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Omega-3 Fatty Acids in the Treatment of Psychiatric Disorders

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Abstract

The importance of omega-3 fatty acids for physical health is now well recognised and there is increasing evidence that omega-3 fatty acids may also be important to mental health. The two main omega-3 fatty acids in fish oil, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have important biological functions in the CNS. DHA is a major structural component of neuronal membranes, and changing the fatty acid composition of neuronal membranes leads to functional changes in the activity of receptors and other proteins embedded in the membrane phospholipid. EPA has important physiological functions that can affect neuronal activity. Epidemiological studies indicate an association between depression and low dietary intake of omega-3 fatty acids, and biochemical studies have shown reduced levels of omega-3 fatty acids in red blood cell membranes in both depressive and schizophrenic patients.

Five of six double-blind, placebo-controlled trials in schizophrenia, and four of six such trials in depression, have reported therapeutic benefit from omega-3 fatty acids in either the primary or secondary statistical analysis, particularly when EPA is added on to existing psychotropic medication. Individual clinical trials have suggested benefits of EPA treatment in borderline personality disorder and of combined omega-3 and omega-6 fatty acid treatment for attention-deficit hyperactivity disorder. The evidence to date supports the adjunctive use of omega-3 fatty acids in the management of treatment unresponsive depression and schizophrenia. As these conditions are associated with increased risk of coronary heart disease and diabetes mellitus, omega-3 fatty acids should also benefit the physical state of these patients. However, as the clinical research evidence is preliminary, large, and definitive randomised controlled trials similar to those required for the licensing of any new pharmacological treatment are needed.

The importance of omega-3 fatty acids for physical well-being has been recognised for several decades.[1] Amongst other health benefits, omega-3 fatty acids have anti-inflammatory, antithrombotic, antiarrhythmic and hypolipidaemic effects.[1] Because of this, these fatty acids are beneficial in the prevention and treatment of physical illnesses ranging from coronary heart disease[2] to rheumatoid arthritis.[3] *Homo sapiens* evolved in an omega-3-rich nutritional environment.[4] Over the last century, dietary intake of omega-3 fatty acids has declined, whereas there has been an increase in the amount of omega-6 fatty acids. This altered balance of fatty acids is regarded as detrimental to the health of the population.[1]

More recently, there has been increasing evidence that omega-3 fatty acids are important not only for physical health but also for brain development and function.[5-7] As a result, there has been increasing interest in the use of omega-3 fatty acids for the treatment of mental health problems. This review summarises the background, rationale, published double-blind clinical trials and clinical implications relating to omega-3 fatty acids in the treatment of psychiatric disorders.

1. Background and Rationale

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are considered to be the most important omega-3 fatty acids in relation to brain function. The parent fatty acid for the omega-3 series is α-linolenic acid (ALA) [see figure 1], which is regarded as an essential fatty acid because it can be obtained only from the diet. Other omega-3 fatty acids, including EPA and DHA, can be metabolised from ALA by a process of desaturation, elongation and β-oxidation.[1] However, this process is very inefficient[8] and in practice most EPA and DHA comes from food sources. The main food providing EPA and DHA is fish, and the fish in turn obtain these omega-3 fatty acids by eating algae. Fish oil contains a mixture of EPA, DHA and other fatty acids. Highly purified EPA and DHA are now available.

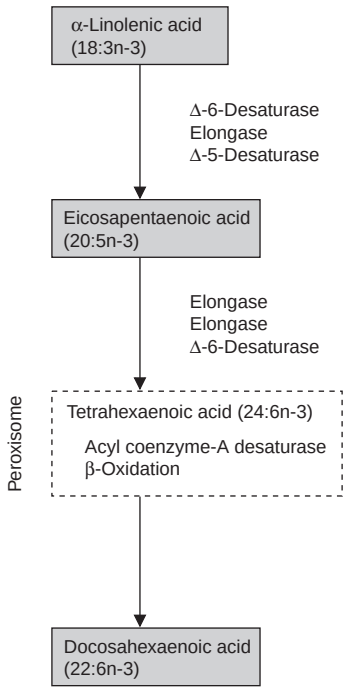

Fig. 1. Pathway for the synthesis of eicosapentaenoic acid and docosahexaenoic acid from the parent essential fatty acid, α-linolenic acid.

