Internet-Based, Randomized, Controlled Trial of Omega-3 Fatty Acids for Hyperactivity in Autism

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Objective: Preliminary evidence suggests that omega-3 fatty acids may reduce hyperactivity in children with autism spectrum disorder (ASD). We sought to examine the feasibility of a novel, Internet-based clinical trial design to evaluate the efficacy of this supplement. **Method:** E-mail invitations were sent to parents of children aged 5 to 8 years enrolled in the Interactive Autism Network. All study procedures, including screening, informed consent, and collection of outcome measures took place over the Internet. The primary outcome measures were parent- and teacher-rated changes in hyperactivity on the Aberrant Behavior Checklist (ABC-H). **Results:** During the 6-week recruitment period, 57 children from 28 states satisfied all eligibility criteria and were randomly assigned to 1.3 grams of omega-3 fatty acids or an identical placebo daily for 6 weeks. Outcome assessments were obtained from all 57 participants and 57 teachers, and the study was completed in 3 months. Children in the omega-3 fatty acid group had a greater reduction in hyperactivity (−5.3 points) compared to the placebo group (−2.6 points), but the difference was not statistically significant (1.9-point greater improvement in the omega-3 group, 95% CI = −2.2 to 5.2). Adverse events were rare and not associated with omega-3 fatty acids. Participant feedback was positive. **Conclusion:** Internet-based, randomized controlled trials of therapies in children with ASD are feasible and may lead to marked reductions in the time and cost of completing trials. A larger sample size is required to definitively determine the efficacy of omega-3 fatty acids. Clinical trial registration information—Omega-3 Fatty Acids for Hyperactivity Treatment in Autism Spectrum Disorder; http://clinicaltrials.gov; NCT 01694667. J. Am. Acad. Child Adolesc. Psychiatry, 2014;53(6):658–666. **Key Words:** autism, nutritional supplement, alternative medicine, hyperactivity

Autism spectrum disorders (ASDs) are estimated to affect as many as 1 in 50 children in the United States,[1] and are characterized by impairments in communication, social interaction, and repetitive behavior.[2] Complementary and alternative medical (CAM) therapies, such as omega-3 fatty acids, digestive enzymes, and high-dose vitamins are widely used to treat ASD, despite little or no evidence of efficacy and safety.[3] Traditional, clinic-based, randomized controlled trials (RCTs) of therapies for ASD are expensive and slow. We sought to determine whether it would be feasible to conduct an RCT of an intervention for ASD entirely over the Internet with the goal of developing a platform for rapidly evaluating promising therapies. We selected omega-3 fatty acids as the intervention in this first, Internet-based randomized controlled trial (IB-RCT) in ASD because hyperactivity is a common problem among children with ASD and because standard pharmacological treatments have unpredictable effects and more side effects in children with ASD.[4,5]

Two prior small pilot studies found nonsignificant trends suggesting that omega-3 fatty acids may reduce hyperactivity in children with ASD.[6,7] Amminger *et al.* randomly assigned 13 children with ASD to 6 weeks of omega-3 fatty acids versus. placebo and found that the hyperactivity score on the Aberrant Behavior Checklist (ABC-H) was reduced by 4.0 points in the treatment group compared to an increase of 3.0 points in the placebo group ($p = .098$), a nonsignificant result with an effect size of 0.71.[6] Bent *et al.* randomly assigned 27 children with ASD to 12-weeks of

omega-3 fatty acids versus placebo and found that hyperactivity was reduced by 2.7 points on the ABC-H in the omega-3 group compared to 0.3 points in the placebo group ($p = .4$), a statistically nonsignificant difference (effect size = 0.38).[7] Both prior studies were small and had insufficient power to definitively determine efficacy but showed trends favoring the omega-3 fatty acid group.

