

# Schizophrenia: omega-3 fatty acid medicines

Evidence summary

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[www.nice.org.uk/guidance/esuom19](http://www.nice.org.uk/guidance/esuom19)

## Key points from the evidence

The content of this evidence summary was up-to-date in September 2013. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#), [BNF for children \(BNFc\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

## Summary

The randomised controlled trial (RCT) evidence for using omega-3 fatty acid medicines in people with schizophrenia is limited and the results are not consistent.

**Regulatory status:** off-label.

<p><b>Effectiveness</b></p> <ul style="list-style-type: none"> <li>• Inconclusive evidence from 8 placebo-controlled RCTs in people with schizophrenia.</li> <li>• 4 RCTs show some statistically significant (but possibly minimal clinical) improvement in symptoms with omega-3 fatty acids.</li> <li>• 4 RCTs show no difference between omega-3 fatty acids and placebo.</li> </ul>	<p><b>Safety</b></p> <ul style="list-style-type: none"> <li>• Summary of product characteristics cautions around moderate increase in bleeding time and use in people with non-insulin dependent diabetes with aspirin-sensitive asthma.</li> <li>• Potential changes in weight and lipid metabolism.</li> </ul>
<p><b>Patient factors</b></p> <ul style="list-style-type: none"> <li>• Well-tolerated; mild gastrointestinal symptoms (dyspepsia, nausea, diarrhoea) may occur.</li> <li>• Number of capsules to take each day could be high.</li> </ul>	<p><b>Resource implications</b></p> <ul style="list-style-type: none"> <li>• Between £41 and £71 for 28 days' treatment based on 5 capsules per day of Omacor (or generic) or 10 capsules per day of Maxepa.</li> </ul>

## Key points

There are numerous products on the UK market that contain omega-3 fatty acids. Amongst them there are 14 that have a current licence as a medicinal product. The majority of the oral formulations are indicated for use as adjuvant treatment in secondary prevention of myocardial infarction and for treatment of hypertriglyceridaemia when dietary measures are not sufficient.

Three other products with UK marketing authorisation contain named unsaturated fatty acids that belong to the group of omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid).

None is licensed for schizophrenia, so use of these products is off-label. Using omega-3 fatty acids to treat schizophrenia has been studied in 8 relevant RCTs, 7 of which were analysed in a Cochrane systematic review ([Irving et al. 2006](#), updated 2009). However, the evidence was limited because the RCTs were small (30–122 people in each trial), short term (up to 16 weeks), and often reported selective or incomplete data.

All 8 RCTs recruited people with schizophrenia diagnosed using Diagnostic and Statistical Manual of Mental Disorders 4<sup>th</sup> edition (DSM-IV), and most of the RCTs added omega-3 fatty acids to existing antipsychotic drug treatment in people with chronic schizophrenia.

The results from the RCTs were not consistent. Of the 8 RCTs, 4 reported some statistically significant improvement in symptoms, favouring omega-3 fatty acids compared with placebo ([Peet et al. 2001a](#), [Peet et al. 2001b](#), [Peet and Horrobin 2002](#) and [Emsley et al. 2002](#)). These changes in scores on rating scales may represent 'minimally improved' on the Clinical Global Impression (CGI) scale ([Levine et al. 2008](#), [Leucht et al. 2006](#)); however, this remains a subject of debate ([Irving et al. 2006](#)). The remaining 4 found no difference between omega-3 fatty acids and placebo ([Fenton et al. 2001](#), [Emsley et al. 2006](#), [Berger et al. 2007](#) and [Manteghiy et al. 2008](#)).

Safety data from the short-term RCTs suggested that omega-3 fatty acids were well tolerated. One study suggested a possible link with diarrhoea ([Fenton et al. 2001](#)) and another with possible increases in bleeding time and weight gain ([Emsley et al. 2008](#)), which are consistent with summaries of product characteristics.

The [Cochrane systematic review](#) concluded that the overall RCT evidence was not conclusive, and that the use of omega-3 fatty acids for people with schizophrenia remains experimental.

### About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

## Overview for healthcare professionals

### Regulatory status of omega-3 fatty acids

Purified omega-3 fatty acids are available as approved medicinal products or as food supplements. Food supplements are not regulated in the same way as medicines, and therefore their constituents may vary more, potentially affecting efficacy and safety.

There are numerous products on the UK market that contain omega-3 fatty acids. Amongst them there are 14 that have a current licence as a medicinal product. The majority of the oral formulations are indicated for use as adjuvant treatment in secondary prevention of myocardial infarction and for treatment of hypertriglyceridaemia when dietary measures are not sufficient.

Three other products with UK marketing authorisation contain named unsaturated fatty acids that belong to the group of omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid).

Omega-3 fatty acid medicines are not licensed for treating schizophrenia in the UK, therefore the use of approved medicinal products for this indication is off-label.

The place in therapy of omega-3 fatty acid medicines for their licensed indications is covered in several NICE clinical guidelines. These are summarised in the key therapeutic

topic publication on [omega-3 fatty acids](#), which supports the Quality, Innovation, Productivity and Prevention (QIPP) medicines use and procurement work stream.

In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using omega-3 fatty acid medicines outside their authorised indications.