Omega-3 fatty acids have important effects on brain function. DHA is a major structural component of phospholipid in neuronal cell membranes.[9] Altering the lipid environment of the phospholipid bilayer leads to functional changes in the activity of receptors and other proteins embedded in the membrane phospholipid.[10] EPA is not present in neuronal cell membranes, but has other important physiological functions, including a role as precursor for eicosanoids and modulator of cytokines that have neurotransmitter and neuromodulatory activity.[10] Thus, there are many potential mechanisms whereby omega-3 fatty acids can modulate brain function.

The first suggestion that omega-3 fatty acids might be helpful for the treatment of mental disorder was made by Rudin,[11] who suggested that mental health problems were caused by omega-3 fatty acid deficiency and reported successful treatment of a number of patients with flax oil, which is a rich source of ALA. However, this work was largely ignored. The modern resurgence of interest in the therapeutic benefits of omega-3 fatty acids was the direct result of observations that levels of omega-3 fatty acids are reduced in the cell membranes of erythrocytes of patients with schizophrenia and depression.[12-14] The first studies with fish oil derivatives were carried out in schizophrenic patients, and this was closely followed by studies in patients with mood disorders. Studies in patients with depression were further supported by epidemiological evidence showing that international variations in the prevalence of depression correlated closely with fish consumption in the national diet.[15] This early finding has been supported by further studies showing fish

Table I. Omega-3 fatty acids in the treatment of schizophrenia: double-blind, placebo-controlled trials

Study	Dosage regimen	Outcome
Peet et al.[19]	Add-on; EPA 2 g/day	EPA > DHA = placebo
Peet et al.[19]	Mono; EPA 2 g/day	EPA > placebo
Peet and Horrobin[21]	Add-on; ethyl EPA 1, 2 and 4 g/day	EPA > placebo In clozapine subgroup only, 2g most effective
Emsley et al.[20]	Add-on; ethyl EPA 3 g/day	EPA > placebo for schizophrenic symptoms and also tardive dyskinesia
Berger et al.[23]	Add-on; ethyl EPA 2 g/day	EPA > placebo for dose of antipsychotic
Fenton et al.[22]	Add-on; ethyl EPA 3 g/day	EPA = placebo

Add-on = added to existing medication; **DHA** = docosahexaenoic acid; **EPA** = eicosapentaenoic acid; **mono** = monotherapy.

consumption correlates not only with rates of depression, but also with rates of bipolar disorder,[16] homicide[17] and postnatal depression.[18]

2. Schizophrenia

The first pilot study compared an EPA-enriched oil, a DHA-enriched oil and a corn oil (high omega-6) placebo formulation, added to existing antipsychotic medication for 3 months in a group of symptomatic schizophrenic patients.[19] It was found that patients on the high EPA treatment all showed clinical improvement, whereas those treated with DHA did not differ from placebo in their therapeutic response. Subsequently, all studies in schizophrenia have focussed on EPA or a mixture of EPA and DHA, with no studies using pure DHA.

A summary of all available placebo-controlled trials of EPA in schizophrenia is shown in table I. Several themes arise from these findings. First, all but one of the studies has reported benefits from EPA treatment in either the primary or the secondary statistical analysis, however, the results are not consistent across the studies. In two studies[19,20] the addition of EPA to the existing antipsychotic medication led to an overall improvement in symptoms. One of these studies[20] found improvement after 12 weeks of treatment, not only in schizophrenia symptoms but also in tardive dyskinesia, which is a movement disorder seen particularly in schizophrenic patients treated long-term with older antipsychotic drugs. A third study[21] which compared 1, 2 or 4 g/day of highly purified ethyl EPA added to existing antipsychotic medication for 12 weeks reported no overall improvement in schizophrenic symptoms at any dose. However, a marked improvement in schizophrenic symptoms resulting from treatment with 2 g/day of ethyl EPA was seen in the subgroup of patients who were receiving clozapine treatment. This differential benefit of EPA in clozapine-treated patients was not replicated by Emsley et al.,[20] though their findings may have been confounded by a strong beneficial effect of EPA on tardive dyskinesia, which is found less amongst patients treated with clozapine. A fourth study[22] found no benefit from adding 3 g/day of ethyl EPA to existing antipsychotic medication. Two studies[19,23] have suggested that EPA may have an 'antipsychotic sparing' effect in patients undergoing their first treatment for schizophrenia. In the first of these studies[19] schizophrenic patients were treated with either EPA or placebo as a monotherapy. The primary endpoint of the study was the requirement for standard antipsychotic medication. By the end of the 3-month study period all 12 patients in the placebo group required treatment with antipsychotic drugs, whereas only 6 of the 14 patients given EPA required such treatment. Despite the difference in antipsychotic drug usage, symptom ratings were significantly lower at the end of the study in the EPA group relative to the placebo group. In the second study,[23] first-episode schizophrenic patients were given ethyl EPA or placebo in addition to standard treatment with risperidone. At the end of treatment it was found that patients given ethyl EPA required significantly lower dosages of antipsychotic medication to produce the same clinical benefit, and they also experienced substantially less cognitive decline than those given placebo.

