TECHNICAL COMMENTARY

NeuRA Discover. Conquer. Cure.

SCHIZOPHRENIA LIBRARY

Lipids

Introduction

Lipids, as fundamental membrane constituents, make up as much as 50-60% of the human brain's weight. The main lipid compounds present in the brain are essential fatty acids (EFAs), which bind largely to glycerophospholipids (GPLs). Due to the unique chemical structure of GPLs, they have a tendency to form bilayers, and consequently cellular membranes are comprised of a phospholipid bilayer structure. The fluidity of this membrane is determined by the EFA and cholesterol content. Different membranes have different requirements for ion channels, receptor activity and neurotransmitter release and so have different EFA concentration, for example excitable membranes, such as synapses, have a particularly high concentration of EFA.

There are several types of GPL, which each have distinct EFA composition. In the adult human brain these include phosphomonoesters (PME), such as phosphatidylethanolamine (PtdEtn), phosphatidylcholine (PtdCh, also lecithin), as well as phosphatidylserine (PtdSer) and phosphatidylinositol (PI). Phosphodiester (PDE) compounds include glycerophosphatidylcholine (GPCh) and mobile phospholipids (MP). Phosphomonoesters are precursors in phospholipid membrane synthesis, while phosphodiesters are phospholipid membrane breakdown products.

The two primary essential fatty acid series are n-3 (omega-3) and n-6 (omega-6). Linoleic acid (LA, 18:2n-6) and alphalinolenic acid (α-LA, 18:3n-3) are the parent compounds of these two EFA series, and both have 18 carbon atoms. Metabolites of LA and α-LA are referred to as 'derived EFAs', and include arachidonic acid (AA, 20:5n-6), docosahexaenoic acid (DHA, 22:6n-3) or eicosapentaenoic acid (EPA, 20:5n-3) and their products (eicosanoids) such as prostaglandins, thromboxanes, prostacyclins and leukotrienes. Derived EFAs are also known as 'bioactive lipids', and regulate the structure and function of membrane receptors, ion channels and enzymes, as well as influencing synaptic plasticity, processes such as neuronal migration, and signal transduction (via second messengers) which may be disrupted in schizophrenia.

The metabolism of the LA and α-LA compounds into bioactive lipids (derived EFAs) is catalysed by the phospholipases A_2 (PLA_2), which are an enzyme superfamily defined by an ability to catalyse the hydrolysis of the middle ester bond of a GPL substrate, usually releasing a free fatty acid and a lysophospholipid. Early systems categorised PLA_2s into calcium (Ca^{2+}) -dependent and -independent subgroups, however more recent gene profiling has identified eleven subgroups of PLA_2s. PLA_2 activity is a key determinant of cell membrane composition, as well as modulating regulatory processes and second messenger pathways.

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

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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, there is a dose dependent response or if results are reasonably 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 six systematic reviews that met our inclusion criteria[3-8].

- Moderate quality evidence suggests there are reduced levels of EFAs and GPL in cellular membranes of people with schizophrenia, with most consistent results being for linoleic acid, AA and DHA.
- Moderate to low quality evidence finds a large effect of reduced DHA in first-episode patients, with no differences in lipid hydroperoxides.
- Moderate quality evidence suggests fatty acids are reduced in the red blood cell membranes of people with schizophrenia, particularly in patients treated with first generation antipsychotics.
- Moderate to low quality evidence suggests administration of omega-3 may be associated with significant improvements in symptoms, with no significant benefit from omega-6 or PGE1.
- Moderate quality evidence suggests decreased frontal PME levels in first-episode psychosis and chronic schizophrenia patients and increased frontal PDE levels in first-episode psychosis patients only. There is also decreased temporal PME and increased temporal PDE levels in first-episode psychosis patients. Chronic patients also showed increased temporal PDE levels.
- Moderate to low quality evidence suggests PLA_2 levels are increased in the frontal and temporal cortices and the putamen of people with schizophrenia.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Berger GE, Wood SJ, Pantelis C, Velakoulis D, Wellard RM, McGorry PD

