

Omega-3 Fatty Acids in Psychiatry: A Review

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Omega-3 fatty acids are long-chain, polyunsaturated fatty acids found in plant and marine sources. Unlike saturated fats, which have been shown to have negative health consequences, omega-3 fatty acids are polyunsaturated fatty acids that have been associated with many health benefits. Omega-3 fatty acids may prove to be efficacious in a number of psychiatric disorders. Mood disorders have been associated with abnormalities in fatty acid composition. Several lines of evidence suggest that diminished omega-3 fatty acid concentrations are associated with mood disorders. Clinical data are not yet available regarding omega-3 fatty acids in the treatment of major depression. However, one double-blind treatment trial has been conducted in bipolar disorder. Also, substantial evidence does exist supporting a potential role of omega-3 fatty acids in schizophrenia, although treatment data are needed. A case has been reported in which a patient with schizophrenia was successfully treated with omega-3 fatty acids. Controlled studies are necessary to explore the potential treatment of schizophrenia with omega-3 fatty acids. Omega-3 fatty acids may also be helpful in the treatment of dementia. Furthermore, omega-3 fatty acids may prove to be a safe and efficacious treatment for psychiatric disorders in pregnancy and in breastfeeding.

KEY WORDS: omega-3 fatty acids; fish oil; bipolar disorder; major depression; dementia.

INTRODUCTION

The use of alternative therapies and dietary supplements is increasingly commonplace. For example, in a random sample of U.S. households, 17.6% of respondents reported using megavitamins or herbal remedies in 1997, almost a 360% increase from 1990. Furthermore, in the same survey, almost 20% of prescription users took concurrent dietary supplements, and more than 60% of patients who reported using alternative therapies did not disclose this information to their doctors (1). Another study of emergency department patients found more than half had tried alternative therapies (2). Most patients who utilize alternative therapies are satisfied with their conventional practitioners and do not primarily rely on alternative treatments (3). Therefore, physicians must be educated about alternative treatments and willing to help patients make rational decisions about appro-

priate integrative medical care. However, despite their popularity, data are lacking regarding many alternative treatments.

Omega-3 fatty acids are long-chain, polyunsaturated fatty acids found in plant and marine sources. Examples of marine-derived omega-3 fatty acids are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Linolenic acid is an omega-3 fatty acid found in plants. Unlike saturated fats, which have been shown to have negative health consequences, omega-3 fatty acids are polyunsaturated fatty acids that have been associated with many health benefits.

For example, omega-3 fatty acids have been found to be helpful in treating hypertension (4), Crohn's disease (5), rheumatoid arthritis (6), and asthma (7). They have been reported to decrease the risk of primary cardiac arrest (8) and coronary artery disease (9), and decrease serum triglycerides (10). Also, encouraging data support a role of omega-3 fatty acids in the prevention of breast (11) and lung cancer (12). Despite the proven health benefits of omega-3 fatty acids, the American diet emphasizes omega-6 fatty acids at the expense of omega-3 fatty

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acids. This is important beginning at the earliest ages of development, as omega-3 fatty acids are crucial in fetal and neonatal brain and nervous system development (13).

As described in this review of the literature, omega-3 fatty acids may prove to be efficacious in a number of psychiatric disorders. Evidence suggests that omega-3 fatty acids may have beneficial effects in (1) mood disorders, including both major depression and bipolar disorder, (2) schizophrenia, and (3) dementia. Furthermore, omega-3 fatty acids may prove to be a safe and efficacious treatment for psychiatric disorders during pregnancy and breastfeeding.

