REVIEW

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Omega-3 Fatty Acids in Depression: A Review of Three Studies

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We review three studies of omega-3 fatty acids in the treatment of depression that were carried out by our research group at the Beer Sheva Mental Health Center. The first study examined eicosapentaenoic acid (EPA) versus placebo as an adjunct to antidepressant treatment in 20 unipolar patients with recurrent major depression. The second study used omega-3 fatty acids in childhood major depression; 28 children aged 6–12 were randomized to omega-3 fatty acids or placebo as pharmacologic monotherapy. The third study was an open-label add-on trial of EPA in bipolar depression. Twelve bipolar outpatients with depressive symptoms were treated with 1.5–2.0 g/day of EPA for up to 6 months. In the adult unipolar depression study, highly significant benefits were found by week 3 of EPA treatment compared with placebo. In the child study, an analysis of variance (ANOVA) showed highly significant effects of omega-3 on each of the three rating scales. In the bipolar depression study, 8 of the 10 patients who completed at least 1 month of follow-up achieved a 50% or greater reduction in Hamilton depression (Ham-D) scores within 1 month. No significant side effects were reported in any of the studies. Omega-3 fatty acids were shown to be more effective than placebo for depression in both adults and children in small controlled studies and in an open study of bipolar depression. (This review discusses three studies, all from our group, completed before the clinical trial registry was initiated.)

Introduction

Omega-3 fatty acids are long-chain polyunsaturated fatty acids (PUFAs). Docosahexaenoic acid (DHA) is composed of 22 carbon atoms and has six double bonds starting from the methyl (omega) end of the chain, whereas eicosapentaenoic acid (EPA) is composed of 20 carbon atoms and has five double bonds starting from the methyl (omega) end of the chain. PUFAs are not synthesized in humans and are ingested mainly via the consumption of fatty cold-water fish. Epidemiological studies from the 1990s and onwards [1,2] suggested that a diet high in this type of fish might have protective function against depression. In support of this hypothesis, a series of biochemical and pharmacological studies suggested that fatty acids modulate neurotransmitter metabolism and cell signal transduction in humans, and, more specifically, that abnormalities in fatty acid and eicosanoid metabolism may play a causal role in depression [3–7].

Several studies of omega-3 fatty acids have been performed in behavioral disorders with few side effects [8]. There is evidence suggesting effects of omega-3 on human spinal fluid serotonin metabolites [5]. Edwards et al. [9] reported changes in fatty acid levels in the diet and red blood cells of depressed patients. Maes et al. [10] reported changes in serum fatty acid composition in depression. Severus et al. [11] proposed that omega-3 fatty acids are the mechanistic "missing link" connecting cardiovascular disease and depression, and therefore represent a key pathophysiological clue to the mechanism of depression.

We herein review three studies: a study of omega oil as an add-on medication in breakthrough unipolar depressions [12], a study of omega oil in pediatric unipolar depression [13], and a small open-label study of omega oil in bipolar depression [14]. All three studies were carried out by our research group in the Beer Sheva Mental Health Center with the approval of the relevant institutional review boards (Helsinki committees).

Beer Sheva Unipolar Depression Study

We first studied a specific omega-3 fatty acid, the ethyl ester of EPA, as an adjunct to antidepressant treatment for breakthrough depression in recurrent unipolar patients on maintenance therapy in double-blind, controlled, randomized, parallel groups.

Patients with current major depression [Diagnostic and Statistical Manual-IV (DSM-IV)] could enter the study if aged 18–75 and had no unstable medical disease, no alcohol or drug abuse, no psychotic features, no history of hypomania or mania, and no psychiatric comorbidity other than panic disorder, dysthymia, or obsessive-compulsive disorder. After baseline physical examination and blood chemistry, the patients were randomized to EPA or placebo according to a prearranged code.

