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Omega-3 fatty acids in bipolar disorder: Clinical and research considerations

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Abstract

Several lines of evidence suggest that ω-3 fatty acids may be important in the pathophysiology, treatment or prevention of bipolar disorder (BD). Electronic and manual searches were conducted in order to review the literature relevant to the etiology and treatment of BDs with ω-3 fatty acids. We also present data from a randomized, double-blind, placebo-controlled pilot study conducted at three sites ($N = 10$) comparing an ω-3 fatty acid (docosahexaenoic acid, DHA) versus placebo, added to psychosocial treatment for women with BD who chose to discontinue standard pharmacologic treatment while attempting to conceive. While some epidemiologic and preclinical data support the role of ω-3 fatty acids in BD, clinical trials to date have yielded conflicting results. In our pilot study of 10 Caucasian women taking DHA while attempting to conceive (BP1 = 9, BPII = 1), age 27–42 years, DHA was well tolerated and suggests that a larger study would be feasible. The elucidation of the potential role of ω-3 fatty acids as a treatment for BD requires further study. The current data are not sufficient to support a recommendation of monotherapy treatment as a substitute for standard pharmacologic treatments. However, judicious monotherapy in selected clinical situations, or adjunctive use, may be warranted pending further data from adequately powered controlled clinical trials. Our pilot trial of DHA in women who plan to stop conventional psychotropics in order to conceive suggests that such trials are feasible.

1. Introduction

Patients with bipolar I disorder (BDI) and bipolar II disorder (BDII) comprise 3.9% of the adult population in the United States [1] and an estimated 30% of the population served by departments of Mental Health and Mental Retardation [2]. BDI is characterized by the occurrence of one or more manic episodes interspersed with episodes of depression. Symptoms of mania include a reduced need for sleep, distractibility, increased activity, psychomotor agitation, and high-risk behavior. Hypomania is similar to mania, but with less severe symptoms. BDII is a form of bipolar disorder (BD) that includes recurrent moderate to severe major depressive episodes as well as hypomanic episodes [3]. BDs are

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life-long, have an early age of onset, and take a tremendous toll on individuals, families, society, and health care systems [4].

Despite recent advances in the development of safer, more effective, and better-tolerated psychotropic medications and advances in psychotherapeutic interventions, patients with BD often experience inadequate or partial response to treatment, loss of effectiveness from previously beneficial treatments, or intolerable adverse effects. The need for new interventions and the high patient acceptability of natural treatments combine to make ω-3 fatty acids (n3FA) an appealing alternative for many patients and clinicians. As described elsewhere in this issue, ω-3 fatty acids are well tolerated, have nonpsychiatric health benefits, and are not teratogenic. In this article, we discuss the rationale for the use of ω-3 fatty acids in BD, including a review of controlled studies to date assessing the efficacy of ω-3 fatty acids as a potential treatment in BD. We then present pilot data of a randomized intervention of ω-3 fatty acids in women with BD who were planning to discontinue traditional psychotropic agents in anticipation of pregnancy, and conclude with both clinical and research recommendations.

1.1. Rationale for the use of ω-3 fatty acids in BD

The hypothesis regarding the use of ω-3 fatty acids as a potential treatment for BD originated from similarities between the actions of common mood stabilizers (lithium and valproate (VPA)) and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on modulating signal transduction pathways [5–8]. Lithium, VPA, and ω-3 fatty acids (both EPA and DHA) exert inhibitory actions at various sites in the second-messenger cascade, which may account for the mood-stabilizing effects of these medications. In particular, all four compounds affect protein kinase C (PKC) activity [9–19]. PKC is a calcium-activated, phospholipid-dependent enzyme that is abundant in the brain, and plays important roles in pre- and post-synaptic regulation of synaptic transmission through effects on neurotransmitter release, receptors and ion channels, neuronal excitability, and gene expression. Given the similarities in mechanisms of action between ω-3 fatty acids and standard mood stabilizers (lithium and VPA), the ω-3 fatty acids may provide an alternative to standard pharmacologic treatment for BD.