Implications of lipid biology for the pathogenesis of schizophrenia

Australian & New Zealand Journal of Psychiatry 2002; 36(3): 355-366

View review abstract online

Comparison 1	**Comparison of bioactive lipid levels in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, unable to assess precision and consistency, direct) suggests reduced levels of EFAs in cellular membranes, particularly red cell membranes, in people with schizophrenia.**
Niacin flush test	
14 studies (N not reported) investigated the effect of niacin (nicotinic acid, Vitamin B3) administration on cutaneous erythema and temperature 'flush' response, mediated by prostaglandin D2; Measurement with thermo-coupled receptors showed 42.9% of schizophrenic patients showed no temperature response to niacin administration, compared to 100% flush response in controls. Similarly, a patch test of cutaneous niacin elicited no response in 70% of schizophrenic patients compared to 100% flush response in controls. These changes were associated with reduced levels of essential fatty acids (EFA) in red cell membranes of schizophrenic patients.	
EFA levels	
7 studies (N not reported) investigated the levels of EFA in cell membranes; Reduced levels of linoleic acid (LA), arachidonic acid (AA) and docosahexaenoic acid (DHA) in red cell membranes, thrombocytes and fibroblasts in people with schizophrenia. Increased EFA peroxidation products were reported in people with schizophrenia. Reduced EFA in red cell membranes were reported in a subgroup of patients with predominantly negative symptoms.	
Consistency in results‡	No measure of consistency is reported.
Precision in results§	No confidence intervals are reported.
Directness of results‖	Niacin test is an indirect investigation of EFA levels. Direct for EFA levels.
Comparison 2	**Comparison of PLA_2 levels in people with schizophrenia vs.**

	healthy controls.
Summary of evidence	**Moderate to low quality evidence (unclear sample size, unable to assess precision and consistency, direct) suggests PLA_2 levels are increased in the frontal and temporal cortices and the putamen in people with schizophrenia.**
PLA_2 levels	
18 studies (N not reported) investigated the levels of phospholipase A_2 enzyme; Overactive PLA_2 (Ca^{2+} independent) was reported in plasma, serum, and platelets in people with schizophrenia. Increased PLA_2 was reported in the magnitude of 27-29% in the temporal and prefrontal cortices; and 44% in the putamen in people with schizophrenia.	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct
Comparison 3	**Comparison of GPL levels in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, unable to assess precision, inconsistent, direct) is unclear about the alterations to GPL levels in cellular membranes in people with schizophrenia.**
GPL levels	
8 studies (N not reported) investigated the levels of GPL membrane constituent; Some evidence reported as much as a 50% increase in PtdSer levels. Reductions in PtdEtn and PtdCho were reported from both post-mortem and in vivo studies.	
Consistency in results	No measure of consistency reported, authors report the evidence to be inconsistent.
Precision in results	No confidence intervals are reported.
Directness of results	Direct
Comparison 4	**Comparison of phospholipid metabolites (measured by ^{31}P MRS) in people with schizophrenia at varying illness stages vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (medium to large samples, direct,**

	unable to assess precision, some in consistency) suggests decreased prefrontal PME levels in first-episode psychosis and chronic schizophrenia patients and increased prefrontal PDE levels in the prefrontal cortex of first-episode psychosis patients only. There is also decreased temporal PME and increased temporal PDE levels in first-episode psychosis patients. Chronic patients show no differences in temporal PME levels, and inconsistent evidence for temporal PDE levels.
PME and PDE levels	
Prefrontal PME *Chronic schizophrenia patients;* 7 of 11 studies (222/415 patients) reported decreased PME levels *Drug naive first-episode psychosis and newly diagnosed schizophrenia patients;* 3 of 3 studies (N = 78), reported decreased PME levels Prefrontal PDE *Chronic schizophrenia patients;* 3 of 10 studies (87/363 patients) reported increased PDE levels 1 of 10 studies (86/363 patients) reported decreased PDE levels *Drug naive first-episode psychosis and newly diagnosed schizophrenia patients;* 3 of 3 studies (N = 78), reported increased PDE levels Temporal PME *Chronic schizophrenia patients;* 7 studies (N = 246) reported no significant difference in PME levels *Drug naive first-episode psychosis patients;* 3 of 3 studies (N = 84), reported decreased PME levels Temporal PDE *Chronic schizophrenia patients;* 3 of 7 studies (130/246 patients) reported increased PDE levels *Drug naive first-episode psychosis patients;* 3 of 3 studies (N = 84), reported increased PDE levels	
Consistency in results	No measure of heterogeneity reported
Precision in results	No confidence intervals provided

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Directness of results	Direct comparison of lipid metabolism in schizophrenia patients and controls