Other evidence suggesting possible efficacy comes from the use of omega-3 fatty acids in different disorders. A recent systematic review found that omega-3 fatty acid treatment leads to modest improvements in overall symptoms and in inattention and hyperactivity in children with attention-deficit/hyperactivity disorder (ADHD, with an effect size = 0.31).[8] A recent, large RCT of omega-3 fatty acids in 362 healthy schoolchildren aged 7 to 9 years found that it led to significant improvements in reading among children with low initial reading scores.[9] Preliminary studies also suggest that omega-3 fatty acids may have benefits in treating depression and schizophrenia.[10,11] Omega-3 fatty acids have been found to have a favorable safety profile.[12] We therefore conducted an IB-RCT to examine the potential of this method and to further examine the safety and efficacy of omega-3 fatty acids in ASD.

METHOD

Participants

The study protocol was approved by the Committees on Human Research at the University of California, San Francisco and at Johns Hopkins University. The trial was registered before enrolling patients at clinicaltrials.gov (NCT 01694667) and took place between September 18, 2012 and December 31, 2012.

Recruitment was limited to children between the ages of 5 and 8 with some verbal ability (as defined by question 1 of the Social Communication Questionnaire or SCQ) who were enrolled in the Interactive Autism Network (IAN), an online registry and longitudinal study of more than 13,000 families of children affected by ASD. Children were defined as having an accurate diagnosis of ASD if they met the following 2 criteria: diagnosis of ASD by a professional, according to parent-report; and a score of >12 on the SCQ. A prior validation study within IAN found that 99% of children meeting these 2 criteria were confirmed to have an ASD diagnosis based on in-person clinical testing with the Autism Diagnostic Observation Schedule (ADOS) or the Autism Diagnostic Interview–Revised (ADI-R).[13]

E-mail invitations were sent to the 863 registered IAN members who met the above criteria and had given prior consent to be contacted about research opportunities. Interested parents completed an initial screening questionnaire by clicking on an embedded link in the e-mail. Children were required to have elevated levels of hyperactivity, defined as a score of >20 on the hyperactivity subscale of the ABC-H, which is 1 standard deviation above the mean score. Children were also required to have a parent (or caregiver) and a teacher willing to complete baseline and outcome assessments by e-mail. Children were excluded if they had used omega-3 fatty acids in the last 6 months or had a known bleeding disorder, an allergy to fish or seafood, or a major medical illness. Parents of children who passed the eligibility screen were asked to complete an online informed consent process that was confirmed by their electronic signature. All participants were given the option of speaking with an investigator by phone before signing informed consent, and the online informed consent process was approved by both participating institutional review boards. After completion of online baseline measures, participating parents received follow-up e-mails weekly to report medication adherence, new medical problems, and outcome assessments (3 and 6 weeks).

Internet-Based Clinical Trial Platform

The flow of participants through each step of the study was managed by an automated Internet-based clinical trial platform developed by experts at IAN (P.L. and J.N.). Once the study launched, all steps of the study proceeded automatically with oversight from IAN staff.

All participants received a phone call from a study investigator within 3 days of randomization to welcome them to the study, to reinforce study instructions, and to answer questions. The data collection system met U.S. Food and Drug Administration (FDA), 21CFR Part11, HL7, and Health Insurance Portability and Accountability Act (HIPAA) compliance criteria for the capture and security of electronic data. Adverse events were monitored by both the study principal investigator (S.B.) and the IAN site principal investigator (P.L.). As soon as a new adverse event was entered by a participant into the online platform, an e-mail message was sent to both principal investigators, who conferred about the adverse event and called the parent to obtain and to document all information. Further details of the platform will be provided in a subsequent publication.

Intervention

Eligible children were randomly assigned to 6 weeks of treatment with omega-3 fatty acids or an identical placebo, which was sent by overnight mail. Omega-3 fatty acids were provided as orange-flavored pudding packets (Coromega, Vista, CA) containing 650 mg of omega-3 fatty acids, including 350 mg of eicosapentanoic acid (EPA) and 230 mg of docosahexanoic acid (DHA), given twice daily for a daily dose of 1.3 g of omega-3 fatty acids (and 1.2 g of DHA + EPA). The 6-week duration of study medication was selected