The study design was a 4-week parallel-group, double-blind add-on. The patients continued their current antidepressant treatment at the same dose as at the time they entered the study. Patients who entered the study had had at least 3 weeks of ongoing treatment with antidepressant drugs at the current therapeutic dose and a score of at least 18 on the Hamilton Depression (Ham-D) Rating Scale (HDRS). The EPA or matching placebo was given 1 g twice daily [12]. HDRS (24-item version) ratings were done at baseline, and weekly thereafter by an experienced psychiatrist (BN) blind to the treatment. One patient dropped out in the placebo group in week 3 due to worsening.

The results are illustrated in figure 1. Twenty patients participated, 17 women and 3 men, mean age = 53.4 (range 28–73). A two-way multivariate analysis of co-variance (MANCOVA) of treatment by time (Greenhouse–Geisser corrected) with covariance for baseline was performed, including the dropout with last value carried forward. The treatment and time showed a statistically significant interaction ($F = 17.6$ $df_{1.6/28.6}$, $P < 0.001$). EPA was significantly different from placebo at week 2 (Newman–Keuls *post hoc* test, $P < 0.001$), week 3 (Newman–Keuls *post hoc* test, $P < 0.001$), and week 4 (Newman–Keuls *post hoc* test, $P < 0.001$). Excluding the dropout, the treatment and time still showed a statistically significant interaction ($F = 12.09$, $df_{1.6/27.8}$, $P < 0.001$). The mean reduction of HDRS on EPA of 12.4 points compared to 1.6 on placebo was clinically meaningful, as 6 of 10 patients on EPA but only 1 of 10 patients on placebo achieved a 50% reduction in HDRS ($P = 0.06$).

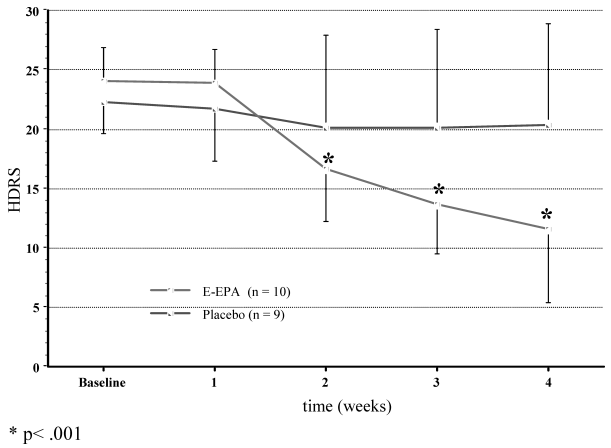

Figure 1. Hamilton Depression Rating Scale results for omega-3 EPA versus placebo in breakthrough unipolar depression. *$P < 0.001$.

This study, which was one of the first therapeutic trials of omega-3 fatty acids in unipolar depression [12], used EPA. Further studies will be necessary to compare the effectiveness of the various fatty acids in treatment of depression, as well as the relevant dose–response curves.

The effect of EPA was significant from week 2 of treatment, similar to the time course for existing antidepressants. The item analysis showed effects of EPA on core depressive symptoms such as depressed mood, guilt feelings, and worthlessness as well as insomnia.

Beer Sheva/Schneider Children's Medical Center Pediatric Depression Study

Major depressive disorder (MDD) is a common and recurrent disorder in children. It is frequently accompanied by poor psychosocial outcome, comorbid conditions, and high risk of suicide and substance abuse, indicating the need for treatment. The prevalence of MDD is estimated to be approximately 2–4% in children [15]. Several randomized, controlled studies have shown 50–60% response to both selective serotonin reuptake inhibitors (SSRIs) and placebo [16,17]. However, these studies included a majority of adolescent children, and the efficacy of biological treatment of prepubertal childhood depression is almost unknown. We found omega-3 fatty acids to be effective in adult depression as an add-on therapy [12]. We therefore performed a controlled study of omega-3 fatty acid in childhood depression, restricting our study to children under age 12.

Children suffering from MDD using the Hebrew translation of the childhood version of the Schedule for Affective Disorders and Schizophrenia [18] were accepted. Excluded were children with unstable physical illness or psychiatric disorders other than anxiety, attention-deficit hyperactivity disorder (ADHD), dysthymia, or tic syndrome.