OMEGA-3 FATTY ACIDS IN MOOD DISORDERS: MAJOR DEPRESSION AND BIPOLAR DISORDER

Mood disorders have been associated with abnormalities of fatty acid composition. Several lines of evidence suggest that diminished omega-3 fatty acid concentrations are associated with mood disorders. First, Hibbeln demonstrated a relationship between the prevalence of major depression and the amount of fish consumed per capita worldwide (14). He found that the prevalence of depression was inversely related to the amount of fish consumed. Second, depletion of total omega-3 fatty acid concentrations has been found in the erythrocyte membranes of patients with major depression (15). Similarly, several investigators have reported a decreased ratio of omega-3 fatty acids to omega-6 fatty acids in the plasma and erythrocytes of patients with major depression, and decreased omega-3 fatty acid concentrations in erythrocytes have also been associated with increased severity of depression (16–18). Additionally, studies suggest that essential fatty acids may impact central serotonergic and dopaminergic neurotransmitter systems (19,20). Higher plasma concentrations of polyunsaturated fatty acids, particularly DHA, have been demonstrated to predict higher concentrations of metabolites of serotonin (5-HIAA) and dopamine (HVA) in cerebrospinal fluid of controls and abstinent alcoholics (19). Additionally, high plasma concentrations of DHA have been shown to predict low concentrations of CSF 5-HIAA among violent, impulsive subjects (20). However, clinical data is not available to determine whether dietary manipulation of fatty acids may impact neurotransmitter metabolite concentrations.

Furthermore, the immune system may play a

role in the mechanism of action of omega-3 fatty acids in mood disorders. Available data support an immunologic etiology of mood disorders, specifically an overactivity of the inflammatory response, and omega-3 fatty acids may dampen such overactivity. For example, investigators have reported a higher expression of T-cell activation markers (21) and anti-phospholipid antibodies in patients with major depression (22). Excessive secretion of macrophages has also been postulated to contribute to major depression (23). Similarly, overactivity of cell-mediated immunity has been associated with mania, and overactivity of the acute phase protein response has been demonstrated in major depression and mania (24,25). The inflammatory process in mood disorders may in fact influence levels of neurotransmitters, especially serotonin. The inflammatory response observed in major depression has been associated with a decreased availability of serum tryptophan (26,27). These data regarding the immunologic etiology of mood disorders support the use of omega-3 fatty acids in their treatment. Omega-3 fatty acids have been demonstrated to be anti-inflammatory and immunosuppressive in the presence of overactivity of the immune system (28–32).

Like available mood stabilizing medications, omega-3 fatty acids appear to influence second messenger systems. Research suggests that all currently available mood stabilizers have inhibitory effects on neuronal second messenger systems, and that this inhibition may be crucial to their mechanisms of action (33). Biochemical studies have shown that high-dose therapy with omega-3 fatty acids leads to the incorporation of these compounds into the membrane phospholipids crucial for cell signaling (34,35), and suppresses phosphatidylinositol-associated second messenger activity (similar to the postulated actions of lithium and valproate) (36).

Clinical data are not yet available regarding omega-3 fatty acids in the treatment of major depression. However, one double-blind treatment trial has been conducted in bipolar disorder (37). Patients received omega-3 fatty acids either as adjunctive medication or as monotherapy for at least one month. The total dosage of omega-3 fatty acids was 9.6 g, composed of 6.2 g of EPA and 3.4 g of DHA. Overall, the duration of remission was significantly greater in the omega-3 fatty acid group compared with the placebo group. Results were also examined for the subgroup of eight patients who entered the study on no mood-stabilizing medications. The four of these patients who received omega-3 fatty acids as mono-

therapy remained in remission for a significantly longer period of time than the four of eight on placebo. The most common adverse effect was loose stools, reported by 62% of the patients who received omega-3 fatty acids.

Certainly, more data are needed concerning omega-3 fatty acids in mood disorders. Data regarding depletion of omega-3 fatty acids in major depression and preliminary treatment data in bipolar disorder indicate that this is a promising new treatment for patients with mood disorders.

OMEGA-3 FATTY ACIDS IN SCHIZOPHRENIA

Christensen and Christensen reported compelling epidemiological data supporting a relationship between dietary fat and schizophrenia (38). They analyzed the course and outcome of schizophrenia in eight countries participating in a World Health Organization international study, and found that 97% ($P = .0002$) of the variation in outcome of schizophrenia could be explained by the variation in national diets. High percentage of fat from vegetables, fish, and seafood tended to be associated with a favorable outcome and course of illness.

