Eicosapentaenoic acid in the treatment of schizophrenia and depression: rationale and preliminary double-blind clinical trial results

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Abstract

It has been hypothesised that polyunsaturated fatty acids (PUFA) play an important role in the aetiology of schizophrenia and depression. Evidence supporting this hypothesis for schizophrenia includes abnormal brain phospholipid turnover shown by $^{31}$P Magnetic Resonance Spectroscopy, increased levels of phospholipase A$_2$, reduced niacin skin flush response, abnormal electroretinogram, and reduced cell membrane levels of n-3 and n-6 PUFA. In depression, there is strong epidemiological evidence that fish consumption reduces risk of becoming depressed and evidence that cell membrane levels of n-3 PUFA are reduced. Four out of five placebo-controlled double-blind trials of eicosapentaenoic acid (EPA) in the treatment of schizophrenia have given positive findings. In depression, two placebo-controlled trials have shown a strong therapeutic effect of ethyl-EPA added to existing medication. The mode of action of EPA is currently not known, but recent evidence suggests that arachidonic acid (AA) if of particular importance in schizophrenia and that clinical improvement in schizophrenic patients using EPA treatment correlates with changes in AA.

Keywords: Schizophrenia; Depression; Eicosapentaenoic acid; Polyunsaturated fatty acids

1. Problems with current pharmacological treatment in psychiatry

The modern era of psychopharmacology began in the 1950s with the discovery of the antipsychotic effect of chlorpromazine, and the antidepressant effects of iproniazid and amitriptyline. These discoveries were not based on any hypotheses but were derived by chance observations. Since these early observations there has been a huge expansion of research into and development of psychotropic drugs. Most of this has been funded by the major pharmaceutical companies, which are by far the biggest financial sponsors of research into treating psychiatric disorders. Most of the new research is focused on receptor and neurotransmitter pharmacology. Initially, hypotheses were developed based on the pharmacology of the drugs which were discovered by chance, and new drugs with the same pharmacology were developed. This has generally meant that the new drugs are very similar to the older ones, though sometimes with less side effects and more specificity for particular neurotransmitter receptors. It seems unlikely that further development along these lines will take us anywhere truly novel. The gold standard for efficacy of psychotropic drugs is the double-blind placebo controlled trial. The efficacy of current treatments is rather limited according to this standard [1,2]. It is well recognized that effectiveness of treatments in the real world is substantially less than efficacy shown in strictly controlled research studies [3,4]. In real life drugs are given to a much wider range of patients, which can be expected to reduce the response rate. Furthermore, a very high proportion of patients do not comply adequately with their treatment or discontinue it altogether, often because of side effects. Such considerations have led to serious questions as to whether current psychotropic drugs have any real beneficial effect on public health. Thus, there is evidence that the long-term social outcome of schizophrenia has not improved in the
decades since the introduction of antipsychotic medication [5]. In bipolar disorder, a recent authoritative review concluded that “despite modern treatments the outcome into old age is still poor, full recovery without further episodes rare, recurrence of episodes with incomplete remission the rule, and the development of chronicity and suicide still frequent” [6].

There is considerable evidence that current psychotropic drugs can have adverse as well as beneficial effects on the natural history of mental illness. The administration of drugs which have potent effects on neurotransmitters and their receptors will inevitably lead to compensatory changes in brain biochemistry [7]. Some of these changes are long-lasting and may even be associated with changes in brain anatomy [8,9]. If the drugs are then suddenly stopped, such compensatory changes will be unopposed and this may lead to an exacerbation of the illness. The most classical clinical example of this is the prolonged increase of anxiety, which often follows discontinuation of benzodiazepines [10]. Similar phenomena occur in the increased risk of manic relapse after lithium discontinuation [11], and rapid severe relapse after sudden discontinuation of clozapine [12]. Antidepressants, particularly the tricyclics have been shown to precipitate mania [13] and to cause rapid cycling of mood [14] in a substantial minority of patients. Brain biochemistry is substantially more abnormal after the prescription of psychotropic drugs, than it was in the drug free state.

It is increasingly recognized that some psychotropic drug side effects are not merely an inconvenience, but are potentially life threatening. Amongst the older drugs, classical antipsychotics given in the long-term cause tardive dyskinesia which is associated with a reduced life expectancy [15]. The older tricyclic antidepressants are seriously toxic in overdose [16], which is problematic in that they are prescribed for patients who are prone to overdose behaviour. There are concerns about the risk of sudden cardiac death at therapeutic doses, not only with the older tricyclic antidepressants [17] but also with antipsychotic drugs [18]. The newer atypical antipsychotic drugs, whilst they are less troublesome in the short term, include worrying effects such as weight gain, elevated triglycerides, and increased rates of diabetes [19]. Increased cardiovascular risk factors are a particular concern in a patient population which takes little exercise, has a poor diet and in which smoking is virtually universal [20].