All participating patients entered the study after at least one parent's written informed consent, following child's

verbal informed consent, and after the parent's commitment to inform the other parent.

The omega-3 trial lasted for 16 weeks. Ratings were made at baseline, 2 weeks, 4 weeks, 8 weeks, 12 weeks, and 16 weeks using Childhood Depression Rating Scale (CDRS), Childhood Depression Inventory (CDI), and Clinical Global Impression (CGI) scales. The CDRS and CGI are clinician rated and the CDI is self-rated by the child patient at each visit.

Patients received two 500 mg or one 1,000 mg capsule daily depending on their ability to swallow a larger capsule. This was chosen as half of the adult dose used by Nemets et al. [12]. Placebo for the 500 mg capsule was olive oil (supplied by Ocean Nutrition, Dartmouth, NS, Canada) containing no omega-3 fatty acids. Placebo for 1,000 mg capsules was safflower oil (74% linoleic acid supplied by Sears Laboratories (Marblehead, MA, USA) containing no omega-3 fatty acids). The 1,000 mg active capsules contained 400 mg EPA and 200 mg DHA per 1,000 mg capsule. The 500 mg active capsules contained 190 mg EPA and 90 mg DHA per 500 mg capsule. These ratios of EPA to DHA are similar to most commercially available preparations, but different from the pure EPA used by Nemets et al. [12].

Twenty-eight children were randomized for the study. Twenty completed at least 2-week ratings and were included in the data analysis. Of the eight who dropped out before 1 month, five were on placebo and three were on omega-3. The only reason for dropout before 2 weeks in the three children of the omega-3 group was noncompliance. The reasons for dropout before 1 month in the placebo group were: (1) appearance of precocious puberty leading to an endocrine workup in one patient, (2) noncompliance in two patients, (3) nonresponse in one patient, and (4) manic episode in one patient.

Of the 20 children who entered data analysis, 10 received placebo and 10 omega-3. There were 7 boys and 3 girls in the placebo group; and 8 boys and 2 girls in the omega-3 group. The mean age in the omega-3 group was 10.0 (range 8.0–12.0) and 10.3 in the placebo group (range 8.0–12.5). Children had been depressed for a mean of 3.5 ± 1.3 months in the omega-3 group and 3.3 ± 1.6 months in the placebo group. In all cases, this was a first depressive episode. In the omega-3 group, there were two children with comorbid ADHD, one with obsessive compulsive disorder, one with separation anxiety, one with dysthymia, and one with chronic tics. In the placebo group, there were three children with ADHD, one with panic disorder, one with separation anxiety, and two with dysthymia. Concurrent medications on stable dose for at least 6 months were two children on methylphenidate in the omega-3 group and three children in the placebo group.

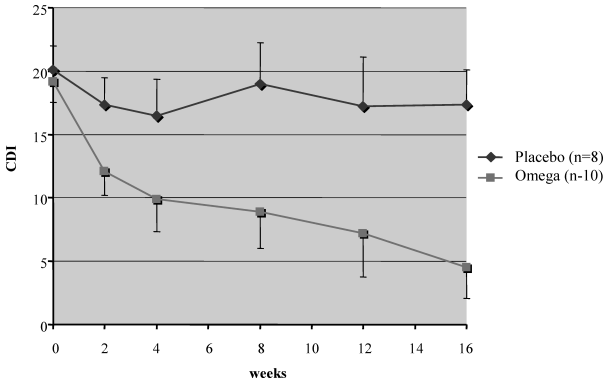

Figure 2. Childhood Depression Inventory results for omega-3 versus placebo in childhood depression. The "*N*" in placebo group was only 8 because two patients were unable to complete the self-rating scale or did it with errors. A two-way repeated measures ANOVA of treatment over time showed a statistically significant interaction ($F = 3.4$, $df_{5,80}$, $P < 0.005$). There was a significant main effect of treatment ($F = 5.5$, $df_{1,16}$, $P < 0.04$) and time ($F = 7.6$, $df_{5,80}$, $P < 0.001$).

