Efficacy of Omega-3 Fatty Acid Supplementation on Improvement of Bipolar Symptoms: A Systematic Review

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The purpose of this review was to examine the current level of evidence regarding the efficacy of omega-3 fatty acid supplementation in improving bipolar disorder symptoms. Of 99 articles meeting initial search criteria, 5 randomized control trials and 2 quasi-experimental studies were selected for review. Omega-3 fatty acid supplementation was effective in 4 of 7 studies. Those using an omega-3 combination of eicosapentaenoic acid and docosahexanoic acid demonstrated a statistically significant improvement in bipolar symptoms, whereas those using a single constituent did not. Dosage variations did not demonstrate statistically significant differences. Due to its benign side effect profile and some evidence supporting its usefulness in bipolar illness, omega-3 may be a helpful adjunct in treatment of selected patients. Future studies are needed to conclusively confirm the efficacy of omega-3s in bipolar disorder, uncovering a new well-tolerated treatment option.

ALTHOUGH OMEGA-3 FATTY acid supplementation has received recent attention in the context of depression (Lin & Su, 2007; Williams et al., 2006), few studies have examined its effects on bipolar disorder. The first study demonstrating a beneficial effect of omega-3 fatty acid supplementation on symptom reduction in bipolar disorder was published in 1999 (Stoll et al.), and the outcomes were encouraging. However, the benefits of omega-3 remain unclear. Since 1999, a nearly equal amount of studies that support, and studies that refute the outcomes have been published (Frangou, Lewis & McCrone, 2006; Hirashima et al., 2004; Sagduyu et al., 2005; Keck et al., 2006; Marangell et al., 2006; Osher, Bersudsky, & Belmaker, 2005). The purpose of this systematic review is to analyze the current evidence evaluating the use of omega-3 fatty acid supplementation in bipolar disorder symptom reduction.

Research has shown positive effects of omega-3 fatty acids on a number of medical conditions, including macular degeneration, retinitis pigmentosa, hypertension, and dyslipidemia (Balk et al., 2006; Hartweg, Farmer, Holman, & Neil, 2007; Hodge et al., 2006; Hodge et al., 2007; Iglesias del Sol & Smulders, 2006; Studer, Briel, Leimenstoll, Glass, & Bucher, 2005). There is some evidence that the healthful benefits of omega-3 fatty acid may extend to major depressive disorder. A recent meta-analysis examining the effect of omega-3 fatty acids on depression reported a reduction in depressive symptoms in participants taking the supplement (Lin & Su, 2007). A previous systematic review (Williams et al., 2006) also concluded that omega-3 fatty acid

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supplementation is effective in the treatment of depression; however, research on the usefulness of omega-3 fatty acid supplementation in treatment of bipolar disorder was not examined in either review.

The physiological rationale supporting the use of omega-3 fatty acid supplementation in bipolar disorder relates to the modulation of signal transduction pathways in the brain. The primary constituents in omega-3 fatty acid, docosahexanoic acid (DHA) and eicosapentaenoic acid (EPA), exert an inhibitory effect on the cell-signaling pathway (Stoll et al., 1999; Marangell et al., 2005). This is similar to the mechanism of action of commonly used mood stabilizers, such as lithium and valproate. Unfortunately, adherence to prescription mood stabilizers by patients has been a problem because side effects often result in the patient discontinuing the medication (Sajatovic, Valenstein, Blow, Ganoczy & Ignacio, 2006). First-generation antipsychotics often have neurological side effects such as extrapyramidal symptoms and tardive dyskinesia, whereas second-generation antipsychotics have a propensity to induce weight gain and alter glucose and lipid metabolism (Lieberman et al., 2005; Sajatovic et al., 2006). These side effects are particularly problematic at higher doses (Lieberman et al., 2005). Several studies have found that nearly half of patients with bipolar disorder were nonadherent with their medications (Sajatovic et al., 2006). The question that researchers of omega-3 and bipolar disease are asking is whether supplementation with omega-3 can support the effect of prescription mood stabilizers in symptom reduction, which may, in turn, reduce dosing requirements, untoward side effects, and nonadherence (Frangou et al., 2006; Hirashima et al., 2004; Keck et al., 2006; Marangell et al., 2006; Osher et al., 2005; Sagduyu et al., 2005).