Fenton WS, Hibbeln J, Knable M

Essential Fatty Acids, Lipid Membrane Abnormalities, and the Diagnosis and Treatment of Schizophrenia

Biological Psychiatry 2000; 47: 8-21

View online review abstract

Comparison	**Comparison of essential fatty acids and their metabolites in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (medium to large samples, direct, unable to assess precision or consistency) suggests EFA concentrations are altered in people with schizophrenia with most consistent results suggesting linoleic acid, arachidonic acid and docosahexaenoic acid are reduced.** **Moderate to low quality evidence (unclear sample size, appears consistent, direct, unable to assess precision) suggests PLA_2 levels are increased in people with schizophrenia.** **Low quality evidence (direct, unclear sample size, unable to assess precision or consistency) is unclear as to any differences in PGE levels or response to niacin administration.**

EFA

Linoleic acid (18:2n-6) 9/9 studies showed reduced EFA concentrations, N = 291

Arachidonic acid (AA) (20: 4n-6): 7/7 studies showed reduced EFA, N = 161

Docosahexaenoic acid (DHA) (22:6n-3): 7/8 studies show reduced EFA, N = 142

Adrenic acid (22:4n-6): 2/3 studies showed reduced EFA, N = 71

Eicosapentanoic acid (20:5n-3): 3/3 studies showed reduced EFA, N = 52

Docosapentaenoic acid (20:5n-3): 2/4 studies showed reduced EFA, N = 164

Gamma linolenic acid (18:3n-6): 2/2 studies show increased EFA, N = 54

Dihomogamma-linolenic acid (20:3n-6): 3/4 studies show increased EFA, N = 150

Docosapentaenoic acid (DPA) (22:5n-6): 1 study showed increased EFA, N = 38

Alphalinolenic acid (ALA) (18:3n-3): 1/2 study showed increased EFA, N = 22

Reduced red blood cell membrane EFA levels were reported in both drug free and treated

schizophrenia. These results were associated with altered measures of membrane dynamics and also with negative symptomatology.	
PLA_2	
Five of six assay studies reported increased PLA_2 levels in people with schizophrenia compared to both healthy controls and non-schizophrenia psychiatric patients. Two of three genetic association studies reported polymorphisms in the cytosolic PLA_2 gene on chromosome one, which were associated with schizophrenia.	
Niacin flush test	
Five of seven studies reported altered 'flushing' response in people with schizophrenia. Flushing response was absent in 24 - 80% of people with schizophrenia compared to a 100% flush response in controls following either oral or topical administration of niacin. The absence of flush response was significantly associated with reduced red blood cell membrane concentration of AA.	
PGE	
Results were inconclusive: assay validity is questioned by the review authors. Two of four studies report increased PGE_1 and PGE_2 levels in people with schizophrenia.	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct.
Comparison 2	**Comparison of phospholipid metabolite levels (measured by ^{31}P MRS) in people with schizophrenia at varying illness stages vs. healthy controls.**
Summary of evidence	**Low quality evidence (small to medium sample sizes, direct, unable to assess precision or consistency) is unclear as to any differences in phospholipid levels in people with schizophrenia.**
PME and PDE	
Two studies (N = 43) report reduced PME and increased PDE in drug naive first-episode schizophrenia patients. Four studies (N = 126) report reduced PME in medicated people with schizophrenia, with no	

difference in PDE. Two studies (N not reported) report correlations between reduced PME and negative symptom profiles, as well as WCST performance.	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct.
Comparison 3	**Effectiveness of essential fatty acid supplementation in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate to low quality evidence (RCTs, small samples, direct, unable to assess precision or consistency) suggests omega-3 may be associated with improvements in symptoms, with no benefits after omega-6 or PGE1 administration.**
Omega-3	
5 RCTs, N = 76, treatment period ranged from 6 weeks to 6 months 5/5 studies reported positive results, with significant improvement in PANSS or SAPS/SANS scores. Results were significantly associated with red blood cell membrane n-3 concentration.	
Omega-6	
4 RCTs, N = 95, treatment period ranged from 6 weeks to 8 months 3/4 studies yielded negative results, with no significant difference between treatment and control groups in tardive dyskinesia, BPRS, or CPRS scores.	
PGE1	
One small trial reported 4/7 patients had transient improvements in symptoms.	
Risks	No significant side effects were reported for any treatments, and no long-term side effects were reported.
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Fraguas D, Diaz-Caneja CM, Ayora M, Hernandez-Alvarez F, Rodriguez-Quiroga A, Recio S, Leza JC, Arango C

