TECHNICAL COMMENTARY

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Anti-inflammatory medications

Introduction

Growing evidence suggests that inflammatory processes may contribute to the development of mental disorders. Pro-inflammatory cytokines interleukin (IL) 4, tumor necrosis factor alpha (TNF-a), soluble IL-2 receptor (sIL-2R), IL-1b, IL-6, soluble receptor of TNF-a type 1 (STNFR1), and C-reactive protein (CRP) have been shown to be elevated in people with bipolar disorder compared to healthy controls. This suggests a potential role for anti-inflammatory agents in the treatment of bipolar disorder. These agents primarily include non-steroidal anti-inflammatory agents (e.g., aspirin, celecoxib), but also omega-3 polyunsaturated fatty acids, N-acetylcysteine (a glutemate modulator) and pioglitazone (an antidiabetic) have anti-inflammatory properties.

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, the most recent and/or comprehensive review 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[1]. Reviews reporting less than 50% of items 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 eight systematic reviews that met inclusion criteria[3-10].

- Moderate to high quality evidence suggests adjunctive omega-3 is more effective than placebo for depression, but not mania symptoms.
- Moderate to high quality evidence finds some benefit of adjunctive celecoxib over placebo for improving mania in people with bipolar disorder.

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- Moderate quality evidence finds some benefit of adjunctive N-acetylcysteine over placebo for depression, with no differences in adverse events. The finding for depression was not consistently found across reviews with slightly different included studies.
- Moderate to low quality evidence finds no benefit of adjunctive aspirin for acute depression.
- Low quality evidence is unable to determine the benefits of pioglitazone for depression.

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Bahji A, Ermacora D, Stephenson C, Hawken ER, Vazquez G

Comparative Efficacy and Tolerability of Adjunctive Pharmacotherapies for Acute Bipolar Depression: A Systematic Review and Network Meta-analysis

Canadian Journal of Psychiatry 2021; 66: 274-88

View review abstract online

Comparison	**Adjunctive aspirin vs. adjunctive placebo for depression in people with bipolar disorder.**
Summary of evidence	**Moderate to low quality evidence (small sample, imprecise, direct) finds no improvement in depression symptoms with adjunctive aspirin.**
Depression	
No differences between groups in depression symptoms; 2 studies, N = 135, RR = 1.91, 95%CI 0.79 to 4.58, $p > 0.05$, I^2 not reported	
Risks	Not reported
Consistency in results‡	Unable to assess
Precision in results§	Imprecise
Directness of results‖	Direct

Bavaresco DV, Colonetti T, Grande AJ, Colom F, Valvassori SS, Quevedo J, da Rosa MI

Efficacy of celecoxib adjunct treatment on bipolar disorder: Systematic review and meta-analysis

CNS and Neurological Disorders - Drug Targets 2019; 18: 19-28

View review abstract online

Comparison	**Adjunctive celecoxib vs. placebo.**

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Summary of evidence	**Moderate to high quality evidence (small sample, consistent, precise, direct) suggest some benefit of adjunctive celecoxib over placebo for improving mania symptoms in people with bipolar disorder.**
Mania	
A significant improvement in mania symptoms with celecoxib; 3 RCTs, N = 121, WMD = 5.54, 95%CI 3.26 to 7.82, $p < 0.001$, $I^2 = 0\%$	
Risks	Not reported
Consistency in results	Consistent
Precision in results	Authors report that the results are precise.
Directness of results	Direct

Colle R, de Larminat D, Rotenberg S, Hozer F, Hardy P, Verstuyft C, Feve B, Corruble E

Pioglitazone could induce remission in major depression: A meta-analysis

Neuropsychiatric Disease and Treatment 2016; 13: 9-16

View review abstract online

Comparison	**Pioglitazone vs. placebo.** **Note; this was the only study included in the review that included only people with bipolar disorder. Review authors rate this study as having a low risk of bias.**
Summary of evidence	**Low quality evidence (small sample, very imprecise) is unable to determine the benefits of pioglitazone for depression in people with bipolar disorder.**
Remission	
Higher rates of remission with pioglitazone, although the difference between groups was not significant; 1 RCT, N = 44, OR = 6.20, 95%CI 0.70 to 58.0, $p < 0.05$ Pioglitazone 15mg/d for 1 week, then 30mg/d for 5 weeks: 5/22 (23%)	

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Placebo: 1/22 (4%) When this study's results were pooled with results of 3 studies of people with major depression, there was a significant difference between groups, favouring pioglitazone.	
Risks	No differences in adverse events.
Consistency in results	Not applicable; 1 RCT
Precision in results	Imprecise
Directness of results	Direct

Kishi T, Miyake N, Okuya M, Sakuma K, Iwata N

N-acetylcysteine as an adjunctive treatment for bipolar depression and major depressive disorder: a systematic review and meta-analysis of double-blind, randomized placebo-controlled trials

