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Review Article

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

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Objective: Inflammation has been implicated in the risk, pathophysiology, and progression of mood disorders and, as such, has become a target of interest in the treatment of bipolar disorder (BD). Therefore, the objective of the current qualitative and quantitative review was to determine the overall antidepressant effect of adjunctive anti-inflammatory agents in the treatment of bipolar depression.

Methods: Completed and ongoing clinical trials of anti-inflammatory agents for BD published prior to 15 May 15 2015 were identified through searching the PubMed, Embase, PsychINFO, and Clinicaltrials.gov databases. Data from randomized controlled trials (RCTs) assessing the antidepressant effect of adjunctive mechanistically diverse anti-inflammatory agents were pooled to determine standard mean differences (SMDs) compared with standard therapy alone.

Results: Ten RCTs were identified for qualitative review. Eight RCTs (n = 312) assessing adjunctive nonsteroidal anti-inflammatory drugs (n = 53), omega-3 polyunsaturated fatty acids (n = 140), *N*-acetylcysteine (n = 76), and pioglitazone (n = 44) in the treatment of BD met the inclusion criteria for quantitative analysis. The overall effect size of adjunctive anti-inflammatory agents on depressive symptoms was −0.40 (95% confidence interval −0.14 to −0.65, p = 0.002), indicative of a moderate and statistically significant antidepressant effect. The heterogeneity of the pooled sample was low (I^2 = 14%, p = 0.32). No manic/hypomanic induction or significant treatment-emergent adverse events were reported.

Conclusions: Overall, a moderate antidepressant effect was observed for adjunctive anti-inflammatory agents compared with conventional therapy alone in the treatment of bipolar depression. The small number of studies, diversity of agents, and small sample sizes limited interpretation of the current analysis.

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Bipolar disorder (BD) is a chronic illness associated with high levels of morbidity and mortality (1, 2). Current psychopharmacological therapies are often insufficient, yielding high rates of treatment resistance with recurrent and persistent depressive episodes (3). Further, current treatments are often poorly tolerated, with clinically substantive side effects including, but not limited to, weight gain,

osteoporosis, insulin resistance, and cardiovascular toxicity (4–6). Therefore, there is an urgent need to elucidate novel targets that may yield improved efficacy, tolerability, and, possibly, disease-modifying effects.

The innate immune system has been proposed as a novel target in the treatment of BD (7, 8). Since Horrobin's initial hypothesis that immunity plays a role in the effects of lithium in BD (9), disparate lines of empirical evidence implicate peripheral and central immune dysfunction in the pathophysiology and phenomenology of BD (7, 10). For example, serum levels of the proinflammatory cytokines interleukin (IL) 4, tumor necrosis factor alpha (TNF-α), soluble IL-2 receptor (sIL-2R), IL-1β, IL-6, soluble receptor of TNF-α type 1 (STNFR1), and C-reactive protein (CRP) have been consistently shown to be elevated in subjects with BD compared with healthy controls (11–13). While there is some variability in cytokine levels during depressive, manic, and euthymic periods, accumulating evidence indicates that peripheral cytokine abnormalities are persistent, suggesting that BD is associated with a chronic low-grade inflammatory state (11, 12, 14–19). Several biologically plausible mechanisms have been proposed to explain the interaction between inflammation and mood disorders, and are reviewed extensively elsewhere (7, 10, 20, 21).

Anti-inflammatory agents have been increasingly investigated as novel treatments of mood disorders (7). Anti-inflammatory agents have been most extensively investigated in major depressive disorder (MDD); in a recent meta-analysis, 14 trials (n = 6262) investigating the antidepressant effects of cytokine inhibitors and adjuvant nonsteroidal anti-inflammatory drugs (NSAIDs) were identified (22). Pooling of effect sizes revealed a moderate antidepressant effect of these agents [standard mean difference (SMD) = −0.34, 95% confidence interval (CI): −0.57 to −0.11], with no significant increase in adverse events (22). Of note, this meta-analysis did not include omega-3 polyunsaturated fatty acids (omega-3s), naturally occurring agents with some anti-inflammatory properties. Omega-3s have been extensively investigated for their antidepressant effects, yielding mixed results (23, 24). Further, aspirin, one of the oldest agents in medicine, was highlighted in a recent review as a potential new therapy for a range of neuropsychiatric disorders owing to its anti-inflammatory effects and ability to reduce oxidative stress (25).

While many more studies have been conducted in the MDD populations, several studies have now evaluated the antidepressant effects of adjunctive anti-inflammatory agents in the treatment of BD. A recent systematic review evaluated qualitatively the effects of *N*-acetylcysteine (NAC), NSAIDs, and omega-3s in BD (26); however, the overall antidepressant effect size of anti-inflammatory agents in BD has yet to be quantified. Therefore, the primary objective of the current review was systematically [in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)], qualitatively and quantitatively to evaluate the antidepressant effects of anti-inflammatory agents in BD. In addition, the current review aimed systematically to evaluate the quality of the included trials in accordance with the recommendations in the *Cochrane Handbook for Systematic Review of Interventions*. Of note, however, the current analysis was not registered with or approved by the *Cochrane Collaboration*. Ongoing clinical trials evaluating anti-inflammatory agents in BD were also reviewed.