The service user view of psychotropic medication echoes many of these concerns. No other area of therapeutics provokes such antagonism. If the treatments we use were experienced as effective and benign, then this level of antagonism would not occur.

There is no doubt that different approaches to the treatment of mental illness are urgently required and that new developments are unlikely to come from permutations of existing neurotransmitter and receptor approaches. New treatments will come either by chance in the same way as the original discoveries, or preferably they will be led by novel hypotheses. The phospholipid hypothesis of mental illness is gaining increasing credibility and has proved to be of substantial heuristic value in the development of apparently effective new treatments. The advantage of these treatment developments is that they are not detrimental and indeed are beneficial to general physical well being as well as to mental health.

2. Evidence supporting the phospholipid hypothesis of schizophrenia

Schizophrenia is one of the most severe mental illnesses. It is characterized by a combination of ‘positive’ symptoms such as hallucinations (e.g., hearing voices) and delusions (e.g., believing that there is a conspiracy to kill you). Together with this are the so-called ‘negative’ symptoms such as lack of drive and motivation, and loss of normal emotional responsiveness. Available drugs are more effective against positive than negative symptoms, and it is the negative symptoms that cause most of the long-term social disability. Unfortunately schizophrenia almost always follows a chronic and relapsing course.

Schizophrenia is distributed remarkably evenly throughout different races and cultures. This implies that the genetic predisposition to schizophrenia was present from the earliest times of Homo sapiens, before the races divided. It also implies that the genes have some survival value, and it has been postulated that they may be linked to essential human characteristics such as language [21] and creativity [22]. The most popular conceptual framework for the aetiology of schizophrenia at the present time is the so-called ‘stress-vulnerability’ model. This suggests that a constitutional predisposition becomes manifest as schizophrenia particularly under conditions of stress which may be either psychosocial stress or physical stress such as drug abuse. No doubt in some situations the genetic predisposition is so strong that the illness would be manifest without stressors.

Aetiological research has focused on attempting to define the genetic and physiological basis of the vulnerability to schizophrenia. The phospholipid hypothesis of schizophrenia [23] proposes that this vulnerability is related to a genetically determined abnormality of phospholipid metabolism, which can be modified by environmental factors such as nutrition. There are several strands of evidence for this, as follows:

a. $^{31}$P Magnetic Resonance Spectroscopy (MRS) studies of unmedicated schizophrenic patients have
shown decreased levels of phosphomonoesters and increased levels of phosphodiester, particularly in the frontal and temporal lobes [24–26]. These are markers of phospholipid synthesis and breakdown. These changes have also been found in unaffected first-degree relatives of schizophrenic patients [27]. In one study it is reported that increased phosphodiester correlates significantly with increased size of cerebral ventricles in the brain [28]. This increased cerebral ventricular size is one of the more consistent morphological findings in the brains of schizophrenic patients, and the correlation with increased phosphodiester suggests a common pathology. Some studies have reported significant correlations between abnormal phospholipid metabolism and schizophrenic symptoms [29,30]. It has also been reported that the decreased phosphomonoesters correlate with reduced levels of arachidonic acid (AA) in red blood cell membranes [31].

b. Increased levels of calcium independent phospholipase A_2 (PLA_2) have been shown in platelets [32], serum [33] and temporal cortex [34] of schizophrenic patients. This enzyme is involved in the breakdown of phospholipids by cleaving fatty acids from the Sn2 position. This is an important part of cell signalling, for example releasing AA, which is vital for brain cell-signalling mechanisms [35].

c. The skin flush response to niacin is much reduced in schizophrenic patients. This was originally observed using oral niacin [36]. This causes generalised flushing and lowers the blood pressure in a significant proportion of healthy subjects but is much less likely to have this effect in schizophrenic patients. A more benign form of this investigation was reported by Ward et al. [37], who applied topical niacin to the skin. There is a marked difference in the flush response between schizophrenic subjects and healthy controls which is found also in unmedicated patients [38] and in some first-degree relatives [39]. This difference in the flush response makes it one of the most robust physiological findings in schizophrenia research. The most likely mechanism for flushing in response to niacin is the release of prostaglandin D_2 [40] which is a cyclo-oxygenase metabolite of AA [41]. This implies that the metabolic pathway of AA is abnormal in schizophrenic patients. A reduced inflammatory response, which depends in part on the same pathways, is also manifested by the relative rarity of rheumatoid arthritis in schizophrenic patients [42].