Psychopharmacology 2020; 237: 3481-7

View review abstract online

Comparison	**Adjunctive N-acetylcysteine vs. placebo.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, inconsistent, precise, direct) finds no differences in depression symptoms between N-acetylcysteine and placebo.**
Depression	
There were no significant differences between groups; 5 studies, N = 305, SMD = -0.08, 95%CI -0.50 to 0.34, p = 0.72, I^2 = 68%	
Risks	No differences in adverse events.
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Nery FG, Li W, DelBello MP, Welge JA

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N-acetylcysteine as an adjunctive treatment for bipolar depression: A systematic review and meta-analysis of randomized controlled trials

Bipolar Disorders 2020; doi: 10.1111/bdi.13039

View review abstract online

Comparison	**Adjunctive N-acetylcysteine vs. placebo.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, some inconsistency, precise, direct) finds a medium-sized improvement in depression symptoms with N-acetylcysteine compared to placebo. Most studies reported no differences in adverse events.**
Depression	
A significant, medium-sized improvement in depression symptoms with N-acetylcysteine; 6 RCTs, N = 248, d = 0.45, 95%CI 0.06 to 0.84, $p < 0.05$, $I^2 = 49\%$ Meta-regression found no moderating effects of baseline depressive symptom scores, dose, or duration of study.	
Risks	5/6 studies found no differences in adverse events.
Consistency in results	Some inconsistency
Precision in results	Precise
Directness of results	Direct

Rosenblat JD, Kakar R, Berk M, Kessing LV, Vinberg M, Baune BT, Mansur RB, Brietzke E, Goldstein BI, McIntyre RS

Anti-inflammatory agents in the treatment of bipolar depression: a systematic review and meta-analysis

Bipolar Disorders 2016; 18: 89-101

View review abstract online

Comparison	**Adjunctive anti-inflammatory medications (nonsteroidal anti-inflammatory drugs, omega-3 polyunsaturated fatty acids, N-acetylcysteine, and pioglitazone) vs. adjunctive placebo.** **Authors report high risk of bias in 5/8 of the included studies.**

Anti-inflammatory medications

Summary of evidence	**Moderate quality evidence (medium-sized sample, consistent, precise, indirect) suggest a medium-sized benefit of adjunctive anti-inflammatory medications for bipolar depression.**
Depression	
A small to medium-sized, significant effect of improved depression with anti-inflammatory agents; 8 RCTs, N = 312, *d* = -0.40, 95%CI -0.14 to -0.65, *p* = 0.002, I^2 = 14%, *p* = 0.32	
Risks	No manic/hypomanic induction or significant treatment-emergent adverse events were reported.
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Indirect; mixed anti-inflammatory medications.

Sarris J, Mischoulon D, Schweitzer I

Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression

Journal of Clinical Psychiatry 2012; 73: 81-6

View review abstract online

Comparison	**4-16 weeks of adjunctive omega-3 vs. adjunctive placebo in people bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (consistent, precise, direct, medium-sized samples) suggests adjunctive omega-3 is more effective than placebo for depression, but not mania symptoms.**
Mental state	
A significant, small effect of greater improvement with omega-3 than placebo for depression, but not mania symptoms; Depression: 5 RCTs, N = 291, SMD = 0.338, 95%CI 0.035 to 0.641, *p* = 0.029, I^2 = 30%, *p* = 0.213 Mania: 5 RCTs, N = 291, SMD = 0.198, 95%CI -0.037 to 0.433, *p* = 0.099, I^2 = 0%, *p* = 0.98 Meta-regression revealed studies with smaller samples and/or higher quality had larger effect sizes in the depression analysis. Funnel plot symmetry suggested no likelihood of publication bias.	

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Risks	Not reported
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Zheng W, Zhang QE, Cai DB, Yang XH, Qiu Y, Ungvari GS, Ng CH, Berk M, Ning YP, Xiang YT

N-acetylcysteine for major mental disorders: a systematic review and meta-analysis of randomized controlled trials

Acta Psychiatrica Scandinavica 2018; 137: 391-400

View review abstract online

Comparison	**Adjunctive N-acetylcysteine vs. control (various).**
Summary of evidence	**Low quality evidence (small sample, inconsistent, imprecise, indirect) finds no differences in depression of mania symptoms.**
Depression and mania symptoms	
No significant differences in depression symptoms; 2 RCTs, N = 124, SMD = -0.59, 95%CI -1.48 to 0.30, p = 0.19, I^2 = 83% *No significant differences in mania symptoms;* 1 RCT, N = 74, SMD = -0.38, 95%CI -0.84 to 0.08, p = 0.11	
Risks	Authors report that discontinuation rates were similar between N-acetylcysteine and control.
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Indirect; mixed control conditions

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Explanation of acronyms

CI = confidence interval, *d* = Cohen's d; standardised mean difference, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RR = risk ratio, SMD = standardized mean difference, vs. = versus, WMD = weighted mean difference

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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[11].

† 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).

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. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[11].

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[12]. 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[11];

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

§ 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[13].

‖ 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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