MATERIALS AND METHODS

Search Strategy

The Cochrane Library was searched for existing systematic reviews of bipolar disorder and omega-3 fatty acid supplementation published up to November 2006. Two systematic reviews of omega-3 supplementation were identified: one addressed unipolar depression (Williams et al., 2006) and the other addressed multiple psychiatric disorders (Schachter et al., 2005). Finding no prior systematic reviews specifically addressing the use of omega-3 fatty acid supplementation in treatment of bipolar disorder, we then searched for relevant articles using the following search terms: *bipolar disorder*, *omega-3*, *omega-3 fatty acids*, and *randomized control trials* (RCTs). The following databases were searched: Medline (1966 to October 2006, Week 4), Cumulative Index to Nursing and Allied Health Literature (1982 to October 2006, Week 3), Allied and Complementary Medicine (1985 to October 2006), PsychINFO (1986 to October 2006, Week 3), and Evidence-Based Medicine Reviews, including Cochrane Database of Systematic Reviews (DSR), Database of Abstracts of Reviews of Effects (DARE), American College of Physicians Journal Club ACP), Cochrane Central Register of Controlled Trials (CCTR), and Clinical Evidence (Issue 15, October 2006). The bibliographies of all articles identified through the search were further reviewed for additional pertinent studies.

Criteria for Study Inclusion and Exclusion

Selection criteria included studies of individuals who met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* definition of bipolar disorder and who received supplementation with omega-3 fatty acids or its primary constituents, DHA and EPA. Studies written in a language other than English were excluded from review; however, country of origin was not a restriction. Dates and publications were restricted as detailed in the search criteria. Quasi-experimental studies and RCTs were included for further review. Exclusion criteria included expert opinion, case studies, case controls, and cohort studies. Also excluded were nonclinical or in vitro RCTs, as well as those lacking an omega-3 intervention.

Assessment of Methodological Quality

The methodological quality of each study was assessed using a six-item scale developed by Jadad et al. (1996) and modified to include an additional criterion, intent to treat (ITT) analysis. The Jadad scale assesses randomization, double blinding, description of withdrawals and dropouts, defined outcome measures, study objectives, and a clear description of the intervention. Using the modified Jadad criteria, two reviewers (M.C.D. and T.T.) independently rated the studies, with rating consensus reached through discussion. If a criterion was met, a score of 2 was assigned; if partially met, a 1 was assigned; and if not met, a 0 was scored. For

example, the Sagduyu et al. study partially met the study criteria and was hence assigned a 1. The reviewers determined that in this study, criterion VI, "intervention clearly defined," was only partially met because the study participants adjusted their own omega-3 dose. The omega-3 dosing range of study participants was provided, but there was no explanation addressing how patients self-managed their dosing (Sagduyu et al., 2006). Total possible scores ranged from 0 to 14, with higher scores indicative of greater bias reduction and higher level of quality. We considered a score of ≥ 12 as indicative of good methodological quality.

RESULTS

Ninety-nine potential studies were initially identified by the literature search. Of these, 98 did not meet inclusion criteria. Fourteen additional studies were identified through review of bibliographies. Figure 1 details the steps to inclusion of the final five RCTs and two quasi-experimental studies. In each RCT, a comparison was made between the intervention group given omega-3 supplementation and the control group, who was given placebo. The outcome measure was improvement in bipolar symptoms based on two or more screening questionnaires

