Omega-3 for Bipolar Disorder: Meta-Analyses of Use in Mania and Bipolar Depression

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ABSTRACT

Objective: Studies using augmentation of pharmacotherapies with omega-3 in bipolar disorder have been conducted; however, to date a specific meta-analysis in this area has not been published. Thus, we present the significant findings from meta-analyses of omega-3 in the treatment of bipolar depression and bipolar mania.

Data Sources: PubMed, CINAHL, Web of Science, and Cochrane Library databases were searched for clinical trials up to September 1, 2010, using the search terms *bipolar disorder* OR *bipolar depression* OR *bipolar mania* OR *mania* OR *hypomania* OR *cyclothymia* with the search terms *omega 3* OR *essential fatty acids* OR *polyunsaturated fatty acids* OR *DHA* OR *EPA* OR *fish oil* OR *flax oil*. Clinical trial registries and gray literature (published or unpublished data not readily accessible via main databases) were also searched.

Data Selection: The analysis included randomized controlled studies 4 weeks or longer, with a sample size > 10, written in English, using omega-3 for diagnosed bipolar depression or mania. No criteria were set for age, gender, or ethnicity.

Data Extraction: A random-effects model was used. The model analyzed the standard mean difference between treatment and placebo between baseline and endpoint, combining the effect size (Hedges *g*) data. Funnel plot and heterogeneity analyses (I^2) were also performed.

Data Synthesis: The findings of 5 pooled datasets (n = 291) on the outcome of bipolar depression revealed a significant effect in favor of omega-3 ($P = .029$), with a moderate effect size of 0.34. On the outcome of mania, 5 pooled datasets (n = 291) revealed a nonsignificant effect in favor of omega-3 ($P = .099$), with an effect size of 0.20. Minor heterogeneity between studies on the outcome of bipolar depression was found ($I^2 = 30\%$; $P = .213$), which was not present on the outcome of bipolar mania ($I^2 = 0\%$; $P = .98$). Funnel plot symmetry suggested no significant likelihood of publication bias. Meta-regression analysis between sample size and effect size, however, revealed that studies with smaller sample sizes had larger effect sizes ($P = .05$).

Conclusions: The meta-analytic findings provide strong evidence that bipolar depressive symptoms may be improved by adjunctive use of omega-3. The evidence, however, does not support its adjunctive use in attenuating mania.

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Bipolar disorder is a heritable mental illness that causes profound functional impairment and increased risk of suicide.[1] As bipolar disorder has serious consequences and elicits significant socioeconomic cost, further pursuit of safe and efficacious treatments is required.[2] Omega-3 essential fatty acids may have a potential role as an individual or adjunctive treatment for mood disorders.[3,4] Higher fish consumption has been found to predict a lower occurrence of bipolar disorder,[5] and people with bipolar disorder have been found in one study to significantly have 32% lower erythrocyte docosahexaenoic acid (DHA).[6] The mechanistic underpinnings of omega-3 activity that may be beneficial in mood stabilization involve inhibition of cell-signaling pathways via effects such as T_2 reduction (increasing cell membrane fluidity),[7] anti-inflammation via select cytokine inhibition,[8,9] and phosphoinositide–protein kinase C antagonism.[10] A potential antidepressant effect beneficial in bipolar depression may occur via monoamine reuptake inhibition of serotonin and dopamine (in addition to effects on second messengers and enhanced cell membrane fluidity).[11]

Dozens of clinical trials to date have been conducted on omega-3 and unipolar depression, in addition to notable reviews and meta-analyses.[12–16] However, aside from a 2008 review by Turnbull et al[17] and a Cochrane review,[18] literature in the specific area of omega-3 for treatment of bipolar depression or mania is sparse. A previous systematic review conducted by Montgomery and Richardson[18] did not include a new study by Gracious et al (2010),[19] nor the data from Chiu et al (2005),[20] and was very restrictive in its inclusion criteria (data from only 1 study were included, and thus a meta-analysis could not be performed). The Turnbull et al[17] article, while novel, did not include a meta-analysis. Therefore, the goal of this article is to provide a comprehensive review and meta-analyses from studies specifically using omega-3 in the treatment of bipolar mania and bipolar depression.

