TECHNICAL COMMENTARY

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Essential fatty acids

Introduction

Alternative treatments are investigated as a possible replacement for antipsychotic medication, which can be associated with severe side effects. Alternative therapies may have less debilitating side effects, and so assessing their efficacy is important. Essential fatty acids have been proposed as a potential alternative treatment. The two main EFAs are omega-3 and omega-6. They are important compounds for brain function, as they have impact on membrane receptors, ion channels and synapse function, as well as neuronal development. However, they are not made in the body and must be sourced from the diet. People with schizophrenia have shown to have lower levels of these essential compounds and their products, including omega-3 products docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), its esther, ethyl-eicosapentaenoic acid (E-EPA), omega-6 product arachidonic acid (AA), and their metabolites including prostaglandins.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, which describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found five systematic reviews that met our inclusion criteria.[3-7]

- Overall, low quality evidence is unclear of any benefit of omega-3 as an alternative to

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neuroleptic medication for people with schizophrenia. There could be some benefit of omega-3 fatty acids compared to placebo for preventing transition to psychosis for up to one-year post-treatment in those at ultra-high risk of psychosis.

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de Koning MB, Bloemen OJN, van Amelsvoort TAMJ, Becker HE, Nieman DH, van der Gaag M, Linszen DH

Early intervention in patients at ultra high risk of psychosis: benefits and risks

Acta Psychiatrica Scandinavica 2009; 119: 426-442

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Comparison	**3 months of omega-3 vs. placebo.**
Summary of evidence	**Low quality evidence (small sample, unable to assess precision, direct) suggests some benefit of omega-3 fatty acids over placebo for preventing transition to psychosis for up to one-year.**
Transition to psychosis	
1 RCT, N = 81 *End of treatment – 12 weeks* *Significant treatment effect of omega-3 over placebo, p = 0.028* Omega-3 group = 1/38 (2.6%) Placebo group = 8/38 (21.2%) There were also significant differences in changes from baseline on PANSS and GAF score, in favour of the treatment group (data not reported). *At 1 year* *Significant treatment effect of omega-3 over placebo p = 0.006* Omega-3 group = 2/41 (4.9%) Placebo group = 11/40 (27.5%)	
Risks	No side effects were observed by the end of treatment.
Consistency in results	Not applicable, 1 RCT only.
Precision in results	No confidence intervals are provided.
Directness of results	Direct comparison of omega-3 vs. placebo.

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Essential fatty acids

Irving CB, Mumby-Croft R, Joy LA

Polyunsaturated fatty acid supplementation for schizophrenia

Cochrane Database of Systematic Reviews 2006; 3: Art. No CD001257

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Comparison	**Essential fatty acid supplementation (omega-3: E-EPA or EPA, any dosage) in people with untreated schizophrenia vs. placebo.**
Summary of evidence	**Low quality evidence (small sample, imprecise, direct) is unclear for the benefit of omega-3. Results suggest some improvement in mental state and better study retention.**

Global state, mental state, study retention

Global state

Fewer patients on omega-3 required neuroleptic treatment during the trial;

1 RCT, N = 30, RR = 0.74, 95%CI 0.54 to 1.02, $p < 0.05$

Mental state

Patients supplemented with omega-3 showed greater improvements in PANSS scores;

1 RCT, N = 30, RR = 0.54, 95%CI 0.30 to 0.96, $p = 0.035$

Patients supplemented with omega-3 showed lower endpoint PANSS scores by the end of the trial;

1 RCT, N = 26, MD = -12.50, 95%CI -22.38 to -2.62, $p = 0.013$

Leaving the study early

There was increased retention in the omega-3 group;

1 RCT, N = 30, RR = 0.33, 95%CI 0.04 to 2.85, $p < 0.05$

Risks	Not reported
Consistency in results	Not applicable – one trial only.
Precision in results	Imprecise
Directness of results	Direct

Marshall M, Rathbone J

Early Intervention for psychosis

Cochrane Database of Systematic Reviews 2011; 6: Art. No.: CD004718. DOI: 10.1002/14651858.CD004718.pub3.