Additionally, a Cross-National Collaborative Group epidemiological study of 10 countries revealed a strong inverse relationship between seafood consumption, a measure of long-chain ω-3 fatty acids intake, and lifetime prevalence rates of BD [20]. These findings are consistent with previous cross-national studies that revealed a protective link between increased fish consumption and depression [21–27] and suggest that insufficient dietary intake of ω-3 fatty acids may increase the risk of affective disorders in susceptible individuals.

Evidence for the role of ω-3 fatty acids in BD has also come from two small studies comparing DHA concentrations in bipolar patients or their relatives and healthy controls. In one study, manic patients ($n = 20$) compared to healthy controls ($n = 20$) had significantly reduced levels of DHA, a key ω-3 fatty acids thought to have mood-stabilizing effects [28]. In another parallel-group design study, healthy subjects with at least one first-degree relative with BD were found to have lower blood concentrations of high-density lipoprotein cholesterol and a tendency towards lower ω-3 fatty acids in phospholipids [29].

Postmortem examinations have shown significantly lower DHA concentrations in the prefrontal cortex (Brodmann area 10) of bipolar patients ($n = 27$) relative to healthy controls ($n = 32$) [30]. Mahadik et al. [31] found that DHA levels as well as total ω-3 fatty acid contents were significantly lower in membranes derived from skin fibroblasts from persons with schizophrenia ($n = 12$) than those with BD ($n = 6$) and healthy controls ($n = 8$). There was no difference between the DHA levels of the individuals with BD and the healthy controls. In another study, Ranjekar et al. [32] found significantly lower levels of α-linolenic acid and EPA in the red blood cells of patients with BD when compared to age-matched control subjects.

1.2. Controlled clinical studies in BD

In the first controlled clinical trial of ω-3 fatty acids in BD, Stoll et al. [6] randomly assigned 44 subjects to adjunctive treatment with 9.6 g/day of ω-3 fatty acids (6.2 g/day of EPA and 3.4 g/day of DHA) or placebo (identical capsules of olive oil ethyl esters) for 4 months. Subjects receiving standard pharmacologic treatment for BD at study entry continued to receive those medications at constant dosages throughout the trial. The main outcome measure was the duration of time to exit double-blind treatment due to the emergence of bipolar symptoms severe enough to warrant change in treatment. Because of a presumed delay in the onset of action of ω-3 fatty acids, study authors determined a priori that only those who remained in treatment for a period of one month would be considered evaluable, resulting in a final cohort of 30.

The ω-3 fatty acid treatment group showed a significantly longer period of remission than the placebo group. Additionally, the ω-3 fatty acid group also demonstrated significantly greater improvements on standardized assessments including the clinical global impression (CGI), global assessment of functioning (GAF), and Hamilton rating scale for depression

(HAM-D) at the 4-month outcome point. Interestingly, although small groups, the four subjects taking monotherapy ω-3 fatty acids remained in remission for significantly longer than the four subjects taking placebo monotherapy. The patients tolerated the intervention well, and complaints of side effects were resolved with reductions in dose ($n = 3$). No hospitalizations or emergent suicidal ideation or suicidal behavior were observed.

In a recent, 12-week, double-blind, placebo-controlled trial, Frangou et al. [33] compared two different doses of EPA, 1 g ($N = 24$) and 2 g ($N = 25$) to placebo ($N = 26$) as adjunctive treatment for bipolar depression. There were no significant differences between the EPA groups, but both EPA groups had significant improvements compared to the placebo group.

Additional data from two recent, small, open-label trials suggest that adjunctive ω-3 fatty acids may reduce symptoms of bipolar depression [34] and irritability associated with BD [35]. Hirashima et al. [36] examined the effect of ω-3 fatty acid administration on brain physiology and found greater cell membrane fluidity as detected by lowered $T(2)$ values in bipolar patients after 4 weeks of ω-3 fatty acids.

Results from other controlled trials conducted in a multi-site network were less encouraging [37]. Both studies were 4-month controlled trials in which participants were randomized to blinded treatment with 6 g/day of EPA or placebo, and then offered open treatment with EPA for an additional 8 months. One study examined the safety and efficacy of EPA in participants with acute bipolar depression ($n = 59$), while the other study evaluated the treatment in participants with rapid cycling bipolar depression ($n = 62$). While EPA was well tolerated in both studies, neither study found a significant difference in outcomes between EPA and placebo.