## Evidence statements

- Eight relevant placebo-controlled, randomised controlled trials (RCTs) investigated using omega-3 fatty acids to treat schizophrenia ([Peet et al. 2001a](#), [Peet et al. 2001b](#), [Fenton et al. 2001](#), [Peet and Horrobin 2002](#), [Emsley et al. 2002](#), [Emsley et al. 2006](#), [Berger et al. 2007](#) and [Manteghiy et al. 2008](#)). The first 7 of these were included in a [Cochrane systematic review](#) ([Irving et al. 2006](#)); and [Manteghiy et al. \(2008\)](#) was published after the Cochrane review search cut-off date.
- The RCTs were generally of good methodological quality but were limited because they were small, short term, and presented incomplete data. Consequently, the studies could not be combined in an overall meta-analysis in the [Cochrane systematic review](#).
- The efficacy results were inconsistent. Of the 8 RCTs, 4 reported some statistically significant improvements in clinician-rated schizophrenia-specific symptom scales (the Positive and Negative Symptoms Scale [PANSS]), favouring omega-3 fatty acids compared with placebo ([Peet et al. 2001a](#), [Peet et al. 2001b](#), [Peet and Horrobin 2002](#) and [Emsley et al. 2002](#)). These changes in scores on rating scales may represent 'minimally improved' on the Clinical Global Impression (CGI) scale. ([Levine et al. 2008](#), [Leucht et al. 2006](#)); however, this remains a subject of debate ([Irving et al. 2006](#)). The remaining 4 found no difference between omega-3 fatty acids and placebo ([Fenton et al. 2001](#), [Emsley et al. 2006](#), [Berger et al. 2007](#) and [Manteghiy et al. 2008](#)). See [table 1](#) for summary details.
- The 8 RCTs provided limited safety data for using omega-3 fatty acids to treat schizophrenia for up to 16 weeks. The numbers of adverse events and withdrawal rates tended to be similar for omega-3 fatty acid and placebo groups across the trials, suggesting that omega-3 fatty acids are well tolerated.
- The [Cochrane systematic review](#) concluded that the overall RCT evidence was not conclusive, and that the use of omega-3 fatty acids for people with schizophrenia

remains experimental.

## Summary of the evidence

This section gives a brief summary of the main evidence. A more thorough analysis is given in the [Evidence review](#) section.

Eight relevant RCTs were identified that investigated using omega-3 fatty acids to treat schizophrenia; 7 of these were included in a [Cochrane systematic review](#). The quality of the reported data was often poor, and the studies were small and short term.

### Efficacy

The [Cochrane review](#) reported on 3 RCTs that measured overall mental health. Two RCTs ([Fenton et al. 2001](#) and [Berger et al. 2007](#)) showed that omega-3 fatty acids (ethyl-eicosapentaenoic acid [E-EPA] 2 or 3 g per day) did not lead to any statistically significant improvements in Clinical Global Impression scores or proportion of people achieving symptomatic response compared with placebo at 12 or 16 weeks. One RCT ([Peet et al. 2001b](#)) reported outcomes that favoured omega-3 fatty acids (EPA 2 g per day) compared with placebo at 12 weeks in people who were not receiving antipsychotics before randomisation (fewer days on antipsychotic medication). However, this study was small (n=30) and the effects of treatments were unclear because of the concurrent, additional use of antipsychotic medication part way through the trial.

The [Cochrane review](#) reported on 4 trials that measured mental state using PANSS. In [Peet et al. \(2001b\)](#) (where people were not receiving antipsychotics before randomisation), a statistically significantly higher proportion of people achieved a 25% improvement on PANSS using omega-3 fatty acids (EPA 2 g per day) compared with placebo (number needed to treat 3, 95% confidence interval 2 to 8). However, this change may represent 'minimally improved' on the Clinical Global Impression (CGI) scale ([Levine et al. 2008](#)), and remains a subject of debate ([Irving et al. 2006](#)). In people already using antipsychotic drugs ([Peet et al. 2001a](#)), this outcome was not statistically significant.

The same 2 RCTs ([Peet et al. 2001a](#) and [Peet et al. 2001b](#)) found that the average PANSS total score at the end of each 12-week study favoured omega-3 fatty acids compared with placebo, as did the RCT by [Emsley et al. \(2002\)](#). However, no statistically significant difference was found in the larger 16-week study by [Fenton et al. \(2001\)](#).

Table 1 Summary of the 8 randomised controlled trials

Study	Study duration (n=total randomised)	Placebo (n=total analysed)	Omega-3 fatty acids (n=total analysed)	Main outcome: omega-3 fatty acids compared with placebo
<a href="#">Fenton et al. (2001)</a>	16 weeks (n=90)	n=44	n=43 E-EPA 3 g/day	No significant difference for total PANSS score or CGI score <sup>a</sup>
<a href="#">Peet et al. (2001a)<sup>b</sup></a>	12 weeks (n=55)	n=14	n=15 EPA 2 g/day	Favoured EPA: % change in total PANSS score baseline to end of study (20.1% reduction with EPA compared with 10.7% reduction with placebo, p=0.05); borderline significance
<a href="#">Peet et al. (2001b)<sup>c</sup></a>	12 weeks (n=30)	n=12	n=14 EPA 2 g/day	Favoured EPA: reduction in mean total PANSS score from baseline (25.8 with EPA compared with 22.2 with placebo, p<0.02)  Favoured EPA: days needing antipsychotics (35.1 days with EPA compared with 65.3 days with placebo, p<0.02)

<u>Peet and Horrobin (2002)</u>	12 weeks (n=122)	n=31	E-EPA 1 g/day (n=29), 2 g/day (n=28) or 4 g/day (n=27)	No significant difference for total PANSS score for any EPA dose compared with placebo in people taking typical or atypical antipsychotics, or for EPA 1 g/day or 4 g/day compared with placebo in people taking clozapine  Total PANSS score favoured EPA 2 g/day over placebo in people taking clozapine (26% reduction with E-EPA compared with 6% reduction with placebo, p=0.04)
<u>Emsley et al. (2002)</u>	12 weeks (n=40)	n=20	n=20 E-EPA 3 g/day	Favoured E-EPA: mean % reduction in total PANSS score from baseline (12.6% with E-EPA compared with 3.1% with placebo, p=0.03)
<u>Emsley et al. (2006)</u>	12 weeks (n=84)	n=38	n=39 E-EPA 2 g/day	No significant difference for extrapyramidal symptom rating scale scores
<u>Berger et al. (2007)</u>	12 weeks (n=80)	n=34	n=35 E-EPA 2 g/day	No significant difference for any primary outcome measure of symptom score (assessed by BPRS, SANS, CGI-S, GAF and SOFAS)
<u>Manteghiy et al. (2008)</u>	6 weeks (n=106)	n=43	n=42 omega-3 fatty acids (EPA/ DHA) 3 g/ day	No significant difference for PANSS subscales scores

Abbreviations: BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impressions Scale; CGI-S, Clinical Global Impressions-Severity of Illness scale; DHA, docosahexaenoic acid; E-EPA, ethyl-eicosapentaenoic acid; EPA, eicosapentaenoic acid; GAF, Global Assessment of Functioning scale; n, number of participants; PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms; SOFAS, Social and Occupational Functioning Assessment Scale.