Methods

Search methods for identification of trials

PubMed, PsycInfo, Cochrane, and Embase databases were searched from inception to 15 May 15 2015. The PubMed search was limited to human studies, including clinical trials, observational studies, meta-analyses, and review articles, written in the English language, using the following search string: (bipolar depression *or* bipolar disorder *or* BD) *and* [inflammation *or* immune dysfunction *or* anti-inflammatory *or* celecoxib *or* nonsteroidal anti-inflammatory drugs *or* NSAIDs *or* NAC *or* *N*-acetylcysteine *or* omega-3 polyunsaturated fatty acids *or* pioglitazone *or* infliximab *or* TNF *or* interleukin *or* minocycline or cytokine]. Various combinations of the following search terms were used to search for additional articles in all four databases: bipolar disorder (BD), bipolar depression, inflammation, cytokines, interleukin, anti-inflammatory, infliximab, pioglitazone, aspirin, statin, minocycline, celecoxib, novel treatment, antidepressant, NAC, NSAID, omega-3, creatine, and clinical trial. Reference lists from identified articles were searched manually for additional relevant studies. All identified articles were screened by two independent reviewers (JR and RK) for inclusion in qualitative and quantitative analysis. Where there was disagreement on inclusion, consensus was reached through discussion.

Inclusion criteria

Inclusion criteria were: (i) human studies with participants over the age of 18 years (no upper limit) with a diagnosis of bipolar I disorder (BD-I), bipolar II disorder (BD-II), or bipolar disorder not otherwise specified, as defined by diagnostic and statistical manual or International Classification of Disease criteria (no restrictions on edition used) in any phase of illness except for acute mania; (ii) randomized controlled trials of adjunctive anti-inflammatory agents (e.g., conventional therapy plus adjunctive anti-inflammatory agent) compared with adjunctive placebo (e.g., conventional therapy plus adjunctive placebo); (iii) depression severity assessed and reported using standardized and validated scales; and (iv) data were provided to allow for the calculation of effect size – namely, change in depression scores from baseline to primary endpoint for both treatment and placebo control groups. Where data were not provided, authors were contacted to obtain necessary data. If the authors could not provide the necessary data, the trial was excluded from the quantitative analysis.

Exclusion criteria

Exclusion criteria were: (i) unpublished data, conference abstracts, open-label trials, and observational studies (only included in qualitative review); (ii) studies including placebo control subjects using anti-inflammatory treatments during and/or leading up to the clinical trial without a washout period; (iii) Multiple reports from the same data set (e.g., only original studies were included, to prevent the overweighting of one data set); and (iv) studies including a mixed sample composition, with enrollment not delimited to BD.

Data extraction and statistical analysis

Using a standardized data extraction spreadsheet, data were extracted from included studies by two independent reviewers (JR and RK) systematically to evaluate study characteristics, risks of bias, and depression severity scores required for calculation of effect size. Changes in depression severity scores of adjunctive anti-inflammatory treatment versus conventional therapy alone were used in the analysis. Where mean change and/or standard deviation values were not reported, these were calculated based on reported CIs or p-values.

The prespecified primary outcome was the pooled effect size of change in depression severity of adjunctive anti-inflammatory agents compared with adjunctive placebo (e.g., conventional therapy plus adjunctive placebo) in BD. A prespecified p-value of 0.05 was set to determine the presence of a statistically significant reduction in depression severity. The clinical significance of the reduction in depression severity was determined by the magnitude of Cohen's *d* effect size, as described below. Of note, pooling of response and remission rates was not possible with the current analysis, given the lack of available data from identified articles. As a secondary outcome, subgrouping of studies based on specific agent or class of agents was conducted to evaluate the pooled effect size of each anti-inflammatory agent alone.

Pooling of effect sizes and tests of heterogeneity were conducted using Review Manager 5.3 software. Effect sizes, using Cohen's *d* effect size, where 0.2 = small, 0.5 = medium, and 0.8 = large, were calculated using continuous variables to determine the SMD of change in depression scores for placebo-controlled trials. A random effects model was used. Samples were not subgrouped into responders and nonresponders as an insufficient number of studies reported responder subgrouped analysis.

Pooled effect sizes (SMD) were subgrouped based on the anti-inflammatory agent tested and then pooled to calculate the overall effect size of all anti-inflammatory agents included. Critical values for pooled effect sizes were set at 0.05. Homogeneity in effect sizes was tested using the *Q*-statistic (χ^2) for each agent. Heterogeneity was quantified using the I^2 statistic, where 25% = small, 50% = moderate, and 75% = high heterogeneity (27).