Table II. Omega-3 fatty acids in the treatment of depression: double-blind, placebo-controlled trials

Study	Dosage regimen	Outcome
Nemets et al.[24]	Add-on; EPA 2 g/day	EPA > placebo
Peet and Horrobin[25]	Add-on; EPA 1, 2 and 4 g/day	EPA 1 g/day > placebo
Su et al.[26]	Add-on; fish oil 9.6 g/day	Fish oil > placebo
Marangell et al.[27]	Mono; DHA 2 g/day	DHA = placebo
Keck et al.[29]	Add-on; EPA 6 g/day	EPA = placebo
Frangou and Lewis[30]	Add-on; EPA 1 or 2 g/day	EPA > placebo

Add-on = added to existing medication; **DHA** = docosahexaenoic acid; **EPA** = eicosapentaenoic acid; **mono** = monotherapy.

Whilst these results are encouraging, it is clear that further large-scale studies are required in order to establish the potential role for EPA in the treatment of schizophrenia. Current evidence suggests that these studies might be best focused on treatment early in the first episode, and on the possible enhancement of the efficacy of clozapine.

3. Mood Disorders

Treatment studies in depression have produced more consistent results. The available studies are summarised in table II. In three of the reported studies, EPA or fish oil was given in addition to existing antidepressant treatment to patients who were treatment nonresponders.[24-26] All three studies in unipolar depression gave strongly positive results; two using ethyl EPA[24,25] and one using fish oil.[26] In a dose-finding study using EPA 1, 2 or 4 g/day an effect was seen at a 1 g/day dosage but not at higher dosages.[25] Although this may seem counterintuitive, there is evidence that high doses of EPA, which go well beyond normal dietary intake, can have a deleterious effect on cell membrane fatty acid profiles by displacing other fatty acids.[21] In contrast with the broadly positive findings with EPA, a study using DHA monotherapy showed no therapeutic benefit.[27] This is consistent with an early pilot study in which EPA or DHA were given as monotherapy to a small number of patients with depression. The four patients treated with EPA showed an average 56% improvement on a standard depression rating scale, compared with an 18% improvement in the five patients given DHA.[28]

Two studies in bipolar depression, so far published only as abstracts, have produced conflicting findings. Keck et al.[29] reported no significant benefit from a very high daily dose of EPA (6g) added to existing treatment, whereas Frangou and Lewis[30] reported significant benefit from 1 or 2 g/day of EPA relative to placebo as an add-on treatment. There have been two studies investigating the role of omega-3 fatty acids in the prevention of mood swings for patients with bipolar disorder. The first of these studies, in which fish oil was given in addition to existing treatment with mood stabilisers, reported marked improvement over a 6-month period in patients with bipolar mood disorder.[31] Patients treated with omega-3 fatty acids had a significantly longer period of remission than the placebo group, mainly because of an effect on depression. A second study using 6 g/day of ethyl EPA as adjunctive treatment was negative.[32] Therefore, the possible efficacy of omega-3 fatty acids as mood stabilisers in bipolar disorder is unresolved.

4. Other Psychiatric Disorders

Double-blind, placebo-controlled trials on omega-3 fatty acid treatment have been conducted in borderline personality disorder, obsessive-compulsive disorder and attention-deficit hyperactivity disorder (ADHD).