<sup>a</sup> Unclear whether severity or improvement CGI scale was used.

<sup>b</sup> This study also had a DHA arm (n=16), but only the EPA compared with placebo results are described here.

<sup>c</sup> This study has significant limitations relating to confounding.

## Safety

In the 8 RCTs, the safety of using omega-3 fatty acids in people with schizophrenia was assessed up to a maximum of 16 weeks. An open-label extension to 1 study ([Emsley et al. 2008](#)) assessed safety up to 40 weeks. This limited evidence suggests that omega-3 fatty acids are generally well tolerated in the short term.

The summaries of product characteristics for some omega-3 fatty acid medicines (for example, [Omacor](#), [Teromeg](#) and [Maxepa](#)) report cautions around the possibility of a moderate increase in bleeding time and use in people with non-insulin-dependent diabetes with aspirin-sensitive asthma. The study by [Emsley et al. \(2008\)](#) suggested that clinicians need to be aware of possible increases in bleeding time, as well as potential changes in weight and lipid metabolism, when considering omega-3 fatty acids for people with schizophrenia.

Commonly reported side effects listed in the summaries of product characteristics include dyspepsia and nausea.

## Cost effectiveness and cost

No cost-effectiveness studies of omega-3 fatty acids for use in schizophrenia were identified. The costs of omega-3 fatty acid medicines are given in the table below.

### Table 2 Costs of omega-3 fatty acid medicines

Omega-3 fatty acid medicine	Cost
<u>Omacor</u> 1000 mg capsules (comprising 460 mg E-EPA and 380 mg DHA)	£14.24 for 28 capsules <sup>a</sup> £50.84 for 100capsules <sup>b</sup>
<u>Teromeg</u> 1000 mg capsules (comprising 460 mg E-EPA and 380 mg DHA)	£11.39 for 28 capsules <sup>b</sup> £40.67 for 100 capsules <sup>b</sup>
<u>Maxepa</u> 1000 mg capsules (comprising 170 mg EPA and 115 mg DHA)	£29.28 for 200 capsules <sup>a</sup>
Abbreviations: DHA, docosahexaenoic acid; E-EPA, ethyl-eicosapentaenoic acid; EPA, eicosapentaenoic acid. <sup>a</sup> NHS electronic drug tariff, August 2013 (excluding VAT). <sup>b</sup> MIMS, August 2013 (excluding VAT).	

The dosing regimen used most frequently in the RCTs in this evidence summary was 2 g or 3 g of EPA or E-EPA per day. A dose of 2 g of E-EPA per day is approximately 4 capsules of Omacor per day. The Maudsley Prescribing Guidelines in Psychiatry (11<sup>th</sup> edition) recommends a dose of 5 capsules daily for Omacor, or 10 capsules daily for Maxepa, when treating schizophrenia. The cost of these dosing regimens for 28 days would be £71.18 for Omacor, £56.94 for Teromeg and £40.99 for Maxepa.

## Relevance to NICE guidance programmes

The use of omega-3 fatty acid medicines to treat schizophrenia is not appropriate for referral for a NICE technology appraisal because they are not licensed for this indication.

NICE has published clinical guidelines on:

- [Schizophrenia: core interventions in the treatment and management of schizophrenia in adults in primary and secondary care](#) (NICE clinical guideline 82). An [update](#) of this guideline is currently in progress and is expected to be published in February 2014.
- [Psychosis and schizophrenia: recognition and management of psychosis and schizophrenia in children and young people](#) (NICE clinical guideline 155).

NICE has also published a technology appraisal on [Aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years](#) (NICE technology appraisal guidance 213).

In addition, NICE has published information on [omega-3 fatty acids](#) for cardiovascular disease, which was identified as a key therapeutic topic to support the Quality, Innovation, Productivity and Prevention (QIPP) medicines use and procurement work stream. This publication states that several NICE clinical guidelines recommend against prescribing these supplements for the primary prevention of cardiovascular disease. This includes the NICE clinical guideline on [lipid modification](#) (currently being [updated](#)), the NICE clinical guideline on [familial hypercholesterolaemia](#) and the NICE clinical guideline on [type 2 diabetes](#) (currently being [updated](#)). The [full guideline on type 2 diabetes](#) states that fish oils as a homogeneous therapeutic concept is problematic. There is variation in the fish oil dosage used in studies, and there are financial consequences to prescribing omega-3 supplements when the evidence shows no clear benefit.

For the secondary prevention of cardiovascular disease, the NICE clinical guideline on [myocardial infarction: secondary prevention](#) (currently being [updated](#)) gives a limited role for omega-3 fatty acid supplements. However, as discussed in the NICE guideline, there were limitations with the trial evidence and further research in this area was needed. Several more recent studies have further questioned the cardiovascular benefits of fatty acid supplementation in both primary and secondary prevention.

This key therapeutic topic publication does not cover the use of omega-3 fatty acid medicines in schizophrenia and is **not formal NICE guidance**.

## Intervention and alternatives

The omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential fatty acids. There are numerous products on the UK market that contain omega-3 fatty acids. Amongst them there are 14 that have a current licence as medicinal products. The majority of the oral formulations are indicated for use as adjuvant treatment in secondary prevention of myocardial infarction and for treatment of hypertriglyceridaemia when dietary measures are not sufficient.

Three other products with UK marketing authorisation contain named unsaturated fatty acids that belong to the group of omega-3 fatty acids (EPA and DHA).