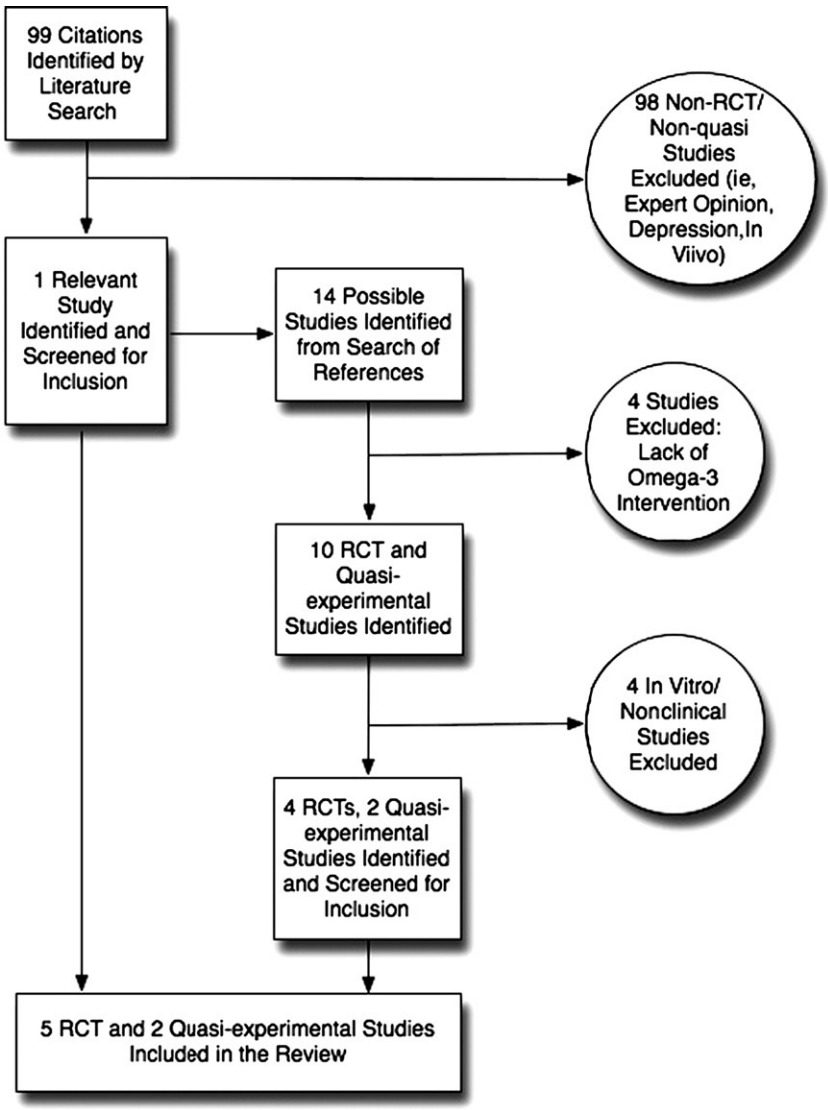

Fig 1. Selection of relevant studies for systematic review.

Table 1. Methodologic Assessment of Study Quality Using Modified Jadad et al. (1996) Scale

Year	Author	Methodologic assessment criteria*							Total score
		I	II	III	IV	V	VI	VII	
1999	Stoll et al.	2	2	2	2	2	2	2	14
2004	Hirashima et al.	2	1	1	2	2	2	2	12
2005	Osher et al.	0	0	2	2	2	2	0	8
2005	Sagduyu et al.	0	0	1	2	0	1	1	5
2006	Keck et al.	2	2	2	2	0	2	2	12
2006	Frangou et al.	2	2	1	2	2	2	2	13
2006	Marangell et al.	2	2	2	2	2	0	0	10

* I = randomization; II = double blinded; III = description of withdrawals and dropouts; IV = defined outcome measures; V = defined study objectives; VI = intervention clearly described; VII = ITT analysis performed. Scoring criteria: 0 = not met, 1 = partially met, 2 = criteria met.

applicable to measurement of bipolar disorder: Young Mania Rating Scale (YMRS), Hamilton Rating Scale for Depression (HRSD), Clinical Global Impression Scale, and Inventory of Depressive Symptomatology (IDS). In addition to screening questionnaires, one study used brain magnetic resonance imaging (MRI) to measure neuronal membrane fluidity hypothesized to affect bipolar symptoms (Hirashima et al., 2004).

Two open-label quasi-experimental studies were included in our review because their study design evaluated bipolar symptom status before and after administration of omega-3 constituents (Osher et al., 2005; Sagduyu et al., 2005). Participants were evaluated for improvement of symptoms. In addition to omega-3 fatty acids, most participants with bipolar disorder continued their usual treatment, which included psychotropic medication, psychological therapy, or both.

Table 1 highlights the methodological quality assessment of each study. Quality scores ranged from 5 (Sagduyu et al., 2005) to 14 (Stoll et al., 1999). In general, studies with the lowest methodological quality scores were quasi-experimental. Four of the seven studies utilized multiple sites, included ITT analysis, accounted for description of participant dropouts and withdrawals, gave clear description of the intervention, and were double blinded.

Table 2 further describes each study, including enrollment, type of intervention used, and length of follow-up. Five of the seven studies involved male and female participants with an age range of 18 to 73 years. Participants in the remaining two studies were exclusively women with a reported mean age of 28.2 years (Hirashima et al., 2004) and an age range of 27 to 42 years (Marangell et al., 2006). In four of the studies, sample sizes were small (<40).