METHOD

Search Strategy

To identify potential studies for meta-analysis, PubMed, CINAHL, Web of Science, and Cochrane Library databases were searched up to September 1, 2010, for human clinical trials using the search terms *bipolar disorder* OR *bipolar depression* OR *bipolar mania* OR *mania* OR *hypomania* OR *cyclothymia* with the search terms *omega 3* OR *essential fatty acids* OR *polyunsaturated fatty acids* OR *DHA* OR *EPA* OR *fish oil* OR *flax oil*. Clinical trial registries were searched for relevant studies to cross-reference with the literature review and to locate unpublished data. A forward search of the identified papers was subsequently performed using a Web of Science cited reference search, in addition to hand-searching the literature, contacting authors and academics for studies in the area, and searching the Internet for gray literature (published or unpublished data not readily accessible via main databases).

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Study Inclusion Criteria

Inclusion criteria for meta-analysis consisted of human studies that (1) were randomized, (2) were placebo controlled, (3) involved use of omega-3 (such as fish oil, eicosapentaenoic acid [EPA], DHA, or flaxseed oil [alpha-linolenic acid]) for the treatment of diagnosed bipolar disorder (manic, depressed, or not otherwise specified), (4) had a duration of 4 weeks or longer, (5) had a total sample size of > 10 (case studies were not included), (6) had sufficient data available for analysis using an established psychiatric scale for depression or mania, and (7) were written in English. All papers that did not meet these criteria were excluded. No criteria were set for gender, age, or ethnicity of subjects.

Studies were selected for inclusion via consensus within the research group. Quality assessment of the papers was independently rated to assess interrater reliability. Each paper was analyzed for methodological quality using a purpose-designed scale that was developed and used in a previous systematic review.[21] This scale is based on 3 primary quality factors: randomization, blinding, and reported withdrawals. The scale also assesses other methodological factors: exclusion criteria, intervention used, control used, and data reporting to provide a quality total rating out of 10. The scale consists of 10 questions; an answer of "yes" = 1 point, an answer of "no" = 0 point, and an answer of "uncertain/not clear" = 0.5 point. The questions are as follows.

1. Was the study described as randomized?
2. Was the randomization protocol detailed and appropriate?
3. Was the study described as double-blind?
4. Was the blinding process detailed and appropriate?
5. Did the study have a control group?
6. Was the control detailed and appropriate?
7. Were there adequate exclusion criteria?
8. Was the intervention used at a therapeutic dose?
9. Was there a description of withdrawals and dropouts?
10. Were the data clearly and adequately reported?

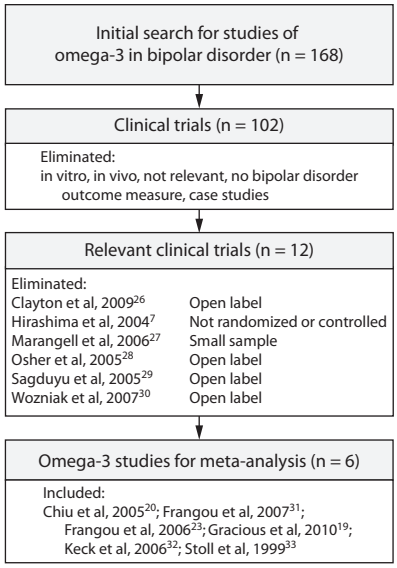
Statistical Analysis

A random-effects model, a conservative technique, was used, as the directional effect of omega-3 in bipolar disorder has not yet been established.[22] The model analyzed the standard mean difference between treatment and placebo between baseline and endpoint, combining the effect size (ES: Hedges *g*) data. Data from Frangou et al (2006)[23] were analyzed as 2 separate studies comparing 1 g of EPA and 2 g of EPA versus placebo. The data from the placebo group were divided into 2 arms (13 per arm) to reduce statistical overinflation (this conservative technique is advised in the Cochrane Review handbook[24]). Data were analyzed via the Comprehensive Meta-Analysis computer program (Biostat; Englewood, New Jersey). The pooled ES was determined using a 95% confidence interval, while significance was determined via *z* tests (significance was considered a *P* value of ≤ .05). Where the mean and standard deviations were not available, the ESs were calculated using the *F* score and sample size. Sensitivity analyses were conducted by comparing the results to a fixed-effects model and via removing studies with lesser homogeneity. A homogeneity test (Higgins I^2) was conducted to ascertain whether the ESs came from a homogeneous source,[25] and a regression analysis was used to assess if any relationship occurred between sample size and results (standard mean difference of ESs).