However, it is worth considering the possibility that an intervention could be more effective for prophylaxis (preventing episodes) than for relieving acute episodes, or more effective in nonrapid cycling patients than in rapid cycling patients. Thus, in spite of the less encouraging findings of these studies, it appears that additional studies are needed to assess the utility of ω-3 fatty acids in BD.

A unique consideration in the treatment of BD is the possibility that a treatment might help with one phase of the illness, such as depression, but simultaneously exacerbate the other phase, e.g. precipitate mania. While no patients have been reported to develop hypomania or mania during the course of controlled clinical trials with ω-3 fatty acids, there is one published case report describing the onset of hypomania in a 35-year old woman with a previous history of major depressive disorder associated with ω-3 fatty acids [38].

1.3. BD and pregnancy

One of the most difficult problems for women with BD is the lack of effective nonteratogenic treatments, especially given the high recurrence rate associated with medication discontinuation [39–41]. First trimester exposure to established mood stabilizers (lithium, VPA, and carbamazepine) is associated with an increased risk of fetal malformations [42–44]. Given this risk, many women with BD choose to discontinue these and all other medications during pregnancy and while trying to conceive. Viguera et al. [45] reported recurrence rates following lithium discontinuation in a cohort of 101 pregnant and nonpregnant women. Over the 64-week period following lithium discontinuation, recurrences occurred in 85.7% of the pregnant/postpartum women and 67.8% of the nonpregnant women. The recurrence rate with a gradual taper (15–30 days) was less, but still 37.1%. Because of this, there has been great interest in exploring the utility of ω-3 fatty acids for women planning pregnancy, pregnant, or lactating. Unlike traditional treatments, addition of ω-3 fatty acids may benefit both mother and fetus, as adequate intake of ω-3 fatty acids is necessary for optimal fetal and infant brain and nervous system development, and DHA is selectively transferred to the developing fetus during pregnancy [46–53]. Stores of EPA are progressively depleted during pregnancy [54]. Hibbeln and others [55] have hypothesized that this may predispose women to affective episodes. Additionally, research suggests that pregnant women only achieve 20–60% of recommended ω-3 fatty acid intake [56]. ω-3 fatty acids (DHA + EPA) have been administered to pregnant women with various other disorders, without adverse effects [57–59]. The US Food and Drug Administration approved the addition of DHA to infant formula in 2001.

1.4. A pilot study of ω-3 fatty acids in women with BD who are planning pregnancy

The following reports findings from a 1 year, parallel group, multi-site, randomized, placebo-controlled pilot study of an ω-3 fatty acid (DHA) versus placebo, added to psychosocial treatment, for women with BD who chose to discontinue all conventional psychotropic medications while attempting to conceive. This pilot study was conducted as an ancillary study in selected sites ($n = 3$) participating in the Systematic Enhancement Program for BD (STEP-BD). STEP-BD procedures and assessments were continued for those women who opted into this arm of treatment (see [60] for complete methodology of the STEP trial). The study was approved by the Institutional Human Subject Review Board of each site and all patients gave verbal

and written informed consent before enrollment in the study.

1.5. Pilot study methods

Participants were randomized to DHA (2000 mg/day) or matching placebo, supplied by Martek Biosciences (Columbia, MD). Additionally, all patients were invited to participate in a collaborative care program for pregnancy (CCP-P). This structured psychosocial program included six sessions with a trained therapist over a 10-week period of time, with a focus on psychoeducation, identification of risk factors, strategies to prevent relapse, and other self-help strategies to maintain wellness. If needed, additional sessions were allowed to complete the workbook. Women were encouraged to have their partner or another member of their support network participate in CCP-P sessions as well.