Both the dosing and the component of omega-3 fatty acid supplementation differed in each of the seven studies. Four of the seven studies used a combination of DHA and EPA (Frangou et al., 2006; Hirashima et al., 2004; Sagduyu et al., 2005; Stoll et al., 1999), whereas the remaining studies supplemented with either DHA (Marangell et al., 2006) or EPA (Osher et al., 2005; Keck et al., 2006). Each study using the combined supplementation of active constituents, DHA and EPA, demonstrated a statistically significant improvement ($P < .05$) in bipolar

Table 2. Research Trials Examining Treatment With Omega-3 Fatty Acid Supplementation in Bipolar Disorder

Year	Author	Patients enrolled (completed)	Follow-up (weeks)	Multisite (Y/N)	Omega-3 dose (g/day)	Symptom improvement (Y/N) ($P < .05$)
Quasi-experimental studies						
2005	Osher et al.	12 (10)	≤24	Y	EPA, 1.5-2.0	NR
2005	Sagduyu et al.	39 (37)	≥12	N	Dose range*: EPA, 0.328-0.518; DHA, 0.219-0.345	Y
RCTs						
1999	Stoll et al.	44 (30)	16	Y	EPA, 6.2; DHA, 3.4	Y
2004	Hirashima et al.	21 (21)	4	Y	High dose: EPA, 5.0-5.2; DHA, 3.0-3.4; other, 0.3-1.7 Low dose: EPA, 1.3; DHA, 0.7	Y
2006	Frangou et al.	75 (71)	12	N	High dose: EPA, 2 Low dose: EPA, 1	Y
2006	Keck et al.	121 (56)	12	Y	EPA, 6	N
2006	Marangell et al.	10 (5)	≤52	Y	DHA, 2	N

NOTE. NR = not reported.

* Dose range self-determined; dosages of EPA/DHA based on 180 mg EPA and 120 mg DHA per 1,000 mg fish oil.

symptoms. Conversely, the three studies using only a single ingredient did not demonstrate significant differences between groups. Among the RCTs, the EPA dosing ranged from 0.3 to 6.2 g/day and that of DHA ranged from 0.2 to 3.4 g/day. Length of follow-up in the RCTs ranged from 4 to 52 weeks, whereas in the two quasi-experimental studies, duration of follow-up was not consistent for each participant (6 months to 5 years; see Table 2). Both quasi-experimental studies were open label, whereas all RCTs were either single or double blinded.

In terms of outcome measures, all but Marangell et al. (2006) identified a minimum of two screening questionnaires applicable to the measurement of bipolar disorder symptoms: YMRS, HRSD, Clinical Global Impression Scale, and Inventory of Depressive Symptomatology. Hirashima et al. (2004) utilized a more unique, biomedical approach in that they looked at two types of outcome measures: bipolar symptom rating scales (YMRS and HRSD) and MRI of the brain. The MRI was used to measure neuronal membrane fluidity, which is an important modulator of several neuronal functions, some of which are hypothesized to affect bipolar symptoms (Hirashima et al., 2004).

A majority of the participants in all but one study (Marangell et al., 2006) were on standard psychotropic medications, with or without psychotherapy. Marangell et al. (2006) conducted a pilot study of women who were planning pregnancy and wanted to control bipolar symptoms without use of standard psychotropic medication. Of the 10 participants enrolled in this study, 4 were randomized to placebo and 6, to active treatment. Although those on active treatment showed symptom improvement, the study lacked statistical power because of its small sample size.

Osher et al. (2005) conducted a quasi-experimental study using participants from two outpatient clinics in Israel. They utilized a clinician-administered HRSD to determine outcome. Comorbidities such as substance abuse or physical illness were part of the exclusion criteria. Sagduyu et al. (2005) was an add-on, open-label study consisting of 37 participants. Their outcome measurement focused on general bipolar symptoms and irritability; therefore, they utilized a Likert scale for irritability, as well as the YMRS.

In all studies, the omega-3 intervention was generally well tolerated. The chief adverse event reported was gastrointestinal (GI) in nature, including loose stools, GI discomfort, or both. However, there were no differences in reported GI events between the placebo (olive oil or liquid paraffin) and the intervention arms of the studies. Although omega-3 fatty acids may cause prolonged bleeding times, none of the studies reported this as an adverse effect. Keck et al. (2006) performed bleeding times at baseline and at 4 weeks after treatment initiation and found no significant differences between the control and treatment groups.

DISCUSSION

This systematic review summarizes evidence from five randomized placebo-controlled and two quasi-experimental trials that evaluated the effectiveness of omega-3 fatty acids in the treatment of bipolar disorder. The intervention in the studies included various combinations of omega-3 active components (DHA, EPA, or both) and variable dosing. Dosing variations did not appear to impact study outcomes; however, the use of single versus combined omega-3 components did. Each study that utilized both EPA and DHA demonstrated a statistically significant improvement in bipolar symptoms. In addition, three of the four studies with the highest methodological quality found positive associations between omega-3 use and bipolar symptom reduction.