Oxidative stress and inflammation in first-episode psychosis: A Systematic Review and Meta-analysis

Schizophrenia Bulletin 2019; 45(4): 742-51

View review abstract online

Comparison	**Docosahexaenoic acid (DHA) and lipid hydroperoxides (LOOH/peroxides) in people with first-episode psychosis vs. controls.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized sample, inconsistent, imprecise, direct) finds a large effect of reduced DHA in first-episode patients, with no differences in lipid hydroperoxides.**
DHA and LOOH/peroxides	
A large, significant effect of lower DHA in first-episode patients; 4 studies, N = 223, *d* = -1.581, 95%CI -2.548 to -0.615, *p* = 0.032, I^2 = 89%, *p* < 0.001 *No significant differences in LOOH/peroxides* 4 studies, N = 398, *d* = 2.567, 95%CI 0.585 to 4.550, *p* = 0.223, I^2 not reported	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Haszto CS, Stanley JA, Iyengar S, Prasad KM

Regionally Distinct Alterations in Membrane Phospholipid Metabolism in Schizophrenia: A Meta-analysis of Phosphorus Magnetic Resonance Spectroscopy Studies

Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 2019; 5: 264–80

View review abstract online

Comparison	**Frontal and temporal PME and PDE levels measured by ^{1}H-MRS in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly inconsistent and precise, direct, some publication bias) finds a medium-sized decrease in PME in the frontal lobe and increased PDE in the temporal lobe of people with schizophrenia. There were no differences in frontal PDE or temporal PME levels.**
PME and PDE	
Frontal lobe *A significant, medium-sized effect of lower PME levels in the frontal regions of people with schizophrenia;* 10 studies, N = 744, *g* = -0.54, 95%CI -1.05 to -0.03, *p* = 0.0038, I^2 = 92% Authors report possible publication bias. *There were no differences in PDE levels;* 17 studies, N = 792, *g* = 0.23, 95%CI -0.06 to 0.53, *p* = 0.12, I^2 = 79% Authors report possible publication bias. Temporal lobe *A significant, medium-sized effect of increased PDE levels in the temporal regions of people with schizophrenia;* 9 studies, N = 319, *g* = 0.55, 95%CI 0.28 to 0.82, *p* < 0.0001, I^2 = 68% Authors report possible publication bias. *There were no differences in PME levels;* 8 studies, N = 270, *g* = -0.08, 95%CI -0.27 to 0.10, *p* = 0.37, I^2 = 25% No publication bias was detected.	
Consistency in results	Inconsistent, apart from temporal lobe PME.
Precision in results	Precise, apart from frontal lobe PME.
Directness of results	Direct

Hoen WP, Lijmer JG, Duran M, Wanders RJA, vanBeveren NJM, Haan L

Red blood cell polyunsaturated fatty acids measured in red blood cells

and schizophrenia: A meta-analysis

Psychiatry Research 2013; 207: 1-12

View review abstract online

Comparison	**Comparison of polyunsaturated fatty acid levels in red blood cell membranes of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, some imprecision, direct) suggests polyunsaturated fatty acids DPA, DHA, LA and AA are reduced in the red blood cell membranes of people with schizophrenia.**

Polyunsaturated fatty acids

18 studies, N = 1,216

All patients vs. controls

Significant, medium to large effect sizes show decreased levels of DPA, DHA, LA and AA in people with schizophrenia (effect sizes reflect increased fatty acids in controls);

DPA: 16 cohorts, $d = 1.14$, 95%CI 0.72 to 1.57, $p < 0.05$, $I^2 = 87.4\%$, $p < 0.001$

DHA: 18 cohorts, $d = 0.67$, 95%CI 0.26 to 1.07, $p < 0.05$, $I^2 = 90.5\%$, $p < 0.001$

LA: 16 cohorts, $d = 0.73$, 95%CI 0.35 to 1.10, $p < 0.05$, $I^2 = 86.0\%$, $p < 0.001$

AA: 19 cohorts, $d = 0.83$, 95%CI 0.48 to 1.17, $p < 0.05$, $I^2 = 87.4\%$, $p < 0.001$

Medicated patients

Significant, medium to large effect sizes show decreased levels of DPA, DHA, LA and AA in medicated people with schizophrenia (effect sizes reflect increased fatty acids in controls);