All participants had a clinical status of ''recovered'', i.e., no more than two moderate mood symptoms, for 6 months before study entry. The mean duration of the time since the last mood episode was 13.22 ± 3.74 months. Participants began double-blind randomized treatment and CCP-P in addition to their baseline medications. Starting at week six, baseline medications were tapered by 25% per week. Women were encouraged not to stop contraception or attempt to become pregnant before week 14 (4 weeks after stopping standard medications). Clinically significant mood worsening that mandating protocol discontinuation was defined a priori as the rate of ''roughening'' (emergence of 3 or more moderate symptoms that do not meet criteria for a full episode). For ethical reasons, we did not want to allow any patient to experience a recurrence (full episode). Participants were followed for up to 1 year of double-blind follow-up. Other outcomes of interest included the longer-term outcome of these interventions, including the ability of these women to safely conceive or transition back to standard treatments.

2. Results

Ten eligible women from three STEP sites (Baylor College of Medicine, Stanford University School of Medicine, and Case Western Reserve) participated in this trial. Of these women, four were randomized to placebo, and six to active treatment. The women ranged in age from 27 to 42 years, with a mean age of 35.00 years. All were Caucasian, and the majority (90%) were diagnosed with BDI (one woman was diagnosed with BDII). They reported an average duration of illness of 14.7 years, ranging from 2 to 23 years. None had previously undergone treatments for infertility. Basic demographic and clinical information, by group, is included in Table 1.

The women tolerated the trial well with no serious adverse events reported over the course of participation, and no discontinuations due to intolerability. The women participated in the CCP-P sessions, with an average of five sessions for the active group, and 6.5 in the placebo group. Two of the women in the active group completed the 52-week trial (33.3%), and of those with premature discontinuation, three were due to emerging or worsening mood symptoms (50%) and one due to noncompliance. Of the three women with emerging symptoms, one was experiencing predominantly anxiety and two were experiencing emerging hypomania. Three of those receiving placebo completed the 52 weeks (75%) with one (25%) discontinuing due to increasing irritability. Given the small numbers, it is not surprising that a log-rank test of survival time in the study showed no significant difference between patients receiving placebo versus active treatment ($P = 0.83$). Three women conceived and ultimately delivered healthy babies (one in the DHA group, two in the placebo group).

Table 1
Demographic and clinical characteristics of pilot sample

	ω-3 ($n = 6$)	Placebo ($n = 4$)
Age	37.83 ± 3.66 years	30.75 ± 3.5 years
Diagnosis	Bipolar I disorder = 5 Bipolar II disorder = 1	Bipolar I disorder = 4
Length of illness	14.67 ± 6.5 years	14.75 ± 6.55 years
Time since last mood episode	18.5 ± 13.28 months	8.0 ± 6.06 months
Lifetime number of manic episodes		
1	2 (33.3%)	1 (25%)
2	2 (33.3%)	—
3–4	—	1 (25%)
5–9	1 (16.7%)	—
10–20	1 (16.7%)	—
20–50	—	1 (25%)
>50	—	1 (25%)
Lifetime number of depressive episodes		
0	1 (16.7%)	—
1	—	—
2	1 (16.7%)	—
3–4	2 (33.3%)	1 (33.3%)
5–9	1 (16.7%)	—
10–20	—	1 (33.3%)
20–50	1 (16.7%)	1 (33.3%) 1 = missing
Number of previous pregnancies	0.67 ± 1.15	1.0 ± 1.41
Number of children	0.33 ± 0.58	0.25 ± 0.50

2.1. Pilot study discussion

This small pilot study is the first to provide an intervention to women with BD who plan to discontinue all psychotropic treatments while trying to conceive. It demonstrates both the feasibility and the challenges in conducting such work, either in research or clinical settings (Table 2). Because of ethical aspects, recruitment was limited to women who were forthcoming about their reproductive plans with their providers, and who were committed to taking advantage of other supports, including the psychoeducation provided as part of the intervention. Randomizing 10 appropriate women willing to accept potential placebo treatment during a very tenuous time was a notable accomplishment.