A major consideration in terms of internal validity of the reviewed studies was small sample size and high level of participant attrition. Five studies had a sample size less than 45. In two of the seven studies (Keck et al., 2006; Marangell et al., 2006), nearly 50% of the participants failed to complete the trial, thereby diminishing confidence in study outcomes. Of these two studies, only one (Keck et al., 2006) performed an ITT analysis; neither found a significant reduction in symptoms.

Of the two quasi-experimental studies included in this systematic review, Osher et al. (2005) had a small sample size but otherwise was stronger methodologically than Sagduyu et al. (2005). In the Sagduyu et al. study, dose range and duration were self-determined by participants. This could lend to greater study bias due to the fact that individual subjectivity would determine dosing, and dosing can vary so widely. Both quasi-experimental studies had a much longer follow-up period compared with the RCTs, which may better represent real-world treatment duration. However, the protracted length of the Sagduyu et al. study, up to 5 years, raises the question

of how likely it is that participants were able to be consistent with their supplements and be adequately monitored for such a long time period. This was not discussed in the study.

Stoll et al. (1999) questioned whether, despite vacuum deodorizing of capsules, participants could truly be blinded to the intervention, as 86% of the omega-3 group noticed a distinct "fishy" aftertaste compared with only 63% of those receiving placebo. Keck et al. (2006, p. 1021) reported that the placebo and omega-3 capsules were "indistinguishable by size, color, odor, and after taste," although how this was determined was not reported. To improve blinding, odor masking needs to be improved or a similar "fishy" odor added to placebo. Because a description of the racial backgrounds of participants was not included in most of the studies, and those that reported race included exclusively Caucasian participants, the results may not be generalizable to patients with bipolar disorder in other racial or ethnic groups.

One important point is that the therapeutic effects of omega-3 fatty acid supplementation may have been masked by concurrent use of psychotropic medication. In addition, dietary intake and self-supplementation of omega-3 were not adequately controlled in the studies.

The inclusion of quasi-experimental studies in the systematic review may have increased heterogeneity. Although quasi-experimental studies provide a lower level of evidence compared with RCTs, their inclusion may contribute to the understanding of the role of omega-3 in bipolar disorder considering the small number of relevant studies addressing this topic. An attempt to increase homogeneity was made by limiting the disease entity to bipolar disorder in outpatient participants with the specific intervention of omega-3. Nonetheless, several factors contributed to some heterogeneity of the analyzed studies, one being the differences in dosing and constituent combinations. Omega-3 interventions ranged from a single dose of a single constituent to self-determined dosing ranges of both constituents. Another factor contributing to heterogeneity was the use of concurrent psychotropic medications. Some studies required all participants to be on psychotropic medications throughout the study, whereas participants in other studies were on no psychotropic medications. Keck et al. (2006) discontinued participant involvement if any symptom exacerbation occurred, whereas Frangou et al. (2006) made medication adjustments during the study period in response to symptom occurrence.

Conclusion

Findings of this systematic review point to the beneficial effects of omega-3 in bipolar disorder; however, the evidence is not strong enough to support the unequivocal recommendation of supplementation at this time.

On the basis of an analysis of these studies, the dosage variation in omega-3 did not relate to bipolar symptom improvement. On the other hand, studies using an omega-3 combination of EPA and DHA demonstrated a statistically significant improvement in bipolar symptoms (Frangou et al., 2006; Hirashima et al., 2004; Sagduyu et al., 2005; Stoll et al., 1999). Studies using a single constituent did not (Keck et al., 2006; Marangell et al., 2006; Osher et al., 2005). This is less likely to be due to chance based on the fact that three of the four studies with the highest methodological quality were the ones that found the positive associations between omega-3 use and bipolar symptom reduction. It should be noted that current evidence does not support replacement of psychotropic medication with omega-3 fatty acids. However, supplementation with omega-3 may support the effect of prescription mood stabilizers in symptom reduction, which may, in turn, reduce dosing requirements, untoward side effects, and nonadherence (Frangou et al., 2006; Hirashima et al., 2004; Keck et al., 2006; Marangell et al., 2006; Osher et al., 2005; Sagduyu et al., 2005).

Omega-3 appears to be a well-tolerated supplement that has some beneficial effects, which may include symptom reduction in bipolar disorder. Due to its benign side effect profile and some evidence supporting its usefulness in bipolar illness, it may be a helpful adjunct in treatment of selected patients. Future studies are needed to conclusively confirm the efficacy of omega-3s in bipolar disorder, uncovering a new well-tolerated treatment option.

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