## Condition

Schizophrenia is a major psychiatric disorder, or cluster of disorders, characterised by

psychotic symptoms that alter a person's perception, thoughts, affect, and behaviour. Each person with the disorder will have a unique combination of symptoms and experiences.

Typically, there is a prodromal period often characterised by some deterioration in personal functioning. This includes memory and concentration problems, unusual behaviour and ideas, disturbed communication and affect, and social withdrawal, apathy and reduced interest in daily activities. These are sometimes called 'negative symptoms'. The prodromal period is usually followed by an acute episode marked by hallucinations, delusions, and behavioural disturbances. These are sometimes called 'positive symptoms', and are usually accompanied by agitation and distress. After resolution of the acute episode, usually after pharmacological, psychological and other interventions, symptoms diminish and often disappear for many people, although sometimes a number of negative symptoms may remain. This phase, which can last for many years, may be interrupted by recurrent acute episodes, which may need additional intervention.

## Alternative treatment options

Schizophrenia: core interventions in the treatment and management of schizophrenia in adults in primary and secondary care (NICE clinical guideline 82) recommends the following:

### Psychological interventions

- Offer cognitive behavioural therapy (CBT) to all people with schizophrenia. This can be started either during the acute phase or later, including in inpatient settings.
- Offer family intervention to all families of people with schizophrenia who live with or are in close contact with the service user. This can be started either during the acute phase or later, including in inpatient settings.

### Pharmacological interventions

- For people with newly diagnosed schizophrenia, offer oral antipsychotic medication. Provide information and discuss the benefits and side-effect profile of each drug with the service user. The choice of drug should be made by the service user and healthcare professional together, considering:

- the relative potential of individual antipsychotic drugs to cause extrapyramidal side effects (including akathisia), metabolic side effects (including weight gain) and other side effects (including unpleasant subjective experiences)
- the views of the carer if the service user agrees.
- Do not initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication).

## **Interventions for people with schizophrenia whose illness has not responded adequately to treatment**

- For people with schizophrenia whose illness has not responded adequately to pharmacological or psychological treatment:
  - review the diagnosis
  - establish that there has been adherence to antipsychotic medication, prescribed at an adequate dose and for the correct duration
  - review engagement with and use of psychological treatments and ensure that these have been offered according to this guideline. If family intervention has been undertaken suggest CBT; if CBT has been undertaken suggest family intervention for people in close contact with their families
  - consider other causes of non-response, such as comorbid substance misuse (including alcohol), the concurrent use of other prescribed medication or physical illness.
- Offer clozapine to people with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least 2 different antipsychotic drugs. At least 1 of the drugs should be a non-clozapine second-generation antipsychotic.

There is no reference to omega-3 fatty acid medicines in the NICE clinical guideline on [schizophrenia](#).

## **Evidence review: efficacy**

This evidence summary outlines the findings of a [Cochrane systematic review](#), which

included 7 randomised controlled trials (RCTs) of omega-3 fatty acids for treating schizophrenia and 1 additional RCT, which was published after the search date for this Cochrane review ([Manteghiy et al. 2008](#)).

## Cochrane review

The Cochrane systematic review on [polyunsaturated fatty acid supplementation for schizophrenia](#) was assessed as up-to-date in February 2009. It identified 8 relevant RCTs, 7 of which compared omega-3 fatty acids with placebo ([Peet et al. 2001a](#), [Peet et al. 2001b](#), [Fenton et al. 2001](#), [Peet and Horrobin 2002](#), [Emsley et al. 2002](#), [Emsley et al. 2006](#) and [Berger et al. 2007](#)). The eighth RCT investigated omega-6 fatty acids, which is not relevant to this evidence summary. These RCTs also provided the key evidence base for 4 additional evidence reviews, some of which were published more recently than the Cochrane review ([Freeman et al. 2006](#), [Ross et al. 2007](#), [Fusar-Poli and Berger 2012](#) and [Politi et al. 2013](#)).

The Cochrane review of the 7 RCTs of omega-3 fatty acids in a total of 501 people with schizophrenia provides the foundation of this evidence summary. For full descriptions of the underlying studies, see the full [Cochrane review](#) characteristics of included studies. They are summarised here.

## Study characteristics

All 7 studies were mixed sex, with the overall age range of participants 15–65 years. Overall study sample size was small. [Peet and Horrobin \(2002\)](#) had the largest sample size (n=122); the other 6 studies ranged from 30 ([Peet et al. 2001b](#)) to 90 ([Fenton et al. 2001](#)) participants.

Study duration ranged from 12 to 16 weeks, took place in a mix of hospital and community settings, and all recruited people with schizophrenia diagnosed using Diagnostic and Statistical Manual of Mental Disorders 4<sup>th</sup> edition (DSM-IV). [Fenton et al. \(2001\)](#) also included people with schizo-affective disorder.

Most participants had chronic schizophrenia and were still symptomatic after treatment with antipsychotics. [Peet et al. \(2001b\)](#) was unique in including people who were recently diagnosed and had no previous treatment with antipsychotics. [Berger et al. \(2007\)](#) randomised relatively young people (15–29 years) experiencing their first psychotic episode. All participants in [Emsley et al. \(2006\)](#) had established neuroleptic-induced

tardive dyskinesia.

Most of the studies compared omega-3 fatty acid capsules given in addition to existing antipsychotic medication with placebo capsules. They used either eicosapentaenoic acid (EPA), its ester, ethyl-eicosapentaenoic acid (E-EPA) or docosahexaenoic acid (DHA). [Peet et al. \(2001a\)](#) also investigated whether there was a difference between EPA and DHA.

[Peet et al. \(2001b\)](#) is the only trial not to use omega-3 fatty acids in addition to existing antipsychotic treatment. In this study, participants were allocated EPA or placebo as sole treatment unless it became necessary to prescribe standard antipsychotic drugs during the trial.