In borderline personality disorder, it was reported that ethyl EPA 1 g/day was superior to placebo in diminishing aggression as well as the severity of depressive symptoms.[33] This is consistent with findings from two double-blind, placebo-controlled trials in healthy subjects, which demonstrated an anti-aggressive effect of DHA.[34,35]

Studies in ADHD have given mixed results. Two double-blind, placebo-controlled studies of DHA in the treatment of ADHD found no significant difference between the effects of DHA and placebo.[36,37]

Other studies using combinations of fish oil and evening primrose oil (containing both omega-3 and omega-6 fatty acids) have shown a significant treatment effect relative to placebo on ADHD symptoms.[38,39] A single study of adjunctive EPA in the treatment of obsessive-compulsive disorder reported no clinical benefit.[40]

Epidemiological studies have indicated that consumption of one fish meal a week is associated with a reduced risk of Alzheimer's disease,[41] although this may be confounded by educational level as better educated people eat more fish.[42] However, there are no published controlled trials of omega-3 fatty acids in the treatment of Alzheimer's disease.

5. Mode of Action

Studies of omega-3 fatty acids in mental disorders such as schizophrenia and depression were stimulated by observations that levels of omega-3 fatty acids were reduced in cell membranes of patients with these conditions. Therefore, it was postulated that supplementation of omega-3 fatty acids may be of therapeutic benefit. In the case of depression this simple relationship might still hold true. Epidemiological studies support a relationship between dietary intake of fish and national prevalence of depression.[15,43] Several, though not all, studies within populations have supported this relationship.[44-47] In depressed patients, a correlation between dietary intake of omega-3 fatty acids and severity of depression has been demonstrated.[48] In schizophrenia, the situation appears to be more complex. Some of the earlier findings of reduced cell membrane levels of both omega-3 and omega-6 fatty acids were confounded by extraneous factors including smoking, medication and storage artefact. More recent studies have given less consistent results.[49] International variations in the long-term outcome of schizophrenia (which has a better outcome in developing countries than in the Western developed world) show correlations with dietary consumption of saturated fat and sugar but not omega-3 fatty acids.[43,50] Separate studies have shown that variations in severity of symptoms within a group of schizophrenic patients correlates with dietary consumption of omega-3 fatty acids,[51] or with polyunsaturated fatty acids more generally.[52] Taken together with evidence of efficacy of EPA in the treatment of schizophrenia, this would indicate that omega-3 fatty acids are capable of modulating the severity of schizophrenia, but that dietary lack of omega-3 fatty acids does not have the same central aetiological importance as they may have in depression.

In treatment studies for both schizophrenia and depression, current evidence suggests that EPA rather than DHA is the effective agent. Whilst this statement must be qualified by the relative paucity of studies using pure DHA, it does raise questions about mode of action. Most investigators initially assumed that DHA would be the primary effective agent, because it is of such considerable structural and functional importance in the brain. If EPA is indeed the active agent, then this would indicate a more indirect effect based on the other biological actions of EPA. Thus, EPA is an eicosanoid precursor,[53] acts at the peroxisome proliferator-activated receptor[54] and (like DHA) can modulate gene expression.[55] It has been suggested that EPA is working as an inhibitor of phospholipase A_2, which is known to be elevated in patients with schizophrenia.[56] Others have suggested that omega-3 fatty acids may act as mood stabilisers by inhibiting protein kinase C, in a similar way to lithium and valproic acid, which are used as mood stabilisers.[57] It has also been suggested that schizophrenia is a proinflammatory condition, which is supported by increased risk of autoimmune disorders in first-degree relatives of schizophrenic patients, and increased levels of proinflammatory cytokines in schizophrenic patients.[58] Thus, EPA could be acting through an anti-inflammatory effect. In support of this concept a recent study has shown that celecoxib, a cyclooxygenase-2 inhibitor, is of therapeutic benefit in schizophrenia.[59] However, at the present time the true mode of action of omega-3 fatty acids is unknown.

