Distractibility</td>
<td>0.4095</td>
<td>0.2727 - 0.5462</td>
<td>0.2371</td>
<td>0.0903 - 0.3840</td>
<td></td>
</tr>
<tr>
<td>Easy anger</td>
<td>0.6824</td>
<td>0.5951 - 0.7697</td>
<td>1.1104</td>
<td>0.9656 - 1.2552</td>
<td></td>
</tr>
<tr>
<td>Impulsiveness</td>
<td>0.5197</td>
<td>0.3937 - 0.6456</td>
<td>0.6180</td>
<td>0.4813 - 0.7548</td>
<td></td>
</tr>
<tr>
<td>Fighting</td>
<td>0.3848</td>
<td>0.2379 - 0.5317</td>
<td>1.1755</td>
<td>1.0882 - 1.2628</td>
<td></td>
</tr>
<tr>
<td>Cooperation</td>
<td>0.5662</td>
<td>0.5662 - 0.5662</td>
<td>1.2331</td>
<td>1.1072 - 1.3591</td>
<td></td>
</tr>
<tr>
<td>Completing work</td>
<td>0.5380</td>
<td>0.5380 - 0.5380</td>
<td>0.3829</td>
<td>0.2361 - 0.5298</td>
<td></td>
</tr>
<tr>
<td>Wait for turn</td>
<td>0.4298</td>
<td>0.4298 - 0.4298</td>
<td>0.7673</td>
<td>0.6158 - 0.9188</td>
<td></td>
</tr>
<tr>
<td>Academic performance</td>
<td>0.8787</td>
<td>0.8787 - 0.8787</td>
<td>1.1092</td>
<td>0.9723 - 1.2461</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions
The combination of \( \alpha_3 \) and \( \alpha_6 \) was safe and effective in improving behavior and learning in the group that was studied. The current study is a pilot, and replication of the findings is required before we can advocate supplementation as a routine practice for children with behavior and learning difficulties that are refractory to standard management. At the same time, it is possible to infer from the results that the participants of the study may have benefitted further if treatment with \( \alpha_3 \) and \( \alpha_6 \) had been continued.

Author Contributions
HP conceived and designed the study, interpreted the data, and drafted the manuscript. HP and KCJ analyzed and interpreted data. All authors collected data and read and approved the final manuscript.

Declaration of Conflicting Interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval
The study was registered in Sri Lanka Clinical Trials Registry (Trial Registration No: SLCTR/2009/006). Ethical clearance was obtained from the Ethical Review Committee of Lady Ridgeway Hospital for Children.

References