This small pilot study suggests that it is feasible to conduct a larger study of the use of ω-3 fatty acids in women with BD who choose to discontinue all conventional psychotropic medications while attempting to conceive. Specifically, a gradual medication taper combined with a brief psychoeducational psychotherapy intervention and careful follow-up may prevent severe decompensation as none of the women in the study had a marked exacerbation of symptoms or required hospitalization. Unfortunately, the small size of the pilot study precludes comment on the possible efficacy of DHA as a preventive agent. However, several aspects of the study inform future studies. DHA was well tolerated, and participants were enthusiastic about the possibilities of mood stabilizing benefits in addition to health benefits to mother and fetus. One recruitment challenge was the fact that many patients objected to the possibility of being randomized to placebo. Although this is a common issue to placebo-controlled trials, it appeared to be a greater problem in this study because ω-3 fatty acids are readily available in health food stores. In addition, the delay of 14 weeks from the start of the study to the time when patients were allowed to attempt conception was difficult for many patients. While this allowed for a slow taper of baseline medication, in many cases the potential participants had already delayed attempting to conceive and expressed a sense of urgency.

Table 2
Outcomes of pilot study of ω-3 for women planning pregnancy

	ω-3 ($n = 6$)	Placebo ($n = 4$)
Average number of CCP-P sessions	5.0 (1.55)	6.5 (1.0)
Number completed 52-week protocol	2 (33.3%)	3 (75%)
Reasons for discontinuation		
Emerging/worsening symptoms	1 (16.7%)	—
Noncompliance with protocol	2 (33.3%)	—
Other	1 (16.7%)	1 (25%)
Number of pregnancies while in trial	1 (16.7%)	2 (50%)
Average days in trial		
261.67 ± 69.02 days		
307.25 ± 63.45 days		
Number of adverse events	0	0
Number of serious adverse events	0	0

3. Conclusions

The pilot work suggests that it is feasible to conduct an adequately powered trial of the use of ω-3 fatty acids in women with BD who choose to discontinue all conventional psychotropic medications while attempting to conceive. Overall, the elucidation of the potential role of ω-3 fatty acids as a treatment for BD as well as pregnancy in patients with BD requires further study. The current data are not sufficient to support a recommendation of monotherapy treatment as a substitute for standard pharmacologic treatments. However, judicious monotherapy use in select clinical situations, or adjunctive use, may be warranted pending further data from controlled clinical trials. Future studies will need to address the relative roles of DHA and EPA as well as dose-response studies.