Omega-3 fatty acids were given as various supplements, and the specific dose varied. [Fenton et al. \(2001\)](#) compared 3 g/day E-EPA with placebo but also gave all participants an additional supplement of vitamin E. [Peet et al. \(2001a\)](#) and [Peet et al. \(2001b\)](#) compared 2 g/day EPA with placebo. [Peet and Horrobin \(2002\)](#) compared different doses (1 g/day, 2 g/day or 4 g/day) of E-EPA with placebo. [Berger et al. \(2007\)](#) and [Emsley et al. \(2006\)](#) compared a single dose of 2 g/day E-EPA with placebo, whereas [Emsley et al. \(2002\)](#) compared 3 g/day E-EPA with placebo. The omega-3 supplements used in the RCTs do not all have a licence as medicine in the UK.

The [Cochrane review](#) reported 4 main outcomes: global state, mental state, adverse events and leaving the study early. It reported that none of the studies included data on mortality, direct measures of compliance, relapse, patient and carer satisfaction, social functioning or cost of treatment.

The main symptom scales reported included:

- Clinical Global Impression (CGI) scale:
  - A 3-item clinician-rated scale that measures illness severity (CGI-S), global improvement or change (CGI-C) and therapeutic response.
  - The CGI-S is rated on a 7-point scale with severity ranging from 1 (normal) to 7 (the most severely ill patients). CGI-C ranges from 1 (very much improved) to 7 (very much worse). Therapeutic response ranges from 0 (marked improvement and no side effects) to 4 (unchanged or worse and side effects outweigh the therapeutic effects). Each component of the CGI is rated separately; there is no overall score.

- Positive and Negative Syndrome Scale (PANSS):
  - A brief clinician-rated scale used to assess mental state and severity of psychopathology. There are 30 items; each item is scored on a scale of 1 (absent) to 7 (extreme). PANSS can be divided into 3 subscales measuring severity of general psychopathology, severity of positive symptoms (PANSS-P) and severity of negative symptoms (PANSS-N). A low score indicates low levels of psychopathology.

The [Cochrane review](#) stated that allocation concealment was reported and represented a low risk of bias in all RCTs except [Emsley et al. \(2002\)](#) and [Fenton et al. \(2001\)](#) where it was not described – leading to an unclear risk of bias. Similarly, blinding was reported and represented a low risk of bias in all RCTs except [Emsley et al. \(2002\)](#), where it was not described, also leading to an unclear risk of bias.

## Efficacy – overall improvements

[Peet et al. \(2001b\)](#), [Fenton et al. \(2001\)](#) and [Berger et al. \(2007\)](#) reported data for different measures of overall mental health score, described as 'global state' in the [Cochrane review](#).

In [Peet et al. \(2001b\)](#) (where people were not receiving antipsychotics before randomisation), after a maximum follow-up period of 12 weeks, less people receiving omega-3 fatty acids (11/15) needed standard antipsychotics by the end of the trial compared with those receiving placebo (15/15), but this was not statistically significant (n=30, [risk ratio](#) (RR) 0.74; 95% confidence interval [CI] 0.54 to 1.02, p=0.067). The same study reported that the mean number of days people in the study were free of standard antipsychotics was significantly less for those randomised to receive omega-3 fatty acids compared with placebo (35.1 days [standard deviation {SD} 34.7] compared with 65.3 days [SD18.9], p<0.02). The effects of treatments were unclear because of the concurrent, additional use of antipsychotic medication part way through the trial.

In [Fenton et al. \(2001\)](#), there was no difference between omega-3 fatty acid and placebo group average CGI end point scores up to 16 weeks (n=87, mean difference 0.00; 95% CI -0.29 to 0.29).

In [Berger et al. \(2007\)](#), there was no significant difference between omega-3 fatty acids and placebo in the number of people achieving a symptomatic response by 12 weeks (n=69, RR 0.90; 95% CI 0.50 to 1.63, p=0.73).

## Efficacy – mental state

[Peet et al. \(2001a\)](#) and [Peet et al. \(2001b\)](#) both deemed an improvement of greater than 25% on the PANSS as clinically meaningful. This remains a subject of debate ([Irving et al. 2006](#)). [Levine et al. \(2008\)](#) suggest a PANSS percentage change of around 21% to 33% is equivalent to 'minimally improved' on the CGI-C scale. In [Peet et al. \(2001b\)](#) (where people were not receiving antipsychotics before randomisation), more people achieved this level of symptom improvement with omega-3 fatty acids compared with placebo (n=30, RR for not achieving 25% improvement 0.54; 95% CI 0.30 to 0.96, p=0.035, number needed to treat 3; 95% CI 2 to 29). In people already using antipsychotic drugs ([Peet et al. 2001a](#)), this outcome was not statistically significant (n=29, RR for not achieving 25% improvement 0.62; 95% CI 0.37 to 1.05, p=0.073).

In [Peet et al. \(2001b\)](#), average PANSS scores by the end of the trial were statistically significantly lower with omega-3 fatty acids compared with placebo (n=26, mean difference -12.50; 95% CI -22.38 to -2.62, p=0.013). In [Peet et al. \(2001a\)](#), this outcome was of borderline statistical significance (n=29, mean difference -10.40; 95% CI -20.35 to -0.45, p=0.041). An unrelated publication [Leucht et al. \(2006\)](#) suggested that a PANSS reduction of between 10 and 15 points is equivalent to 'minimally improved' on the CGI-C scale.

The [Cochrane review](#) also suggests that in [Emsley et al. \(2002\)](#), the percentage change in PANSS score from baseline to the end of the trial favoured omega-3 fatty acids over placebo (n=40, mean percentage change in PANNS score 12.6% [SD 12.6] with omega-3 fatty acids compared with 3.1% [SD 13.3] with placebo).

In contrast to these 3 studies favouring omega-3 fatty acids over placebo, in the slightly larger study by [Fenton et al. \(2001\)](#), there was no statistically significant difference in average PANSS scores by the end of the trial (n=87, mean difference -1.00; 95% CI -8.15 to 6.15, p=0.78).