Clinical Points

- Current evidence supports omega-3 in adjunctive treatment of bipolar depression.
- Current evidence, however, does not support omega-3 in the treatment of bipolar mania.
- Clinicians are advised to recommend increased dietary omega-3 or daily supplementation of approximately 1 g to 1.5 g of mixed EPA and DHA (higher ratio of EPA).

Figure 1. Meta-Analysis Inclusion Flowchart



RESULTS

As detailed in Figure 1, an initial search of 168 studies in the area revealed 12 potential studies, of which 6 randomized controlled trials (n = 291) met the final criteria for inclusion (Table 1). The mean trial length was 12.6 weeks (range, 4–16 weeks), with a mean sample size of 37.8 (range, 14–121). The outcome measure used for mania was the Young Mania Rating Scale (YMRS),[34] while the outcome measures used for depression were the Hamilton Depression Rating Scale (HDRS),[35] Children's Depression Rating Scale,[36] and Inventory of Depressive Symptomatology-Clinician Rated.[37] With respect to samples, Chiu et al[20] was the only study of omega-3

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Table 1. Omega-3 Bipolar Disorder Studies Included in Meta-Analyses: Study Characteristics

Study	Dose	Design	Duration (wk)	Patients (n)	Mean Age (y)	Clinical Characteristics	Comedication	Outcomes[a]	Results[b]	Quality Analysis[c]
Flaxseed oil										
Gracious et al, 2010[19]	Flaxseed oil capsules titrated to maximum of alpha-linolenic acid 6.6 g vs placebo	Randomized, DB, PC	16	51	13	*DSM-IV* bipolar I/II YMRS score ≥ 4 (children and adolescents)	Stable psychotropic medication	CDRS-R YMRS	No significant differences between groups occurred Fewer dropouts with flaxseed oil than placebo	9
EPA										
Frangou et al, 2007[31]	EPA 2 g/d or liquid paraffin placebo capsules	Randomized, DB, PC	12	14	42	*DSM-IV* bipolar I HDRS-17 score > 10 (women)	Stable lithium	HDRS	No statistically significant differences were found between the groups on HDRS	7.5
Frangou et al, 2006[23,d]	EPA 1 or 2 g/d vs placebo capsules	Randomized, DB, PC	12	75	47	*DSM-IV* bipolar I/II HDRS-17 score > 10	Stable psychotropic medication > 8 wk	HDRS-17 YMRS	A significant reduction of 1 g and 2 g EPA vs placebo on HDRS, but not on YMRS	9.5
Keck et al, 2006[32,e]	EPA 6 g/d or placebo capsules	Randomized, B, PC	16	121	44	*DSM-IV* bipolar I/II or bipolar NOS (current MDD or rapid cycling)	A stable therapeutic dose of a mood stabilizer	IDS-C YMRS	No significant difference between EPA or placebo on any outcome	8
EPA/DHA										
Chiu et al, 2005[20]	EPA 4.4 g and DHA 2.4 g/d or olive oil placebo capsules	Randomized, DB, PC	4	15 (14[f])	NA	*DSM-IV* bipolar I (acute mania)	Valproate (fixed dose 20 mg/kg/d)	YMRS	Reductions in both groups on YMRS from baseline, but no difference between groups	6
Stoll et al, 1999[33]	EPA 6.2 g and DHA 3.4 g/d vs placebo capsules	Randomized, DB, PC	16	44 (30[f])	43	*DSM-IV* screening for mania and depression	Medication treatment as usual	HDRS YMRS	Omega-3 group significantly reduced HDRS scores over placebo, but not on YMRS	9.5