Peet and colleagues (39) measured the erythrocyte membrane essential fatty acid composition in 23 patients with schizophrenia and controls. Patients studied had been chronically hospitalized and treated with antipsychotic medications. Patients with schizophrenia exhibited significantly lower levels of EPA and DHA when compared with healthy controls. In addition, patients had lower levels of two omega-6 fatty acids, linoleic and arachidonic acids. In another study, patients with schizophrenia who had been medicated with neuroleptics and living in the community were found to have lower essential fatty acids levels in their plasma and red blood cell membranes than controls (40). The tendency appeared to be familial, as first degree relatives also had lower essential fatty acid levels than controls. Also, Peet *et al.* (41) reported that dietary analysis of 20 patients with schizophrenia yielded significant relationships between dietary omega-3 fatty acid status and the severity of schizophrenic symptoms and tardive dyskinesia. Patients with less severe symptomatology reported higher consumption of omega-3 fatty acids. Conflicting data exist regarding the efficacy of evening primrose oil in schizophrenia, which is a rich source of omega-6 fatty acids (42,43).

Omega-3 fatty acids may play different roles in subtypes of schizophrenia. Glen *et al.* (44) studied the erythrocyte membranes of patients with either positive or negative persistent symptoms of schizophrenia. Patients ($N = 25$) were assessed with the Brief Psychiatric Rating Scale (BPRS). Patients with persistent positive symptoms had significantly more conceptual disorganization, hallucinations, and unusual thought content, while those with persistent negative symptoms had more emotional withdrawal, motor retardation, and blunted or inappropriate affect. Only those patients with persistently negative symptoms exhibited lower levels of long-chain polyunsaturated fatty acids and higher levels of saturated fatty acids, in contrast to those with predominantly positive symptoms and controls. The investigators suggested that these findings were consistent with the classification of schizophrenia as two distinct disease entities, categorized by either predominantly positive or negative symptoms.

As the case with mood disorders, schizophrenia has also been associated with alterations in immunologic function. This may explain a possible mechanism of action of antipsychotic medications and provide support for the use of omega-3 fatty acids in schizophrenia. Overactivity of cell-mediated immunity and the acute phase protein response has been associated with schizophrenia, and antipsychotic drugs may have immunosuppressive effects (45–47). As previously mentioned, omega-3 fatty acids have been demonstrated to exert anti-inflammatory and immunosuppressive effects in the presence of overactivity of the immune system (48–52). Additionally, Yao *et al.* (53) determined fatty acid composition in erythrocytes of patients with schizophrenia before and after withdrawal from haloperidol. They found a highly significant decrease in the levels of polyunsaturated fatty acids in both patients who were treated with haloperidol and those who were drug-free for over 5-weeks. The investigators hypothesized that decreased levels of polyunsaturated fatty acids may result from defective uptake of fatty acids into phospholipid membranes, which affects membrane fluidity, and that membrane dynamics may be altered in schizophrenia.

While substantial evidence does exist supporting a potential role of omega-3 fatty acids in schizophrenia, treatment data are lacking. A case has been reported in which a patient with schizophrenia was successfully treated with a daily dose of 2 g of EPA (54). No adverse effects were experienced. Con-

trolled studies are necessary to explore the potential treatment of schizophrenia with omega-3 fatty acids.

OMEGA-3 FATTY ACIDS IN DEMENTIA

Omega-3 fatty acids may also be helpful in the treatment of dementia. Investigators have demonstrated phospholipid abnormalities in the brains of patients with Alzheimer's disease (55). Specifically, postmortem assessment of brain tissue samples have demonstrated reduced omega-3 fatty acid content in the parahippocampal cortex in subjects with Alzheimer's disease compared to controls (56). Moreover, in a prospective, naturalistic study, dietary habits of 5,386 nondemented subjects were assessed at baseline (57). At follow-up, fish consumption was found to be inversely related to incident dementia. While no controlled trials of omega-3 fatty acids have been conducted in the treatment of dementia, a case has been reported in which a 77-year-old patient with Alzheimer's Dementia improved clinically over several months with dietary changes of increased fish intake (58). While rating scales of his mental status were not reported, noted improvements included decreased restless and destructive behavior, regaining the ability to dress himself, improved fine motor skills, and enhanced insight into his condition. Authors suggest that increased dietary fatty acids were likely responsible for improvements, although admission to a nursing home is a confounding variable. While controlled studies are essential, available data suggest that omega-3 fatty acids may have a possible role in the prevention and treatment of dementia.

OMEGA-3 FATTY ACIDS: A PSYCHOTROPIC FOR PREGNANCY AND POSTPARTUM?