The [Cochrane review](#) reported no efficacy outcome data from [Peet and Horrobin \(2002\)](#) or [Emsley et al. \(2006\)](#).

## Additional randomised controlled trial

A double-blind, placebo-controlled RCT by [Manteghiy et al. \(2008\)](#) included 85 adult inpatients (average age 37–39 years) with schizophrenia diagnosed using DSM-IV

(average illness duration 14–15 years). The study recruited 106 participants, but 21 people were excluded; it is not clear at what stage. Participants were randomised to risperidone (2–8 mg/day) plus placebo, or risperidone (2–8 mg/day) plus omega-3 fatty acids (3 g/day) for 6 weeks. One capsule (1 g) of omega-3 fatty acids contained 360 mg EPA and 240 mg DHA.

No statistically significant differences in PANSS (positive and negative symptoms, general psychopathology, formal thought disorder, agitation and suspiciousness) were found between the 2 groups at any time point assessed (weeks 0, 3 and 6).

## Evidence review: safety

The summary of product characteristics (SPC) for the omega-3 fatty acid medicines, Omacor and Teromeg, describe the only contraindication as hypersensitivity to the active substance, to soya or any of the capsule excipients. Moderate increases in bleeding time have been reported with high doses, therefore a special warning for use is described to make allowance for the increased bleeding time in people who are at high risk of haemorrhage and those taking anticoagulants.

The SPC for Maxepa also advises to use with caution in people with non-insulin-dependent diabetes with aspirin-sensitive asthma. This is alongside precautions to monitor people with bleeding disorders and drugs affecting coagulation.

Commonly reported side effects in the SPCs (occurring at a frequency between 1 in 10 and 1 in 100 people) include dyspepsia and nausea. Uncommon side effects (frequency between 1 in 100 and 1 in 1000 people) include gastroenteritis, hypersensitivity, dizziness, dysgeusia (distortion of taste), abdominal pain, gastrointestinal disorders, gastritis, and upper abdominal pain.

In the Cochrane review, most of the adverse event information came from the small, short-term study by Peet and Horrobin (2002) (n=122, 12-week follow-up). This reported that adverse events were rare and were not significantly different between omega-3 fatty acids and placebo. Further information from Fenton et al. (2001) (n=90, 16-week follow-up) found omega-3 fatty acids did not result in any drug-related movement disorders, but may be associated with diarrhoea.

The Cochrane review concluded that there were no differences between omega-3 fatty acids and placebo in the numbers of people leaving the studies early (n=595, 6

randomised controlled trials [RCTs], risk ratio [RR] 0.86; 95% confidence interval [CI] 0.50 to 1.48), suggesting that omega-3 fatty acids are tolerated as well as placebo in the short term.

The safety of omega-3 fatty acids was also reported in [Emsley et al. \(2008\)](#). This study reported safety outcomes for 72 people with schizophrenia who were included in the 12-week, double-blind RCT by [Emsley et al. \(2006\)](#), 47 of whom also entered a 40-week, open-label extension phase. Adverse event reporting was similar for omega-3 fatty acid (ethyl-eicosapentaenoic acid [E-EPA] 2 g/day) and placebo groups. During the 12-week blinded phase, there was a small increase in mean body mass index (BMI) and bleeding time in the omega-3 fatty acid group, but these were not statistically significantly different to the placebo group. There was a small absolute increase in mean BMI during the open-label phase of the study in people continuing to use omega-3 fatty acids, and decreases in total cholesterol and HDL-cholesterol levels.

## Evidence review: economic issues

### Cost effectiveness

No cost-effectiveness studies of omega-3 fatty acids for use in schizophrenia were identified.

### Cost

The costs of omega-3 fatty acid medicines are given in the table below.

Omega-3 fatty acid medicine	Cost
<a href="#">Omacor</a> 1000 mg capsules (comprising 460 mg E-EPA and 380 mg DHA)	£14.24 for 28 capsules <sup>a</sup> £50.84 for 100 capsules <sup>b</sup>
<a href="#">Teromeg</a> 1000 mg capsules (comprising 460 mg E-EPA and 380 mg DHA)	£11.39 for 28 capsules <sup>b</sup> £40.67 for 100 capsules <sup>b</sup>
<a href="#">Maxepa</a> 1000 mg capsules (comprising 170 mg EPA and 115 mg DHA)	£29.28 for 200 capsules <sup>a</sup>

Abbreviations: DHA, docosahexaenoic acid; E-EPA, ethyl-eicosapentaenoic acid; EPA, eicosapentaenoic acid.

<sup>a</sup>[NHS electronic drug tariff](#), August 2013 (excluding VAT).

<sup>b</sup>[MIMS](#), August 2013 (excluding VAT).

The dosing regimen used most frequently in the randomised controlled trials (RCTs) in this evidence summary was 2 g or 3 g of eicosapentaenoic acid (EPA) or ethyl-eicosapentaenoic acid (E-EPA) per day. A dose of 2 g of E-EPA per day is approximately 4 capsules of [Omacor](#) per day. The Maudsley Prescribing Guidelines in Psychiatry (11<sup>th</sup> edition) recommends a dose of 5 capsules daily for Omacor, or 10 capsules daily for Maxepa, when treating schizophrenia. The cost of these dosing regimens for 28 days would be £71.18 for Omacor, £56.94 for Teromeg and £40.99 for Maxepa.

## Current drug usage

[Prescription cost analysis for England](#) (2012) showed that there were 589,600 items of omega-3-acid ethyl esters ([Omacor](#) and generic EPA/DHA capsules) dispensed in England in 2012 at a cost of £14,258,200. In addition, 28,400 items of omega-3 marine triglycerides ([Maxepa](#) capsules and liquid) were dispensed at a cost of £770,800. It is not known for which indications these items were prescribed.

## Evidence strengths and limitations

The methodological quality of the 8 randomised controlled trials (RCTs) included in this evidence summary was good because in most of the cases, the process of randomisation, blinding and allocation concealment was described adequately.