DPA: 8 cohorts, $d = 1.31$, 95%CI 0.61 to 2.02, $p < 0.05$, $I^2 = 90.4\%$, $p < 0.001$

DHA: 11 cohorts, $d = 0.65$, 95%CI 0.18 to 1.13, $p < 0.05$, $I^2 = 87.3\%$, $p < 0.001$

LA: 9 cohorts, $d = 1.30$, 95%CI 0.57 to 2.03, $p < 0.05$, $I^2 = 91.4\%$, $p < 0.001$

AA: 12 cohorts, $d = 0.78$, 95%CI 0.34 to 1.21, $p < 0.05$, $I^2 = 86.0\%$, $p < 0.001$

Medication-naïve patients

Significant, large effect sizes show decreased levels of DPA, DHA, and AA in medication-naïve people with schizophrenia (effect sizes reflect increased fatty acids in controls);

DPA: 5 cohorts, $d = 1.35$, 95%CI 0.62 to 2.05, $p < 0.05$, $I^2 = 82.2\%$, $p < 0.001$

DHA: 6 cohorts, $d = 1.25$, 95%CI 0.61 to 1.89, $p < 0.05$, $I^2 = 82.8\%$, $p < 0.001$

AA: 6 cohorts, $d = 1.52$, 95%CI 0.50 to 2.53, $p < 0.05$, $I^2 = 92.7\%$, $p < 0.001$

No significant differences in LA levels;

LA: 5 cohorts, *d* = 0.24, 95%CI -0.17 to 0.65, *p* > 0.05, I^2 = 55.4%, *p* = 0.062 Medication-free patients *No significant differences between groups;* DPA: 3 cohorts, *d* = 0.49, 95%CI -0.42 to 1.40, *p* > 0.05, I^2 = 88.2%, *p* < 0.001 DHA: 4 cohorts, *d* = -0.13, 95%CI -1.29 to 1.02, *p* > 0.05, I^2 = 94.4%, *p* < 0.001 LA: 4 cohorts, *d* = 0.38, 95%CI -0.03 to 0.79, *p* > 0.05, I^2 = 58.9%, *p* = 0.063 AA: 4 cohorts, *d* = 0.16, 95%CI -0.10 to 0.42, *p* > 0.05, I^2 = 4.2%, *p* = 0.372 Authors report that the quality of the studies was moderate.

Consistency in results	Inconsistent
Precision in results	Precise for the all patients' analysis, medicated DHA and AA analysis, medication-naïve LA, and medication-free LA.
Directness of results	Direct

Van der Kemp WJM, Klomp DWJ, Kahn RS, Luijten PR, Hulshoff Pol HE

A meta-analysis of the polyunsaturated fatty acid composition of erythrocyte membranes in schizophrenia

Schizophrenia Research 2012; 141: 153-161

View review abstract online

Comparison	**Comparison of polyunsaturated fatty acid levels in red blood cell membranes of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, precise, direct, unable to assess consistency) suggests medium to large effects of decreased polyunsaturated fatty acids in tred blood cell membranes of people with schizophrenia, particularly in patients treated with first generation antipsychotics.**
Polyunsaturated fatty acid levels	
14 studies, N = 873 All patients vs. controls *Significant, medium to large effect sizes show reduced levels of AA, DPA and DHA in people with schizophrenia;*	