The effect of omega-3 is highly significant. Of those on omega-3 treatment, 7 out of 10 had a greater than 50% reduction of CDRS. Of those on placebo, none of 10 patients had a greater than 50% reduction in CDRS ($P = 0.003$, Fisher exact test). Four of 10 patients in the omega-3 group met remission criteria of Emslei et al. [16] of CDRS <29 at study exit, and no patient in the placebo group did so ($P =$ NS). The results on a second, self-report instrument (CDI) were quite similar, and may be seen in figure 2. The "*N*" in the placebo group was only 8 because two patients were unable to complete the self-rating scale or did so with errors. A two-way repeated measures analysis of variance (ANOVA) of treatment over time showed a statistically significant interaction ($F = 3.4$, $df_{5,80}$, $P < 0.005$). There was a significant main effect of treatment ($F = 5.5$, $df_{1,16}$, $P < 0.04$) and time ($F = 7.6$, $df_{5,80}$, $P < 0.001$). CGI results were also highly significant. With CDI, *post hoc* analyses did not find a specific week where treatment diverged from placebo. For CDRS and CGI (see Ref. 13, data not shown here), the *post hoc* analysis showed a significant effect of omega-3 versus placebo from week 8.

The very small placebo effect in this study is unusual for studies of childhood depression [16,17], but is similar to our previous study of omega-3 in adult depression [12]. We speculated in the adult study that it may have been due to low expectations for this food additive in recurrently depressed and "experienced" patients; however, the children in this study had been ill for a much shorter time than the previously studied adults.

The previous study in adults used EPA, the precursor of DHA. The present study used a combination of EPA and DHA (at a ratio of 2:1) that is commonly available

as an over-the-counter preparation. The present study is the first to our knowledge of omega-3 treatment in prepubertal childhood depression.

Beersheva Bipolar Depression Study

Since the original Stoll et al. bipolar prophylaxis study published in 1999 [19], there had been relatively little additional published research on the use of omega-3 fatty acids in bipolar disorder. One abstract [20] reported that omega oil (1 or 2 g of EPA per day) was superior to placebo when added to ongoing treatment, although this study suffered from methodological problems. Preliminary results from a multicenter research project carried out by the Stanley Foundation reported negative findings when 6 g per day of EPA was added to ongoing mood stabilizers in the treatment of depressed and rapid-cycling bipolar patients [21,22]. Aware of the critical need for antidepression treatments which might not carry the risk of precipitating a manic episode in bipolar patients, we decided to conduct an open-label trial of EPA in bipolar depression.

Twelve bipolar patients were drawn from two ongoing outpatient mood disorders clinics at the Beer Sheva Mental Health Center. Omega was offered to these patients due to the presence of resistant depression ($n = 2$), nonpsychotic breakthrough depression in spite of adequate treatment with mood stabilizers ($n = 2$) or mood stabilizer plus antidepressant ($n = 1$), residual depressive symptoms in patients receiving lithiuim ($n = 4$), or patients reporting onset of depression ($n = 3$, one patient on lithium and two patients who received the omega oil as monotherapy). Five patients were female, seven male. The age ranged from 26 to 57 years (mean 39.5 ± 11); length of illness ranged from 6 months to 22 years (mean 9.8 ± 7). Ham-D 24 Rating Scales were filled out by a treating clinician (YO or YB) at baseline, and at monthly intervals for up to 6 months (or until cessation of the trial). Patients were treated with 2 g of EPA daily (based on the Beer Sheva unipolar study), unless otherwise indicated, in the form of two gelatin capsules taken in morning and evening.