However, overall, the evidence base for using omega-3 fatty acid medicines off-label to treat schizophrenia is limited. The studies were small. The largest study was by [Peet and Horrobin \(2002\)](#) (n=122) but some of the evidence came from studies recruiting fewer participants, including key studies ([Peet et al. 2001a](#) and [Peet et al. 2001b](#)) that included just 14 or 15 people in the analysis of the omega-3 fatty acid arm of the trial.

Data reporting in some of the larger trials was assessed by the [Cochrane review](#) as being selective or incomplete. This meant that potentially valuable information was not usable or comparable between studies.

The studies were short in duration. None assessed efficacy outcomes for longer than 16 weeks. Short-term fluctuations in schizophrenia symptoms may have biased the results of these trials. The outcomes were measured in these trials using clinician-rated symptom scales (such as Positive and Negative Syndrome Scale [PANSS] or Clinical Global Impression [CGI]), and did not include important patient-orientated outcomes, such as social functioning, ability to work, patient and carer satisfaction, or family burden.

The study that recruited people with schizophrenia who had no previous treatment with antipsychotics (Peet et al. 2001b) had very significant limitations because initiation of antipsychotic drugs was permitted, and occurred, part way through the trial in both omega-3 fatty acid and placebo treatment groups. Therefore, it is unclear whether outcome differences between the groups were related to omega-3 fatty acids or coincided with the initiation of antipsychotic drugs.

The evidence from Peet et al. (2001b) and Berger et al. (2007) is more applicable to people newly diagnosed with schizophrenia experiencing a first episode, whereas the other RCTs are more relevant to people with chronic schizophrenia.

## Summary for patients

A [summary written for patients](#) is available on the NICE website.

## References

Abbott Healthcare Products Limited (2008) [Omacor summary of product characteristics](#) [online; accessed 12 July 2013]

Amdipharm Mercury Company Limited (2012) [Teromeg 1000 mg capsules summary of product characteristics](#) [online; accessed 12 July 2013]

Berger GE, Proffitt TM, McConchie M et al. (2007) [Ethyl-eicosapentaenoic acid in first-episode psychosis: a randomized, placebo-controlled trial](#). *The Journal of Clinical Psychiatry* 68: 1867–75

Emsley R, Myburgh C, Oosthuizen P et al. (2002) [Randomized, placebo-controlled study of ethyl-eicosapentaenoic acid as supplemental treatment in schizophrenia](#). *The American Journal of Psychiatry* 159: 1596–8

Emsley R, Niehaus DJH, Koen L et al. (2006) The effects of eicosapentaenoic acid in tardive dyskinesia: a randomized, placebo-controlled trial. Schizophrenia Research 84: 112–20

Emsley R, Niehaus DJH, Oosthuizen PP et al. (2008) Safety of the omega-3 fatty acid, eicosapentaenoic acid (EPA) in psychiatric patients: results from a randomized, placebo-controlled trial. Psychiatry Research 161: 284–91

Fenton WS, Dickerson F, Boronow J et al. (2001) A placebo-controlled trial of omega-3 fatty acid (ethyl eicosapentaenoic acid) supplementation for residual symptoms and cognitive impairment in schizophrenia. The American Journal of Psychiatry 158: 2071–4

Freeman MP, Hibbeln JR, Wisner KL et al. (2006) Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. The Journal of Clinical Psychiatry 67: 1954–67

Fusar-Poli P, Berger G (2012) Eicosapentaenoic acid interventions in schizophrenia: meta-analysis of randomized, placebo-controlled studies. Journal of Clinical Psychopharmacology 32: 179–85 doi: 10.1097/JCP.0b013e318248b7bb

General Medical Council (2013) Prescribing guidance: prescribing unlicensed medicines [online; accessed 12 July 2013]

Health & Social Care Information Centre (2013) Prescription cost analysis - England, 2012 [online; accessed 12 July 2013]

Irving CB, Mumby-Croft R, Joy LA (2006) Polyunsaturated fatty acid supplementation for schizophrenia. Cochrane Database of Systematic Reviews Issue 3: CD001257 doi: 10.1002/14651858.CD001257.pub2

Leucht S, Kane JM, Etschel E et al. (2006) Linking the PANSS, BPRS, and CGI: clinical implications. Neuropsychopharmacology 31: 2318–25 doi: 10.1038/sj.npp.1301147

Levine SZ, Rabinowitz J, Engel R et al. (2008) Extrapolation between measures of symptom severity and change: an examination of the PANSS and CGI. Schizophrenia Research 98: 318–22

Manteghiy A, Shakeri MT, Koohestani L et al. (2008) Beneficial antipsychotic effects of omega-3 fatty acids add-on therapy for the pharmacological management of patients with

schizophrenia. Iranian Journal of Psychiatry and Behavioral Sciences 2: 35–40

David Taylor (Editor), Carol Paton (Co-Editor), Shitij Kapur (Co-Editor) (2012) The Maudsley Prescribing Guidelines in Psychiatry, 11th Edition. Wiley-Blackwell

National Health Service England and Wales (2013) NHS electronic drug tariff [online; accessed 5 August 2013]

National Institute for Health and Clinical Excellence (2013) Psychosis and schizophrenia: recognition and management of psychosis and schizophrenia in children and young people. NICE clinical guideline 155

National Institute for Health and Clinical Excellence (2009) Schizophrenia: core interventions in the treatment and management of schizophrenia in adults in primary and secondary care. NICE clinical guideline 82

National Institute for Health and Clinical Excellence (2011) Aripiprazole for schizophrenia in people aged 15 to 17 years. NICE technology appraisal guidance 213

National Institute for Health and Clinical Excellence (2013) Omega-3 fatty acid supplements. Key therapeutic topic 4

Peet M, Brind J, Ramchand CN et al. (2001a, 2001b) Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia. Schizophrenia Research 49: 243–51

Peet M, Horrobin DF (2002) A dose-ranging exploratory study of the effects of ethyl-eicosapentaenoate in patients with persistent schizophrenic symptoms. Journal of Psychiatric Research 36: 7–18

Politi P, Rocchetti M, Emanuele E et al. (2013) Randomized placebo-controlled trials of omega-3 polyunsaturated fatty acids in psychiatric disorders: a review of the current literature. Current Drug Discovery Technologies 10: 245–53 doi: 10.2174/1570163811310030007

Ross BM, Seguin J, Sieswerda LE (2007) Omega-3 fatty acids as treatments for mental illness: which disorder and which fatty acid? Lipids in Health and Disease 6: 21 doi: 10.1186/1476-511X-6-21

Seven Seas Ltd (2012) [Maxepa summary of product characteristics](#) [online; accessed 12 July 2013]

## Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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### Declarations of interest

No relevant interests declared.