6. Side Effects

The more common adverse effects of fish oil preparations, particularly in higher dosages, include nausea, fishy belching and looseness of the stools.[60] Because of these effects, the blinding of some of the earlier studies of fish oils in the treatment of mental health problems has been questioned.[61] These problems are much less apparent with purified ethyl ester preparations of omega-3 fatty acids. The safety of omega-3 fatty acids is evident from their acceptance by the regulatory authorities of several countries. For example, the US FDA recognises the safety of menhaden oil up to a dose of 3 g/day of EPA plus DHA,[62] the ethyl esters of EPA plus DHA are registered for prescription in the UK in doses up to 4 g/day[60] and pure ethyl EPA has been marketed in Japan in doses up to 2.7 g/day since 1990.[63]

Most of the other associated effects of omega-3 fatty acids are beneficial, particularly in relation to cardiovascular disease. This is important in a population with mental health problems; patients with both depression and schizophrenia have been shown to be at substantially increased risk of coronary artery disease.[64,65] Furthermore, some of the commonly used antipsychotic medications, such as clozapine and olanzapine, are associated with elevated plasma triglyceride levels, which are normalised during treatment with omega-3 fatty acids.[21]

Omega-3 fatty acids generally do not appear to have clinically significant effects on bleeding time,[66] but caution has been urged when using these preparations in high dosages, or for patients with pre-existing haemorrhagic disorders or those on anticoagulant treatment. There have been concerns that omega-3 fatty acid treatment might worsen glycaemic control in patients with diabetes mellitus, but this has not been substantiated in two meta-analyses.[67,68]

7. Diet, Health Supplements or Pharmaceutical Preparations?

The available evidence supporting the benefits of omega-3 fatty acids for mental health raises the question of how best to increase intake of this nutrient. Epidemiological studies in depression suggest that one or two fish meals a week might confer protection against subsequent development of depressive illness.[44] This is similar to the recommended level of fish intake for the prevention of cardiovascular disease. There are concerns about contamination of fish with dioxins, dioxin-like compounds and methyl mercury.[69] For this reason many countries have issued advice about the maximum quantities of fish that should be consumed, which in some cases includes advice about different types of fish as well as particular cautions for women who are pregnant or of childbearing potential. As this advice varies somewhat between countries, local sources should be consulted.

The evidence suggests that dosages of 1–2 g/day, particularly of EPA, are required. This level cannot be safely attained by diet alone. Fish oil preparations available from health food stores and pharmacists are of variable quality and composition, and are potentially unsafe in high dosage because of contaminants that vary between products. Pharmaceutical grade omega-3 fatty acid preparations will deliver the necessary quantity of omega-3 fatty acids within the dosages that are already prescribed for lipid and cardiovascular disorders.

8. Clinical Implications

The potential role of omega-3 fatty acids for mental health is just one aspect of a huge body of evidence suggesting abnormalities of phospholipid and fatty acid metabolism in schizophrenia.[70] The use of omega-3 fatty acids in the treatment of mental health problems is the first therapeutic approach to emerge from this body of evidence. Most research has been performed on omega-3 fatty acids in the treatment of depression and schizophrenia. These are best described as pilot studies and in most cases they have produced encouraging positive findings, although with some discrepancies. There is no longer any point in conducting further small pilot studies in mood disorders and schizophrenia. Very large, definitive randomised controlled trials similar to those required for the licensing of any new pharmacological treatment are needed.

There remains the question of whether the available information should be applied clinically in the current state of knowledge. It is well recognised that depression and schizophrenia are associated with very high rates of coronary heart disease.[64,65] It is accepted that changes in nutrition, including the consumption of one or two meals of fish per week, will significantly reduce the rate of coronary heart disease.[2] It is noteworthy that a number of other nutrients that are beneficial to cardiac health, such as folic acid,[71] also have some evidence of benefit as adjunctive treatments in depression and schizophrenia.[72,73] Therefore, it is the opinion of these reviewers that nutritional advice, including advice on consumption of fish, should form part of the holistic management of all patients with mood disorders and schizophrenia. If that advice also helps to improve the mental state, then that is an added bonus.

9. Conclusion and Recommendations

Should omega-3 fatty acids be prescribed as pharmacological agents for people with depression and schizophrenia? No omega-3 preparation is currently licensed for such indications and the clinical research evidence is preliminary and not definitive. However, it is worth noting that most treatment guidelines will include some recommendations that are based more on opinion than on conclusive evidence. It is the opinion of these reviewers that the prescription of omega-3 fatty acids is justified for depressive and schizophrenic patients who have not responded optimally to standard treatments. Many patients choose such approaches for themselves, and clinicians should at least be aware of the evidence base and be able to give sensible advice.

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