d. There are several studies showing reduced levels of n-3 and n-6 PUFA in cell membranes from erythrocytes [43–45], fibroblasts [46] and brain [47] of schizophrenic patients. However, most of the studies are confounded by the possible effects of medication, smoking and other factors, so further studies are required.

e. The electroretinogram (ERG) is abnormal in schizophrenic patients. It is well recognized that depletion of n-3 polyunsaturated fatty acids (PUFA) in nonhuman primates leads to reduced amplitude of the ERG [48]. The same abnormality has been shown in schizophrenic patients, which may imply an n-3 deficiency in the retina of schizophrenic patients [49]. Retinal fatty acid levels reflect those in the brain [50]. However, this finding again was confounded by the possible effects of antipsychotic medication, so it requires replication in an unmedicated patient population.

f. Although schizophrenia is remarkably consistent in incidence in different countries, there are variations in outcome, such that developing countries have a better long-term outcome of schizophrenia than western developed countries. This finding has never been satisfactorily explained and is usually assumed to be related to cultural differences. However, an epidemiological study found that international variations in the outcome of schizophrenia, showed a strong correlation with the relative amounts of saturated and unsaturated fats in the national diet, such that eating relatively more unsaturated and less saturated fats was associated with a better outcome [51]. We have found within a group of schizophrenic patients, that those who consumed more n-3 PUFA in their normal daily diet had less severe schizophrenic symptoms [52].

3. Phospholipid abnormalities in relation to other aetiological hypotheses of schizophrenia

Overall, the evidence suggests that there is increased breakdown of phospholipid in schizophrenic patients which particularly affects arachidonic acid metabolism. It is of interest that the phospholipid hypothesis is entirely consistent with current mainstream hypotheses regarding the aetiology of schizophrenia. These current hypotheses propose a genetically determined abnormality in either neurotransmitter receptor function or neurodevelopment.

3.1. Neurotransmitters

Altering phospholipid metabolism and composition affects neurotransmitter receptor function by at least two mechanisms. Receptors are embedded in a phospholipid matrix and changing the fatty acid microenvironment leads to changes in the physical disposition and function of the neurotransmitter receptor leading to altered binding characteristics [53,54]. Secondly fatty acids and their derivatives are themselves intimately involved in cell signalling processes [35,55,56].
3.2. Neurodevelopment

The neurodevelopmental hypothesis of schizophrenia proposes that there is a genetically determined abnormality of neurodevelopment which therefore manifests itself from the foetus onwards, but which may be compounded by environmental insults such as cerebral anoxia at birth [57]. It is therefore of great significance that the polyunsaturated fatty acids, particularly docosahexaenoic acid (DHA) and AA, are essential for normal neurodevelopment [58].

4. Evidence for a role of omega-3 PUFA in depression

Unlike schizophrenia the incidence of depression varies widely between nations. Incidence of depression has increased markedly in recent decades and the age of onset is younger particularly in western countries [59]. It does appear that there is a genetic predisposition to mood disorder [60]. However, the epidemiological data strongly suggest that there is an important environmental factor which varies between nations and which has recently become more pronounced. Compelling evidence has now emerged that one of the major factors predicting variations in the prevalence of depression is the dietary intake of n-3 PUFA [61]. This evidence can be summarised as follows:

a. The national dietary intake of fish can be used as a proxy for n-3 intake. A strong positive correlation has been found between national dietary fish intake and the rate of major depression [62] and postpartum depression [63].

b. A population study in Finland showed that the likelihood of having depressive symptoms was significantly higher among infrequent fish consumers. Those who consumed much n-6 PUFA by using vegetable cooking oils had a increased rate of depression [64].

c. Plasma and red blood cell levels of n-3 fatty acids are reduced significantly in depressive patients [65,66]. This has been shown in unmedicated patients [67]. It is reported that dietary and erythrocyte n-3 levels correlate with severity of depression [65], as does the ratio of n-3 to n-6 fatty acids in erythrocyte membranes [68].

Overall, the epidemiological evidence that n-3 fatty acids in the diet are protective against depression is convincing. This closely echoes the data on heart disease. It is well recognized that there is a close association between n-3 consumption in the diet and the incidence of heart disease [69]. The striking similarity between findings in heart disease and depression is of special interest because people with an episode of major depression have a trebled risk of cardiac mortality later in life [70]. There has previously been no clear explanation for the association between depression and heart disease, but dietary deficiency of n-3 fatty acids could be a common aetiological factor. The modern epidemic of diseases including diabetes, hypertension, coronary heart disease and obesity cluster together as manifestations the ‘metabolic syndrome’ which is highly prevalent [71]. It may be that depression should be regarded as part of this cluster of diseases, since people who have a depressive episode are at increased risk of developing not only coronary heart disease but also diabetes [72] and hypertension [73].