AA: *d* = -0.44, 95%CI -0.63 to -0.25, *p* < 0.01 DPA: *d* = -0.90, 95%CI -1.14 to -0.63, *p* < 0.01 DHA: *d* = -0.66, 95%CI -0.82 to -0.49, *p* < 0.01 *No significant difference in levels of LA;* LA: *d* = -0.16, 95%CI -0.39 to 0.06, *p* > 0.05 <u>Medication-naïve patients</u> *Significant, large effect sizes show levels of AA, DPA and DHA were lower in untreated patients than in controls;* AA: *d* = -0.86, 95%CI -1.47 to -0.26, *p* < 0.01 DPA: *d* = -0.93, 95%CI -1.22 to -0.63, *p* < 0.01 DHA: *d* = -0.78, 95%CI -1.06 to -0.49, *p* < 0.01 *No significant difference in levels of LA or DTA;* LA: *d* = -0.06, 95%CI -0.34 to 0.23, *p* > 0.05 DTA: *d* = -0.13, 95%CI -0.52 to 0.26, *p* > 0.05 <u>First generation antipsychotic-treated people with schizophrenia</u> *Significant, medium to large effect sizes show reduced fatty acids in patients;* LA: *d* = -0.63, 95%CI -1.11 to -0.14, *p* < 0.01 AA: *d* = -0.931, 95%CI -1.29 to -0.58, *p* < 0.01 DPA: *d* = -1.06, 95%CI -1.35 to -0.76, *p* < 0.01 DHA: *d* = -0.65, 95%CI -1.13 to -0.17, *p* < 0.01 DTA: *d* = -1.29, 95%CI -1.72 to -0.85, *p* < 0.01 DGLA: *d* = -0.76, 95%CI -1.26 to -0.27, *p* < 0.01 EPA: *d* = -0.56, 95%CI -0.90 to -0.22, *p* < 0.01 <u>Second generation antipsychotic-treated people with schizophrenia</u> *Significant, medium effect size shows reduced DHA in patients;* DHA: *d* = -0.58, 95%CI -0.81 to -0.36, *p* < 0.01 *No significant difference in levels of LA, AA, or DPA;* LA: *d* = 0.10, 95%CI -0.57 to 0.77, *p* > 0.05 AA: *d* = -0.14, 95%CI -0.38 to 0.11, *p* > 0.05 DPA: *d* = -0.65, 95%CI -1.65 to 0.34, *p* > 0.05	
Consistency in results	Unable to assess
Precision in results	Mostly precise

Lipids

Directness of results	Direct

Explanation of acronyms

AA = arachidonic acid, CI = confidence interval, Ca^{2+} = calcium^{2+}, *d* = Cohen's *d* and *g* = Hedges' *g* = standardized mean differences (see below for interpretation of effect sizes), DGLA = dihomo-γ-linelenic acid, DHA = docosahexaenoic acid, DPA = docosapentanoic acid, DTA = docosatetraenoic acid, EFA = Essential Fatty Acids, EPA = eicosapentaenoic acid, GPL = glycerophospholipids, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), LA = linoleic acid, α-LA = alpha-linolenic acid, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PLA_2 = phospholipase A_2, ^{31}P-MRS = Phosphorus Magnetic Resonance Spectroscopy, PDE = Phosphodiester, PME = Phosphomonoester, PtdCh = phosphatidylcholine, PtdEtn = phosphatidylethanolamine, PtdSer = phosphatidylserine, vs. = versus

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; 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.

† Different effect measures are reported by different reviews.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomized 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 treatment effect[9].

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).

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, an 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. An RR or OR of 1.00 means there is no difference between groups. lnOR stands for logarithmic OR where an 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.

Correlation coefficients indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r^2 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 dependent 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.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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.

‡ Inconsistency refers to differing estimates of treatment 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 substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

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

§ 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, this criteria should be relaxed[10].

‖ 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 so is 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.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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. Berger GE, Wood SJ, Pantelis C, Velakoulis D, Wellard RM, McGorry PD (2002): Implications of lipid biology for the pathogenesis of schizophrenia. *Australian & New Zealand Journal of Psychiatry* 36: 355-66.
4. Fenton WS, Hibbeln J, Knable M (2000): Essential Fatty Acids, Lipid Membrane Abnormalities, and the Diagnosis and Treatment of Schizophrenia. *Biological Psychiatry* 47: 8-21.
5. van der Kemp WJM, Klomp DWJ, Kahn RS, Luijten PR, Hulshoff Pol HE (2012): A meta-analysis of the polyunsaturated fatty acid composition of erythrocyte membranes in schizophrenia. *Schizophrenia Research* 141: 153-61.
6. Hoen WP, Lijmer JG, Duran M, Wanders RJA, van Beveren NJM, de Haan L (2013): Red blood cell polyunsaturated fatty acids measured in red blood cells and schizophrenia: a meta-analysis. *Psychiatry Research* 207: 1-12.
7. Haszto CS, Stanley JA, Iyengar S, Prasad KM (2019): Regionally Distinct Alterations in Membrane Phospholipid Metabolism in Schizophrenia: A Meta-analysis of Phosphorus Magnetic Resonance Spectroscopy Studies. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* 5: 264–80.
8. Fraguas D, Diaz-Caneja CM, Rodriguez-Quiroga A, Arango C (2017): Oxidative Stress and Inflammation in Early Onset First Episode Psychosis: A Systematic Review and Meta-Analysis. *International Journal of Neuropsychopharmacology* 20: 435-44.
9. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
10. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*