[a]Bipolar mania or bipolar depression outcomes used for meta-analysis.
[b]Significant = $P < .05$.
[c]Scale of 1 to 10 (higher = better quality).
[d]Frangou 2006 study separated into 2 sets of data for analysis (1 g and 2 g of EPA).
[e]Effect size calculated via *F* score and sample size.
[f]Data available from completers.
Abbreviations: B = implied blinding (not clearly stated), CDRS-R = Children's Depression Rating Scale-Revised, DB = double-blind, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, HDRS = Hamilton Depression Rating Scale, HDRS-17 = 17-Item Hamilton Depression Rating Scale, IDS-C = Inventory of Depressive Symptomatology-Clinician Rated, MDD = major depressive disorder, NA = not available, NOS = not otherwise specified, PC = placebo-controlled, YMRS = Young Mania Rating Scale.

in a sample with acute mania, Keck et al[32] used a sample with rapid-cycling bipolar disorder, and Frangou et al (2007)[31] studied women with bipolar disorder type I. All studies used both mania and depression outcomes except Frangou et al (2007),[31] which solely used the HDRS. Stable psychotropic medications commonly used by the participants in the studies were lithium, valproate, and antipsychotics. The quality of all studies (with the exception of Chiu et al[20]) was rated as high (mean = 8.25; range, 6–9.5 out of 10) with regard to being randomized and blinded, using a placebo control, and having an adequate dosage and duration of treatment and adequately reported data. The Chiu et al study,[20] which was rated as 6 out of 10 on the quality scale, had a low starting level of HDRS depression (mean baseline = 1.05; authors contacted for raw data) and thus was excluded from the bipolar depression meta-analysis. Gracious et al[19] were also contacted for data and subsequently provided the data for analysis.

While all of the studies favored omega-3 on outcomes for bipolar depression and mania, this finding achieved significance in only 2 individual bipolar depression studies.[23,33] No study revealed a significant positive finding on the outcome of mania. The pooled data of 5 studies (6 data sets) in the bipolar depression meta-analysis revealed an

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Figure 2. Meta-Analysis: Omega-3 Versus Control in Bipolar Depression

Study	Standard Difference in Means	Lower Limit	Upper Limit	*P* Value	Relative Weight
Gracious et al, 2010[19]	0.058	−0.491	0.607	.836	19.87
Frangou et al, 2007[31]	0.451	−0.610	1.512	.405	7.13
Frangou et al, 2006[23] (1 g)	0.612	−0.077	1.302	.082	14.44
Frangou et al, 2006[23] (2 g)	0.452	−0.226	1.130	.191	14.80
Keck et al, 2006[32]	0.042	−0.323	0.406	.823	31.38
Stoll et al, 1999[33]	1.016	0.254	1.778	.009	12.38
Pooled data	0.338	0.035	0.641	.029	

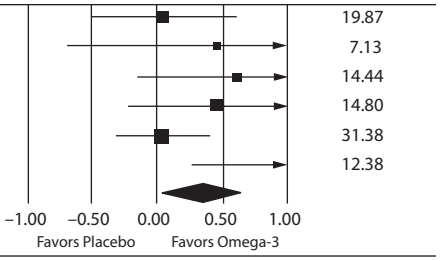


Figure 3. Meta-Analysis: Omega-3 Versus Control in Bipolar Mania

Study	Standard Difference in Means	Lower Limit	Upper Limit	*P* Value	Relative Weight
Gracious et al, 2010[19]	0.123	−0.427	0.672	.661	18.36
Frangou et al, 2006[23] (1 g)	0.425	−0.257	1.107	.222	11.93
Frangou et al, 2006[23] (2 g)	0.103	−0.567	0.774	.763	12.33
Keck et al, 2006[32]	0.184	−0.181	0.549	.323	41.67
Chiu et al, 2005[20]	0.117	−0.931	1.166	.827	5.04
Stoll et al, 1999[33]	0.277	−0.444	0.997	.452	10.68
Pooled data	0.198	−0.037	0.433	.099	

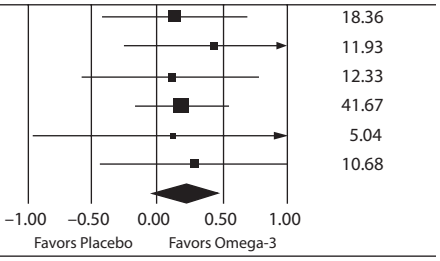
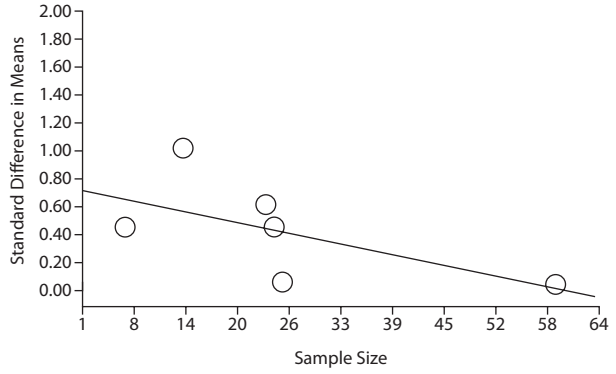