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Comparison	**3 months of omega-3 fatty acids (eicosapentaenoic acid 0.84g per day; docosahexaenoic acid 0.7g/day) vs. placebo.**
Summary of evidence	**Low quality evidence (small sample, imprecise, direct) suggests that omega-3 may reduce the risk of transition to psychosis for up to 12 weeks compared to placebo**
Transition to psychosis	
Reduced transition to psychosis in the omega-3 group at 12 weeks; 1 RCT, N = 76, RR = 0.13, 95%CI 0.02 to 0.95, *p* = 0.045	
Risks	None reported
Consistency in results	Not applicable, 1 RCT only.
Precision in results	Imprecise
Directness of results	Direct

Preti A, Cella M

Randomized-controlled trials in people at ultra-high risk of psychosis: A review of treatment effectiveness

Schizophrenia Research 2010; 123: 30-36

View review abstract online

Comparison	**3 months of omega-3 Polyunsaturated Fatty Acids (PUFAs) vs. placebo.**
Summary of evidence	**Low quality evidence (small sample, imprecise, direct) suggests omega-3 PUFAs may reduce the risk of transition to psychosis for up to 12 months compared to placebo.**

Transition to psychosis	
Significant large effect of reduced risk of transition to psychosis at 1 year for the omega-3 PUFAs; Omega-3, 2/41 (4.8%) transition vs. placebo, 11/40 (27.5%) transition 1 RCT, N = 81, RR = 0.177, 95%CI 0.042 to 0.750, *p* = 0.019	
Dropout rates	
1 RCT, N = 81 Drop-outs = 5 (Treatment = 3, Control = 2)	
Risks	Not reported
Consistency in results	Not applicable, 1 RCT only.
Precision in results	Imprecise
Directness of results	Direct

Ross BM, Seguin J, Sieswerda LE

Omega-3 fatty acids as treatments for mental illness: which disorder and which fatty acid?

Lipids in Health & Disease 2007; 6: 21

View review abstract online

Comparison	**Effectiveness of essential fatty acid supplementation (omega-3, omega-6, or prostaglandin) in untreated schizophrenia vs. placebo.**
Summary of evidence	**Low quality evidence (small sample, unable to assess precision, direct) is unclear as to the benefit of omega-3 as an alternative to neuroleptic medication.**
Omega-3 treatment	
One trial, N = 26 unmedicated patients, following 12 weeks of 2g/day, reported small reductions in PANSS scores. Patients were given antipsychotic medications if required during the trial, and those patients receiving omega-3 had fewer days requiring antipsychotic medication compared to placebo.	

Essential fatty acids

Risks	Not reported
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, g = grams, MD = mean difference, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = Positive and Negative Syndrome Scale, PUFAs = Polyunsaturated Fatty Acids, RR = risk ratio, vs. = versus, UHR = Ultra High Risk

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small.[8]

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect.[8]

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

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Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula.[8]

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed.[9]

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Irving CB, Mumby-Croft R, Joy LA (2006): Polyunsaturated fatty acid supplementation for schizophrenia. *Cochrane Database of Systematic Reviews*.
4. 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 & Disease* 6: 21.
5. de Koning MB, Bloemen OJN, van Amelsvoort TAMJ, Becker HE, Nieman DH, van der Gaag M*, et al.* (2009): Early intervention in patients at ultra high risk of psychosis: benefits and risks. *Acta Psychiatrica Scandinavica* 119: 426-42.
6. Preti A, Cella M (2010): Randomized-controlled trials in people at ultra high risk of psychosis: A review of treatment effectiveness. *Schizophrenia Research* 123: 30-6.
7. Marshall M, Rathbone J (2011): Early intervention for psychosis. *Cochrane Database of Systematic Reviews*: CD004718.
8. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
9. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*