Ham-D scores at baseline and at endpoint of follow-up for the 10 patients who completed at least 1 month of follow-up are presented in figure 3. As can be seen, 8 of the 10 patients achieved a 50% or greater reduction in Ham-D scores within 1 month. One patient achieved a 20% reduction, but due to suicidality, was hospitalized for a course of electro convulsive therapy (ECT) (although this might seem counterintuitive, the emergence of suicidal tendencies as a patient begins to recover from a deep depression is a not uncommon phenomenon). The remaining patient achieved a greater

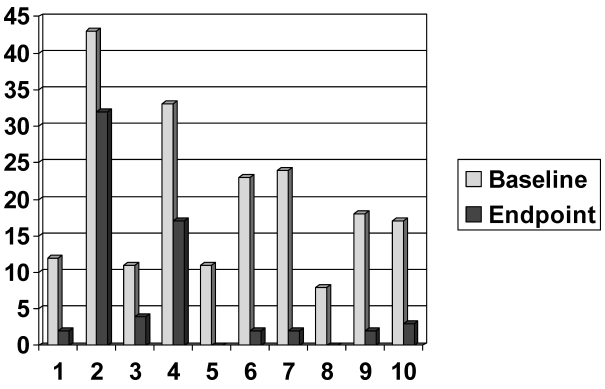

Figure 3. Hamilton Depression Rating Scale results for omega-3 EPA add-on in 10 bipolar depressed patients. Patient 2 became suicidal and stopped omega-3 after 1 month to begin a course of ECT; patient 4 achieved a Hamilton Depression score of 9 after 5 months on omega-3, but relapsed somewhat due to intense back pains in month 6.

than 50% reduction by the end of month 2. Two patients did not complete the first month of follow up—one patient reported feeling some improvement after 3 weeks, but requested to return to fluoxetine (familiar to her from previous depressive episodes) rather than continue on omega oil. A second patient was lost to follow-up.

The final patient to enroll in the study did not complete the entire 6-month follow-up period due to discontinued availability of the EPA preparation. This patient was euthymic 2 weeks after stopping omega oil, but became manic 2 months later.

Three patients who reported remission of the depression and chose to stop the omega oil experienced a recurrence of depressive symptoms within 1–2 months, and again reported remission within a month after resumption of omega-3.

No patient developed manic symptoms during the trial.

This study must be regarded as very preliminary, both because of the open-label design and because of the small sample size. While no patient in this study developed signs of mania while taking omega oil, one case report exists which suggests that this may happen [23], and this is an issue that requires continuing attention. As in all previous reported studies, the patients in this study were treated in an outpatient setting, so that the most severe bipolar depressions (requiring hospitalization) are not represented, and no conclusions should be drawn about the use of omega in severe depression. At the same time, it may be noted that omega-3 fatty acids may provide therapeutic benefit in related conditions in which negative effects are a part of the clinical picture [24].

Although the ultimate utility of omega-3 fatty acids in bipolar depression can only be established by proper

double-blind, placebo-controlled studies, we believe that these initial results are encouraging, especially for mild-to-moderate bipolar depression, and justify the continuing exploration of its use.

Conclusion

Our research results with omega-3, with the emphasis on EPA, have been consistently positive. It was also encouraging that no major side effects were reported in any of the studies reviewed here. Replication, however, is the gold standard in biological psychiatry, and the field, while developing rapidly, is not showing unanimity of findings (see reviews by Williams et al. [25] and Osher et al. [26]). Although there seems to be mixed evidence that DHA is effective in depression [21,27–29], it is unclear if DHA interferes with the antidepressant effects of EPA (e.g., changes the required dose). Little is actually known about the possible mechanisms of action. It is not clear why large doses of omega (EPA) are sometimes ineffective [21,30], whereas smaller doses (1–2 g per day) are usually found to be effective. Most studies to date have used omega oil as an add-on to other psychiatric medications, and it is not clear to what extent it may be useful as monotherapy in adult unipolar depression.

This relatively inexpensive compound, widely discussed in the popular media, has been an example of the possibilities for investigator-initiated research that may have a significant impact on patient care.

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Conflict of Interest

The authors state that they have no conflict of interest pertaining to this manuscript.

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