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References

[1] R.C. Kessler, P. Berglund, O. Demler, R. Jin, E.E. Walters, Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication, Arch. Gen. Psychiatry 62 (6) (2005) 593–602.
[2] T.M. Kashner, T. Suppes, A.J. Rush, K.Z. Altshuler, Measuring use of outpatient care among mentally ill individuals: a comparison of self reports and provider records, Eval. Program Plann. 22 (1) (1999) 31–39.
[3] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorder. DSM-IV-TR,, Washington, DC, American Psychiatric Association, 2000.
[4] F.K. Goodwin, K.R. Jamison, Manic Depressive Illness, Oxford University Press, New York, 1990.
[5] R.I. Sperling, A.I. Benincaso, C.T. Knoell, et al., Dietary omega-3 polyunsaturated fatty acids inhibit phosphoinositide formation and chemotaxis in neutrophils, J. Clin. Invest. 91 (2) (1993) 651–660.
[6] A.L. Stoll, W.E. Severus, M.P. Freeman, et al., Omega-3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial, Arch. Gen. Psychiatry 56 (5) (1999) 407–412.
[7] B. Mirnikjoo, S.E. Brown, H.F. Seung-Kim, et al., Protein kinase inhibition by omega-3 fatty acids, J. Biol. Chem. 276 (14) (2001) 10888–10896.
[8] S.I. Rapoport, F. Bosetti, Do lithium and anticonvulsants target the brain arachidonic acid cascade in bipolar disorder, Arch. Gen. Psychiatry 59 (7) (2002) 592–596.
[9] T.L. Casebolt, R.S. Jope, Long-term lithium treatment selectively reduces receptor-coupled inositol phospholipid hydrolysis in rat brain, Biol. Psychiatry 25 (1989) 329–340.
[10] T.L. Casebolt, R.S. Jope, Effects of chronic lithium treatment on protein kinase C and cyclic AMP dependent protein phosphorylation, Biol. Psychiatry 29 (1991) 33–243.
[11] L.A. Speizer, M.J. Watson, L.L. Brunton, Differential effects of omega-3 fish oils on protein kinase activities in vitro, Am. J. Physiol. 261 (1991) E109–E114.
[12] O. Holian, R. Nelson, Action of long-chain fatty acids on protein kinase C activity: comparison of omega-7 and omega-3 fatty acids, Anticancer Res. 12 (1992) 975–980.
[13] R.H. Lenox, D.G. Watson, J. Patel, J. Ellis, Chronic lithium administration alters a prominent PKC substrate in rat hippocampus, Brain Res. 570 (1992) 333–340.
[14] H.K. Manji, R. Etcheberrigaray, G. Chen, J.L. Olds, Lithium decreases membrane-associated protein kinase C in hippocampus: selectivity for the alpha isozyme, J. Neurochem. 61 (1993) 2303–2310.
[15] H.K. Manji, G. Chen, J.K. Hsiao, E.D. Risby, M.I. Masana, W.Z. Potter, Regulation of signal transduction pathways by mood-stabilizing agents: implications for the delayed onset of therapeutic efficacy, J. Clin. Psychiatry 57 (1996) 34–46.
[16] H.K. Manji, J.M. Bebchuk, G.J. Moore, D. Glitz, K.A. Hasanat, G. Chen, Modulation of CNS signal transduction pathways and gene expression by mood-stabilizing agents: therapeutic implications, J. Clin. Psychiatry 60 (suppl 2) (1999) 27–39.
[17] G. Chen, H.K. Manji, D.B. Hawver, C.B. Wright, W.Z. Potter, Chronic sodium valproate selectively decreases protein kinase C alpha and epsilon in vitro, J. Neurochem. 63 (1994) 2361–2364.
[18] J.A. Bitran, H.K. Manji, W.Z. Potter, F. Gusovsky, Down-regulation of PKC alpha by lithium in vitro, Psychopharmacol. Bull. 31 (2) (1995) 449–452.