Omega-3 fatty acids are promising candidates for use during pregnancy and lactation, with health benefits for both the mother and baby. The etiology of postpartum depression may involve depletion of maternal omega-3 fatty acids, a common occurrence during pregnancy (59,60). Also, Hibbeln described a relationship between per capita fish consumption in 27 countries and the development of postpartum depression, with higher fish consumption appearing to be a protective factor (61,62).

Diets low in omega-3 fatty acids have been associated with elevated rates of preterm deliveries (63), and omega-3 fatty acid supplementation in the form

of fish oil has been demonstrated to prolong gestation and protect against preterm delivery (64). Furthermore, in a cross-sectional case-control study, low levels of maternal erythrocyte omega-3 fatty acids were associated with increased risk of preeclampsia (65). Additionally, retrospective dietary analysis has suggested that the consumption of omega-3 fatty acids during pregnancy may be protective against the development of cerebral palsy (66).

The neonate, who relies on maternal stores of omega-3 fatty acids during gestation, is also dependent on maternal essential fatty acids while breastfeeding. Commercial formula preparations are not supplemented with omega-3 fatty acids, despite evidence that omega-3 fatty acids are required for healthy brain and retinal development (67). Data suggest that infant formulas should be supplemented with omega-3 fatty acids, especially in cases of prematurity (68,69). Maternal dietary supplementation with omega-3 fatty acids has been shown to increase the omega-3 fatty acid content of breast milk (70). There are no known risks of maternal supplementation of omega-3 fatty acids to the breastfeeding baby in the published English language medical literature.

DISCUSSION

Enough evidence exists to merit further study of omega-3 fatty acids in several psychiatric disorders. At present, the psychotropic medications that are available are often associated with intolerable or troublesome adverse effects. Omega-3 fatty acids may provide efficacious and well-tolerated treatment as antidepressant, mood stabilizing, and antipsychotic medication, and also may treat or prevent dementia. Also compelling, unlike so many available drugs, omega-3 fatty acids appear to be not only safe, but *beneficial*, during pregnancy and breastfeeding. Additionally, omega-3 fatty acids may confer many health benefits, as previously mentioned.

Certainly, with the potential of alleviating symptoms of major mental illnesses and with other associated health benefits, universally promoting the consumption and supplementation of omega-3 fatty acids may be tempting. However, at this time, certain limitations exist regarding practical use of omega-3 fatty acids in psychiatric disorders. First, although the public in general has become enamored with "natural" alternatives to medications, the food supplement industry is not regulated with the same vigilance as the pharmaceutical industry. Hence, without strict

monitoring, products may not contain pure ingredients, or the exact ingredients listed on the package. Second, food supplements or "natural" remedies are rarely covered by a patient's insurance, and many do not have the resources to pay for such products. Third, because of the paucity of data regarding treatment, optimal dosages of omega-3 fatty acids for the disorders discussed are currently unknown. Commercially available preparations may contain EPA, DHA or combinations of both. Typical preparations include 180 mg of EPA and 120 mg of DHA, although some brands contain more. Generally, doses studied in research protocols are higher, and patients and their doctors may want to keep this in mind.

While generally well-tolerated, possible side effects must be taken into account. Mild gastrointestinal side effects have been reported in treatment trials. Additionally, omega-3 fatty acids may prolong bleeding time (71–73). Bleeding time has been shown to be maximally increased after six weeks of treatment with omega-3 fatty acids (73). No adverse events have been reported in relation to bleeding problems, but clinicians should monitor their patients for signs and symptoms of abnormal bleeding, such as petechiae and ecchymosis. Patients should be made aware of this possible effect, and they should alert their doctors of abnormal bleeding. Concomitant medications that may increase bleeding, such as aspirin and coumadin, should be taken into consideration.

Advising patients to make dietary changes is also complicated. While the consumption of fish has been shown to have many health benefits, many of our natural resources have been marred by pollution, and fish from some areas may be contaminated (74,75). The most valid recommendations that can be made at present include (1) continued clinical research of the psychotropic benefits of omega-3 fatty acids, (2) the determination of optimal dosages for therapeutic purposes, and (3) the production of pure omega-3 fatty acid products that meet the same rigorous standards as are applied to pharmaceuticals.

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