5. Treatment of schizophrenia and depression with n-3 PUFA

The clinical and biochemical findings relating n-3 PUFA deficiency to schizophrenia and depression, invite investigation of treating these conditions with n-3 PUFA. The main PUFA in fish oil are eicosapentae-noic acid (EPA) and docosahexaenoic acid (DHA). They have very different biological functions and it is therefore important to identify whether any possible therapeutic benefit comes from the EPA or the DHA. Studies using EPA are summarised in Table 1.

5.1. Studies in schizophrenia

In an initial open label pilot study we gave concentrated fish oil to twenty patients who still had significant schizophrenic symptoms despite current antipsychotic drug treatment [52]. We found a significant improvement in schizophrenic symptomology, and a striking improvement in tardive dyskinesia, a movement disorder which can occur in untreated schizophrenic patients but which can be worsened by long term treatment with conventional antipsychotic drugs. This effect on tardive dyskinesia is of particular interest because this movement disorder appears to be a manifestation of the fundamental neuropsychological deficit in schizophrenia [74]. In a subsequent study [75], we attempted to distinguish between the possible clinical effects of EPA and DHA by comparing an EPA enriched oil, DHA enriched oil and a corn oil placebo given in addition to existing antipsychotic medication for three months. The subjects were 45 outpatients who were still significantly symptomatic despite stable antipsychotic medication, which was considered optimal by the treating psychiatrist. Improvement in the EPA group was significantly superior to that in the DHA group, and EPA was also superior to placebo on a secondary analysis based on percentage improvement. All patients treated with EPA improved, and half of them improved more than 25% on the total PANSS rating scale score.
The effect of DHA was numerically, though not significantly, worse than placebo. Two further studies used highly purified ethyl EPA. In a multi centre study in the UK [76], 115 patients were given one, two or four grams of ethyl EPA or placebo in addition to their background antipsychotic medication which was either typical antipsychotic drugs, atypical antipsychotics or clozapine. The distinction between different types of antipsychotic is important because the older ‘typical’ drugs cause extrapyramidal side-effects, the newer ‘atypical’ antipsychotics are much less likely to cause this type of side effect, and clozapine is unique because it has greater efficacy than other antipsychotic drugs for reasons which are not understood. All patients were highly symptomatic at the start of the study. Patients on a background medication of clozapine showed a clear and highly significant benefit relative to placebo from having ethyl EPA added to their treatment regime, with an average improvement of 25% in PANSS rating scale scores. Depression ratings also improved. In contrast there was a large placebo effect but no additional benefit when ethyl EPA was added to other antipsychotic agents. It was found that the 2 g dose was the most effective and that the effect decreased at the higher 4 g dosage. We measured changes in erythrocyte membrane fatty acids. There was a dose related increase in membrane levels of EPA, which indicates compliance with treatment. With the two-gram dose, not only EPA but also DHA and AA showed a significant increase in clozapine-treated patients. Multiple regression analysis across all treatment groups and background medications indicated that the rise in AA predicted clinical improvement but changes in DHA or EPA did not relate to clinical change. A further placebo controlled double blind trial of ethyl-EPA added to existing medication was carried out in the USA [77]. This study had a negative outcome. In contrast, a South African study found that 3 g daily of ethyl-EPA as an add-on treatment led to significant improvement in both schizophrenic symptoms and tardive dyskinesia over a 12 week treatment period [82].

In addition to the studies of EPA added on to existing antipsychotic medication, there are several reports of EPA used as a sole treatment in schizophrenia. In one study in India, EPA or placebo was given to 26 unmedicated schizophrenic patients [75]. Antipsychotic drugs were permitted only if this was clinically imperative. By the end of the three months study all 12 patients on placebo required treatment with antipsychotic drugs whilst in the EPA group 6 out of 14 patients were maintained on EPA alone and had a better clinical outcome. This double blind study is supported by two single case reports. Puri et al. [78] described a patient who showed marked improvement on ethyl EPA which has now been sustained for three years. In addition, they reported normalisation of membrane fatty acid levels and even an apparent reversal of cerebral ventricular dilatation. Su et al. [79] reported a patient with an acute exacerbation of schizophrenic symptoms during pregnancy who improved dramatically when treated with n-3 fatty acids as a mono-therapy.