[19] F.A. Kim, A. Sing, T. Kaneko, The vHNF1 homeodomain protein establishes early rhombomere identity by direct regulation of Kreisler expression, Mech. Dev. 122 (12) (2005) 1300–1309.
[20] S. Noaghiul, J.R. Hibbeln, Cross-national comparisons of seafood consumption and rates of bipolar disorders, Am. J. Psychiatry 160 (12) (2003) 2222–2227.
[21] R. Edwards, M. Peet, J. Shay, D. Horrobin, Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients, J. Affect. Disorders 48 (2–3) (1998) 149–155.
[22] J.R. Hibbeln, Fish consumption and major depression, Lancet 351 (9110) (1998) 1213.
[23] J.R. Hibbeln, Long-chain polyunsaturated fatty acids in depression and related conditions, in: M. Peet, I. Glen, D.F. Horrobin (Eds.), Phospholipid Spectrum Disorder in Psychiatry, Marius Press, Carnforth, England, 1999, pp. 195–210.
[24] T. Hirayama, Life-Style and Mortality. A Large-Scale Census-Based Cohort Study in Japan. Contributions to Epidemiology and Biostatistics, S. Karger Publishing, Basel, Switzerland, 1990.
[25] A. Tanskanen, J. Tuomilehto, H. Viinamaki, Cholesterol, depression and suicide, Br. J. Psychiatry 176 (2000) 398–399.
[26] A. Tanskanen, J.R. Hibbeln, J. Hintikka, K. Haatainen, K. Honkalampi, H. Viinamaki, Fish consumption, depression, and suicidality in a general population, Arch. Gen. Psychiatry 58 (5) (2001) 512–513.
[27] A. Tanskanen, J.R. Hibbeln, J. Tuomilehto, et al., Fish consumption and depressive symptoms in the general population in Finland, Arch. Gen. Psychiatry 52 (4) (2001) 529–531.
[28] C.C. Chiu, S.Y. Huang, K.P. Su, et al., Polyunsaturated fatty acid deficit in patients with bipolar disorder, Eur. Neuropsychopharmacol. 13 (2) (2003) 99–103.
[29] S. Sobczak, A. Honig, A. Christophe, et al., Lower high-density lipoprotein cholesterol and increased omega-6 polyunsaturated fatty acids in first-degree relatives of bipolar patients, Psychol. Med. 34 (1) (2004) 103–112.
[30] R.K. McNamara, C.G. Hahn, N.M. Richtand, R.J. Jandacek, P. Tso, Reductions in the principle brain omega-3 fatty acid, docosahexaenoic acid, in postmortem prefrontal cortex of patients with schizophrenia, bipolar disorder, and major depressive disorder, but not multiple sclerosis or Alzheimer's disease, Biol. Psychiatry 59 (2006) S30.
[31] S.P. Mahadik, S. Mukherjee, D.F. Horrobin, K. Jenkins, E.E. Correnti, R.E. Scheffer, Plasma membrane phospholipids fatty acid composition of cultured skin fibroblasts from schizophrenic patients: comparison with bipolar patients and normal subjects, Psychiatry Res. 63 (1996) 133–142.
[32] P.K. Ranjekar, A. Hinge, M.V. Hegde, M. Ghate, A. Kale, et al., Decreased antioxidant enzymes and membrane essential polyunsaturated fatty acids in schizophrenic and bipolar mood disorder patients, Psychiatry Res. 121 (2003) 109–122.
[33] S. Frangou, M. Lewis, P. McCrone, Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study, Br. J. Psychiatry 188 (2006) 46–50.
[34] Y. Osher, Y. Bersudsky, R.H. Belmaker, Omega-3 eicosapentaenoic acid in bipolar depression: report of a small open-label study, J. Clin. Psychiatry 66 (6) (2005) 726–729.
[35] K. Sagduyu, M.E. Dokucu, B.A. Eddy, G. Craigen, C.F. Baldassano, A. Yildiz, Omega-3 fatty acids decreased irritability