## Appendix: Search strategy and evidence

# selection

## Search strategy

### General background, guidelines and technology assessments

- Broad internet search: Google: *allintitle: omega-3 OR omacor OR maxepa OR PUFA filetype:pdf*
- Trip Database

### MEDLINE (via Ovid)

1. exp Fatty Acids, Omega-3/ (15762)
2. ((Omega-3 or n-3) adj ("fatty acid\$" or "polyunsaturated fatty acid\$" or PUFA)).ti,ab. (9839)
3. ("eicosapentaenoic acid\$" or EPA or "ethyl-eicosapentaenoic acid\$" or E-EPA or "docosahexanoic acid\$" or DHA or "alpha-Linolenic acid\$").ti,ab. (18310)
4. (Omacor or Maxepa or "omega-3-marine triglycerides" or Lovaza or "Krill oil").ti,ab. (280)
5. 1 or 2 or 3 or 4 (29221)
6. exp Schizophrenia/ (83135)
7. schizophreni\$.ti,ab. (87663)
8. 6 or 7 (107440)
9. 5 and 8 (217)
10. limit 9 to english language (201)

### Embase (via Ovid)

1. omega-3 fatty acid/ (16332)

2. ((Omega-3 or n-3) adj ("fatty acid\$" or "polyunsaturated fatty acid\$" or PUFA)).ti,ab. (9516)
3. ("eicosapentaenoic acid\$" or EPA or "ethyl-eicosapentaenoic acid\$" or E-EPA or "docosahexanoic acid\$" or DHA or "alpha-Linolenic acid\$").ti,ab. (17809)
4. (Omacor or Maxepa or "omega-3-marine triglycerides" or Lovaza or "Krill oil").ti,ab. (221)
5. 1 or 2 or 3 or 4 (31561)
6. exp schizophrenia/ (87593)
7. schizophreni\$.ti,ab. (74762)
8. 6 or 7 (96299)
9. 5 and 8 (458)
10. limit 9 to (english language and exclude medline journals) (52)

## **Cochrane Central Register of Controlled Trials (CENTRAL)**

#1 MeSH descriptor: [Fatty Acids, Omega-3] explode all trees 1704

#2 ("Omega-3" or "n 3") next (fatty next acid\*):ti,ab,kw 1318

#3 ("Omega-3" or "n 3") next ("polyunsaturated fatty" or PUFA):ti,ab,kw 548

#4 (eicosapentaenoic next acid\*) or EPA or (ethyl-eicosapentaenoic next acid\*) or E-EPA or (docosahexanoic next acid\*) or DHA or (alpha-Linolenic next acid\*):ti,ab,kw 1748

#5 (Omacor or Maxepa or "omega-3-marine triglycerides" or Lovaza or "Krill oil"):ti,ab,kw 87

#6 #1 or #2 or #3 or #4 or #5 2964

#7 MeSH descriptor: [Schizophrenia] explode all trees 4493

#8 schizophreni\*:ti,ab,kw 8501

#9 #7 or #8 8501

#10 #6 and #9 31

## CRD HTA, DARE and EED database

1. ("omega-3" or "n 3" or PUFA) OR (eicosapentaenoic or EPA or ethyl-eicosapentaenoic or E-EPA or docosahexanoic or DHA or alpha-Linolenic ) 940
2. (Omacor or Maxepa or Lovaza or "Krill oil") 2
3. MeSH DESCRIPTOR Fatty Acids, Omega-3 EXPLODE ALL TREES 0
4. #1 OR #2 OR #3 940
5. (schizophreni\*) 817
6. MeSH DESCRIPTOR schizophrenia EXPLODE ALL TREES 428
7. #5 OR #6 817
8. #4 AND #7 25

## Grey literature and ongoing trials

- [NICE Evidence](#)
- [Health Canada – Clinical Trials Search](#)
- [metaRegister of Controlled Trials \(mRCT\)](#)
- [ClinicalTrials.gov](#)

## Manufacturers' websites

- [Seven Seas](#)
- [Abbott](#)

## Evidence selection

The literature search sought to identify the best available evidence for the use of omega-3 fatty acids for treating schizophrenia. The published literature was searched without restriction on study type. Studies investigating omega-3 fatty acids for preventing schizophrenia in people at high risk were excluded.

In the presence of at least 7 relevant randomised controlled trials (RCTs) and 4 systematic reviews, other study types were excluded. A Cochrane systematic review of RCTs on [polyunsaturated fatty acid supplementation for schizophrenia](#) was identified as the best available evidence because it identified the same 7 RCTs that were identified during this literature search, and were included in 4 other recent reviews ([Freeman et al. 2006](#), [Ross et al. 2007](#), [Fusar-Poli and Berger 2012](#) and [Politi et al. 2013](#)) identified as most relevant. The [Cochrane review](#) was also the most methodologically robust of the reviews identified. In addition, results from the RCT by [Manteghiy et al. \(2008\)](#), which was not included in the Cochrane review because it was published after its search date, were deemed relevant and also included in this evidence summary. Additional safety information from [Emsley et al. \(2008\)](#), was also included, but was not in the Cochrane review. Other sources were used for background information and context.

## About 'Evidence summaries: unlicensed or off-label medicines'

NICE evidence summaries for off-label or unlicensed medicines summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

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