Overall, double-blind placebo-controlled trials of EPA in schizophrenia have given positive results. However, the findings are not entirely consistent and further work is necessary to define optimal treatment conditions.

### 5.2. n-3 fatty acids in the treatment of mood disorders

There have been placebo controlled trials of both EPA and DHA in the treatment of depression. In one study, DHA or placebo was given to a group of depressive patients [80]. The DHA was slightly, though not significantly, worse than placebo. In contrast, EPA has been shown to have a strongly positive beneficial

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**Abbreviations:** d-b: double blind; Add-on: added to existing medication; Mono: monotherapy; Plac: placebo.
effect in depression. Peet and Horrobin [81] have reported a study in primary care in which 1, 2 or 4 g per day of ethyl-EPA or placebo were added to the treatment of patients who had failed to respond to initial antidepressant treatment. Patients on ethyl-EPA showed marked improvement relative to those on placebo. Again, this appeared to be dose dependent, which a 1 g dose producing the biggest improvement, but with less effect from dosages of 2 and 4 g. With the 1-g dose, 25% of patients on placebo but 69% of patients EPA showed a reduction of at least 50% in symptoms rated on a standard depression rating scale. A significant treatment effect was found on all three depression rating scales and most of the individual items within those scales. Further strongly positive findings have been reported by Nemets et al. [83] who found a highly significant beneficial effect of EPA added to existing antidepressant treatment for 3 weeks, in a placebo controlled study of unipolar depressive patients who relapsed during maintenance treatment. There is a further single-case report of a treatment-resistant severely depressed and suicidal patient who showed a marked improvement after treatment with ethyl-EPA [84]. In bipolar disorder, Stoll et al. [85] reported a placebo controlled pilot study of 30 patients who were given n-3 PUFA or olive oil in addition to their usual treatment for 4 months. Those given n-3 PUFA had significantly longer periods of remission.

Thus there is convincing evidence that EPA enhances the effect of antidepressants. Further studies are required to define whether EPA is antidepressant as a sole treatment.

6. Why EPA?

In both schizophrenia and depression, the studies indicate that DHA is, if anything, rather worse than placebo in its effects upon symptomology. Only EPA has given significant positive benefits. The results in depression appear more clear cut than those in schizophrenia, which is consistent with the epidemiological and biochemical data suggesting that depression correlates closely with dietary n-3 intake, whereas in schizophrenia there may be a more fundamental biological abnormality of phospholipid metabolism which would be more difficult to correct by simple nutritional intervention.

EPA and DHA have very different biological functions. DHA is a major structural component of neuronal membrane phospholipid, whereas there is only an extremely small amount of EPA in neural tissue. The hypothesis on which this research was based, assumed that DHA would be the more important therapeutic agent because varying levels of DHA in neuronal membranes has significant effects upon the function of neurotransmitter receptors and other proteins embedded in the phospholipid bi-layer.

It is possible that mechanisms underlying the therapeutic effect of EPA are different for schizophrenia and depression. In schizophrenia, the more recent evidence suggests that clinical improvement correlates with changes in AA, rather than EPA or DHA [76]. A central role for AA in schizophrenia has previously been postulated [86]. If EPA is working through an indirect effect on AA levels, this may explain variability of clinical trial results. This raises the possibility of attempting to treat schizophrenia with AA either alone or together with EPA. A small pilot study of AA [87] was terminated because patients appeared more activated and therefore more expressive of their positive psychotic symptoms. This needs to be further explored, particularly in patients with predominant negative symptoms.

Another relevant report is that treatment with clozapine increases apolipoprotein D (ApoD) expression in mouse brain, suggesting that ApoD may be a mediator in the mechanism of action of clozapine [88]. It was further reported that ApoD levels are decreased in serum of schizophrenic patients but substantially increased in prefrontal cortex of schizophrenic and bipolar subjects [89]. More recently, it has been reported that ApoD levels in plasma are increased by clozapine treatment [90]. This implies that increase in brain ApoD might occur as a compensatory mechanism to neuro-pathology and that clozapine enhances this response. ApoD is involved in fatty acid transport and metabolism, and specifically binds AA [91]. These findings are consistent with our clinical trial results showing that clozapine treated patients showed the best response to EPA and that this response was best predicted by changes in AA.75 In this way clozapine and EPA could have a synergistic effect.

7. Conclusion

Evidence that PUFA have a role in mental disorders including depression and schizophrenia, is substantial and increasing. Clinical trials of EPA have given positive results in seven out of eight double-blind trials (Table 1). These studies of EPA appear to have opened a new area of therapeutics for major mental disorders. The benefits of EPA in schizophrenia may depend on an indirect effect upon AA.

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