of patients with bipolar disorder in an add-on, open label study, Nutr. J. 4 (2005) 1–6.
[36] F. Hirashima, A.M. Parow, A.L. Stoll, C.M. Demopulos, K.E. Damico, M.L. Rohan, et al., Omega-3 fatty acid treatment and T(2) whole brain relaxation times in bipolar disorder, Am. J. Psychiatry 161 (10) (2004) 1922–1924.
[37] P.E.,Jr. Keck, J. Mintz, S.L. McElroy, M.P. Freeman, T. Suppes, M.A. Frye, L.L. Altshuler, R. Kupka, W.A. Nolen, G.S. Leverich, K.D. Denicoff, H. Grunze, N. Duan, R.M. Post, Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentanoate in the treatment of bipolar depression and rapid cycling bipolar disorder**,** Biol. Psychiatry, in press.
[38] G. Kinrys, Hypomania associated with omega-3 fatty acids [letter], Arch. Gen. Psychiatry 57 (2000) 715–716.
[39] R.J. Baldessarini, L. Tondo, G.L. Faedda, T.R. Suppes, G. Floris, N. Rudas, Effects of the rate of discontinuing lithium maintenance treatment in bipolar disorders, J. Clin. Psychiatry 7 (10) (1996) 441–448.
[40] G.L. Faedda, L. Tondo, R.J. Baldessarini, T. Suppes, M. Tohen, Outcome after rapid vs. gradual discontinuation of lithium treatment in bipolar disorders, Arch. Gen. Psychiatry 50 (6) (1993) 448–455.
[41] T. Suppes, R.J. Baldessarini, G.L. Faedda, M. Tohen, Risk of recurrence following discontinuation of lithium treatment in bipolar disorder, Arch. Gen. Psychiatry 48 (1991) 1082–1088.
[42] Centers for disease control: valproate: a new cause of birth defects—report from Italy and follow-up from France, Morb. Mort. Weekly Rep. 32 (1983) 438–439.
[43] L.S. Cohen, J.M. Friedman, J.W. Jefferson, E.M. Johnson, M.L. Weiner, A re-evaluation of risk of in utero exposure to lithium, JAMA 271 (1994) 146–150.
[44] F.W. Rosa, Spina bifida in infants of women treated with carbamazepine during pregnancy, N. Engl. J. Med. 324 (1991) 674–677.
[45] A.C. Viguera, R. Nonacs, L.S. Cohen, L. Tondo, A. Murray, R.J. Baldessarini, Risk of recurrence of bipolar disorder in pregnant and nonpregnant women after discontinuing lithium maintenance, Am. J. Psychiatry 157 (2000) 179–184.
[46] M.A. Crawford, A.G. Hassam, P.A. Stevens, Essential fatty acid requirements in pregnancy and lactation with special reference to brain development, Prog. Lipid Res. 20 (1981) 31–40.
[47] W.E. Connor, M. Neuringer, The effects of n-3 fatty acid deficiency and repletion upon the fatty acid composition and function of the brain and retina, Prog. Clin. Biol. Res. 282 (1988) 275–294.
[48] S. Kubow, K.G. Koski, Maternal dietary glucose-lipid interactions modulate embryological development in vivo and in embryo culture, Biol. Reprod. 52 (1) (1995) 145–155.
[49] K.A. High, S. Kubow, n-3 Fatty acids inhibit defects and fatty acid changes caused by phenytoin in early gestation in mice, Lipids 11 (1994) 771–778.
[50] G. Hornstra, M.D. Al, A.C. van Houwelingen, M.M. Foreman-van Drongelen, Essential fatty acids in pregnancy and early human development, Eur. J. Obstet. Gynecol. Reprod. Biol. 61 (1) (1995) 57–62.
[51] S. Glozman, P. Green, B. Kamensky, L. Weiner, E. Yavin, Ethyl docosahexaenoic acid administration during intrauterine life enhances prostanoid production and reduces free radicals generation in the fetal rat brain, Lipids 34 (Suppl) (1999) S247–S248.
[52] R.T. Holman, S.B. Johnson, P.L. Ogburn, Deficiency of essential fatty acids and membrane fluidity during pregnancy and lactation, Proc. Natl. Acad. Sci. 88 (1991) 4835–4839.
[53] Y. Min, K. Ghebremeskel, M.A. Crawford, et al., Pregnancy reduces arachidonic and docosahexaenoic in plasma triacylglycerols of Korean women, Int. J. Vitam. Nutr. Res. 70 (2000) 70–75.
[54] S.J. Otto, A.C. van Houwelingen, M. Antal, et al., Maternal and neonatal essential fatty acid status in phospholipids: an international comparative study, Eur. J. Clin. Nutr. 51 (1997) 232–242.
[55] J.R. Hibbeln, N. Salem Jr., Dietary polyunsaturated fatty acids and depression: when cholesterol does not satisfy, Am. J. Clin. Nutr. 62 (1995) 1–9.
[56] D. Benisek, J. Shabert, R. Skornik, Dietary intake of polyunsaturated fatty acids by pregnant or lactating women in the United States, Obstet. Gynecol. 95 (2000) 77–78.
[57] C.J. Glueck, P. Streicher, P. Wang, D. Sprecher, J.M. Falko, Treatment of severe familial hypertriglyceridemia during pregnancy with very-low-fat diet and n-3 fatty acids, Nutrition 12 (1996) 202–205.
[58] M.T. Bulstra-Ramakers, H.J. Huisjes, G.H. Visser, The effects of 3 g eicosapentaenoic acid daily on recurrence of intrauterine growth retardation and pregnancy induced hypertension, Br. J. Obstet. Gynaecol. 102 (2) (1995) 123–126.
[59] J.L. Onwude, R.J. Lilford, H. Hjartardottir, A. Staines, D. Tuffnell, A randomized double blind placebo controlled trial of fish oil in high risk pregnancy, Br. J. Obstet. Gynecol. 102 (2) (1995) 95–100.
[60] G.S. Sachs, M.E. Thase, M.W. Otto, et al., Rationale, design, and methods of the systematic treatment enhancement program for bipolar disorder (STEP-BD), Biol. Psychiatry 53 (2003) 1028–1042.