Figure 4. Meta-Regression for Sample Size Bias[a]



[a]Circles represent individual studies. Regression slope: $z = -1.92$; $P = .05$.

ES of 0.34 ($z = 2.188$; 95% CI, 0.035 to 0.641), which was statistically significant ($P = .029$; Figure 2). Sensitivity analyses revealed that when only the studies using HDRS outcome were included (Gracious et al[19] and Keck et al[32] removed), the results increased in significance (ES = 0.64; $z = 3.303$; 95% CI, 0.261 to 1.023; $P = .001$). On the outcome of YMRS mania, 5 studies (6 data sets) were included for meta-analysis (Figure 3). Results revealed a nonsignificant trend in favor of omega-3 (ES = 0.20; $z = 1.648$; 95% CI, −0.037 to 0.433; $P = .099$). Sensitivity analyses revealed that when meta-analysis of the data was restricted to acute mania (Chiu et al[20]) or elevated YMRS score (> 14: Gracious et al[19]), only 2 studies met inclusion criteria, with the results still insignificant ($P = .624$). When a fixed-effects model was adopted in place of a random-effects model, the significance of the results was not altered (data not shown).

Methodological limitations existed, with Chiu et al[20] and Frangou et al (2007)[31] having small sample sizes and Chiu et al[20] having a short duration of treatment (4 weeks). Aside from these limitations, sample sizes, outcome measures, concurrent medication used, and duration of treatment were reasonably consistent. However, heterogeneity was found between the 5 studies with respect to the type of omega-3 preparation used (high EPA/DHA blend, EPA, flaxseed oil, EPA/DHA 2:1 ratio) and dosage per day (DHA up to 3.4 g, EPA up to 6.2 mg, alpha-linolenic acid 6.6 g). Tests for heterogeneity revealed minor heterogeneity between bipolar depression studies ($I^2 = 30\%$; $P = .213$) and substantial homogeneity between bipolar mania studies ($I^2 = 0\%$; $P = .98$). A meta-regression analysis of bipolar depression data of the sample sizes and the standard mean ESs revealed a significant association (regression slope $z = -1.923$; $P = .05$; Figure 4), denoting that the smaller studies had larger ESs. This significant association was not found on the bipolar mania outcomes. Interestingly, meta-regression analysis of the quality ratings of the bipolar depression studies showed a trend for higher quality rating of the studies having a greater ES ($z = 1.773$; $P = .076$).

DISCUSSION

The finding from this meta-analysis, that omega-3 supplementation of conventional mood stabilizers significantly reduced depressive symptoms over control interventions, has potentially considerable clinical and public health significance. Omega-3 fish oils may be recommended now in the adjunctive treatment of bipolar disorder, especially in people with comorbid cardiovascular or metabolic conditions. The majority of previous studies in bipolar disorder have revealed inconclusive results in favor of omega-3 over control. The absence of statistical significance may potentially be due to small sample sizes that did not have sufficient power to detect a significant difference. This meta-analysis has addressed this, with a significant effect occurring on the outcome of bipolar depression when the omega-3 study data were combined. However, omega-3 supplementation did not significantly improve manic symptoms. The absence of an effect was

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further supported when the data were restricted to those studies that had samples with either acute mania (Chiu et al[20]) or elevated YMRS scores (> 14: Gracious et al[19]). This finding can advise clinicians that omega-3 confers no additional benefit beyond that of conventional medication in treating mania. This is generally in agreement with previous reviews such as Parker et al,[16] which suggested that the benefit of omega-3 was primarily for depression rather than mania.

