TECHNICAL COMMENTARY

Lipids

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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 bipolar disorders.

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 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, only the most recent and comprehensive 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 that describes a preferred way to present a meta-analysis. Reviews were assigned a low, medium or high possibility of reporting bias* depending on how many items were checked. Reviews rated as having less than 50% of items checked have now been excluded from the library. The PRISMA flow

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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)[1]. 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 two systematic reviews that met our inclusion criteria[2, 3].

- Moderate quality evidence suggests a large effect of reduced erythrocyte docosahexaenoic acid in people with bipolar disorder, with lower quality evidence finding no differences in eicosapentaenoic acid, linolenic acid or arachidonic acid.
- High quality evidence suggests no differences in cholesterol or triglycerides comparing people with bipolar disorder with or without a history of attempted suicide.
- We found no reviews assessing levels of other lipids in people with bipolar disorder.

Bartoli F, Di Brita C, Crocamo C, Clerici M, Carra G

Lipid profile and suicide attempt in bipolar disorder: A meta-analysis of published and unpublished data

Progress in Neuro-Psychopharmacology & Biological Psychiatry 2017; 79: 90-5

View online review abstract

Comparison	**Association between lipid levels and suicide attempts in people with bipolar disorder.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) suggests no differences in cholesterol or triglycerides in people with bipolar disorder with or without suicide attempts.**
Lipids	
No significant differences between people with bipolar disorder with and without suicide attempts in; Cholesterol: 11 studies, N = 1,042, SMD = -0.10, 95%CI: -0.30 to 0.10, $p = 0.34$, $I^2 = 38\%$, $p = 0.10$ LDL-cholesterol: 5 studies, N = 256, SMD = -0.26, 95%CI -0.65 to 0.13, $p = 0.19$, $I^2 = 45\%$, $p = 0.12$ Triglycerides: 7 studies, N = 623, SMD = -0.06, 95%CI -0.31 to 0.19, $p = 0.63$, $I^2 = 37\%$, $p = 0.15$ No risk of publication bias was found.	
Consistency in results‡	Consistent
Precision in results§	Precise
Directness of results‖	Direct

McNamara RK, Welge JA

Meta-analysis of erythrocyte polyunsaturated fatty acid biostatus in bipolar disorder

Bipolar Disorders 2016; 18: 300-6

View online review abstract

Comparison	**Erythrocyte polyunsaturated fatty acids in people with bipolar disorder vs. controls**
Summary of evidence	**Moderate quality evidence (small to medium sample, consistent,**

	precise, direct) suggests a large effect of reduced erythrocyte docosahexaenoic acid in people with bipolar disorder, with no lower quality evidence finding no differences in eicosapentaenoic acid, linolenic acid or arachidonic acid.
Erythrocyte polyunsaturated fatty acids	
Significant, large effect of lower erythrocyte docosahexaenoic acid in people with bipolar disorder; 6 studies, N = 265, d = -0.98, 95%CI -1.33 to -0.63, p = 0.0008, I^2 = 0%, p = 0.4358 *No significant differences in eicosapentaenoic acid, linolenic acid or arachidonic acid;* Eicosapentaenoic acid: 6 studies, N = 265, d = -0.46, 95%CI -1.01 to 0.09, p = 0.0857, I^2 = 57%, p = 0.0385 Arachidonic acid: 6 studies, N = 265, d = -0.18, 95%CI -1.12 to 0.76, p = 0.6447, I^2 = 84%, p < 0.0001 Linolenic acid: 4 studies, N = 198, d = -0.18, 95%CI -0.82 to 0.45, p = 0.4240, I^2 = 45%, p = 0.1418	
Consistency in results	Consistent for erythrocyte docosahexaenoic acid and linolenic acid.
Precision in results	Precise for erythrocyte docosahexaenoic acid, and eicosapentaenoic acid.
Directness of results	Direct

Explanation of acronyms

CI = Confidence Interval, d = Cohen's d, standardised mean difference, I^2 = degree of heterogeneity across study results not explained by chance, N = number of participants, p = probability of obtaining that result (p < 0.05 generally regarded as significant), SMD = standardised mean difference, vs. = versus.

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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[4].

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† 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.

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) that 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[4].

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. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[5]. 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.

Correlation coefficients (eg, r) indicate the strength of association or relationship

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between variables. They are an 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 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.

‡ 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 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, these criteria should be relaxed[6].

‖ 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 that 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. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
2. Bartoli F, Di Brita C, Crocamo C, Clerici M, Carra G (2017): Lipid profile and suicide attempt in bipolar disorder: A meta-analysis of published and unpublished data. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 79: 90-5.
3. McNamara RK, Welge JA (2016): Meta-analysis of erythrocyte polyunsaturated fatty acid biostatus in bipolar disorder. *Bipolar Disorders* 18: 300-6.
4. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
5. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
6. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*.