This meta-analytic study comprised a rigorous literature search process and inclusion criteria of omega-3 data for both depression and mania outcomes. A limitation of this review is that the studies included were restricted to English-language publications. Also, the inclusion of the Gracious et al[19] study, which involved data from children and adolescents derived from a scale additional to the HDRS for bipolar depression (Children's Depression Rating Scale), could be argued to reduce the homogeneity of the results. The inclusion of the study is, however, justified, as a sensitivity analysis revealed a homogeneous statistical effect between its effect size and the other data, and it should be noted that even when this study was removed the results were still statistically significant (detailed earlier in the article). Furthermore, the use of a broader sample age may increase external generalizability, and the use of 2 outcome scales is an accepted protocol for meta-analyses.[13,38,39]

Another important consideration is that documentation of the study participants' dietary patterns and consumption levels of omega-3 was absent in the reviewed studies. Documentation of diet is vital in future omega-3 studies, as this may influence whether a person is responsive to supplementation. Potentially, persons with a Mediterranean diet high in monounsaturated/polyunsaturated fatty acids may not respond as favorably as those with dietary deficiency.[39,40]

Regarding the outcome of bipolar depression, heterogeneity was found via meta-regression analysis between sample sizes and effect sizes; however, as the funnel plot analysis was symmetrical (figure not shown), publication bias is unlikely. These results suggest that while publication bias is not obviously present, there is a chance (as detailed earlier) that smaller studies with more positive results are likely to be published. Curiously, this effect was not mirrored on the mania outcomes. Meta-regression analysis between the quality of studies and the ESs provided a trend effect in favor of better-quality studies having stronger ESs, denoting that positive results were not related to poor trial design.

It remains difficult to advise clinicians on precisely the dose and nature of the omega-3 to be used, as studies have used differing preparations. As described in Table 1, various sources (isolated and purified EPA, EPA/DHA combination, or flax oil) and differing doses were used in the studies. It appears, though, that EPA or higher EPA-to-DHA ratio preparations are potentially more effective. This position is supported by a recent review by Martins,[14] which revealed, via meta-analytic comparison between DHA and EPA, that the effect of DHA monotherapy was not significant, whereas in 13 studies using supplements containing greater than 50% EPA, a significant effect occurred in favor of omega-3 (standard mean difference = −0.446; 95% CI, −0.753 to −0.138; $z = -2.843$; $P = .005$). With respect to the individual efficacy of flax oil, Gracious et al[19] revealed no significant effect; therefore, confidence cannot be extended to use of this polyunsaturated oil in bipolar disorder. This is particularly important, since most studies of omega-3 for psychiatric disorders have involved EPA and DHA, whereas there is little evidence of mood-enhancing effects of alpha-linolenic acid thus far. Regarding dosing, studies such as Stoll et al[33] used very high omega-3 doses, based on the upper limits reported in the cardiovascular literature, in order to avoid underdosing. Data for unipolar depression suggest a therapeutic window hovering around 1,000 mg/d, with loss of benefit at lower and higher doses.[41,42] In the absence of more data, clinicians might consider starting an EPA/DHA mix at a dose of about 1,000 mg/d and increasing gradually in the bipolar patient, although care must be taken, in view of some reports of cycling associated with omega-3 use[41] and a concern over interactions with anticoagulants, particularly at doses greater then 3,000 mg/d.[41]

Omega-3 use in bipolar disorder is well tolerated and does not seem to pose major safety risks when used judiciously. Aside from the potential concern over cycling, and a significantly greater occurrence of minor digestive upsets reported in Keck et al[32] (which also found no increased risk of switching to mania or increase in bleeding times), no other study documented any adverse effects occurring more than with controls. Conversely, omega-3 may also provide benefit for persons with comorbid cardiovascular disease or metabolic disorder, who may be at a greater risk of adverse effects from antipsychotics and mood stabilizers. While extra expense may be a consideration for adjunctive use, the cost of omega-3 is relatively modest in Western countries compared to many other over-the-counter natural products.

In summary, although the weight of evidence does not currently support adjuvant use of omega-3 for mania, meta-analytic evidence strongly supports the use of omega-3 for adjuvant use in the treatment of depressed mood in bipolar disorder. Given the potential benefits and safety, omega-3 deserves greater attention and wider application. There is a pressing need for further research to establish optimum formulation and dosage for omega-3.

Drug names: lithium (Lithobid and others).

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