Assessment of bias

The risk of bias was assessed for all clinical trials included in the quantitative analysis. As per recommendations in the *Cochrane Handbook for Systematic Review of Interventions*, bias was assessed based on the following six domains: sequence generation (e.g., based on the description of randomization), allocation concealment, blinding of outcome assessors, intent-to-treat, for-profit bias, and adverse events bias. Risk of bias was designated to be high if described protocols were concerning for bias in a given domain or if description of the domain was omitted from the primary text. For example, if sequence generation methods were not explicitly described, this domain would be labeled as *high risk*. Where an adequate protocol was described for a given domain, it would be labeled *low risk*.

To assess for publication bias, a funnel plot was created using Review Manager 5.3 Software (The

Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen). An Egger's test could not be conducted as a minimum of ten studies is required (28) and the current analysis identified only eight studies meeting the inclusion criteria.

Results

Search results

After removal of duplicates, the initial search yielded 355 records (Fig. 1). After screening of titles and abstracts, 35 full-text articles and clinical trial protocols were evaluated for inclusion in the analysis. Ten completed RCTs met the inclusion criteria for qualitative review, including five studies of omega-3s (29–33), two of NSAIDs (34, 35), two of NAC (36, 37), and one of pioglitazone (38). Study results and participant demographics are summarized in Table 1. Of these trials, two were excluded from quantitative analysis (31, 37). An RCT of omega-3s by Keck et al. (31) was excluded as changes in depression severity scores were not reported and thus the effect size could not be calculated accurately. An RCT of NAC for maintenance treatment by Berk et al. (37) was excluded as both placebo and treatment groups initially received eight weeks of treatment with open-label NAC prior to commencing the study, with no reported washout period, and randomization occurred in stabilized, largely nondepressed individuals. Of note, both of these trials are discussed in the qualitative analysis, with results summarized in Table 1. In addition to published clinical trials, seven ongoing clinical trials of anti-inflammatory agents for BD were identified on ClinicalTrials.gov, as shown in *Supplementary Table 1* (NCT01403662, NCT01514422, NCT01429272, NCT01797575, NCT01479829, NCT02363738, NCT02294591).

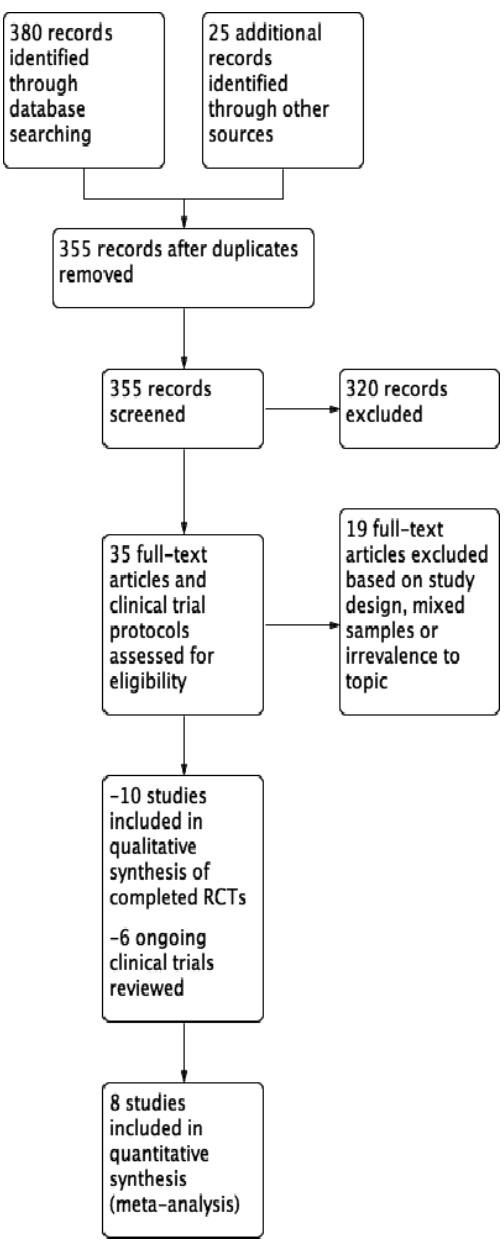

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study selection flow diagram. RCTs = randomized controlled trials.

Assessment of bias

The quality of the included clinical trials was assessed systematically via evaluation of bias in accordance with the *Cochrane Handbook for Systematic Review of Interventions*. Included studies were assessed for bias in six domains – namely, sequence generation, allocation concealment, blinding of outcome assessors, intent-to-treat, for-profit bias, and adverse events bias. The results are summarized in Table 2. Notably, three studies had a high risk for bias for inadequate reporting of adverse events (30, 33, 36). Two studies were found to have a high risk of bias in several categories for inadequate reporting of sequence generation, concealment, blinded outcome analysis, and adequate intent-to-treat analysis (30, 38). Publication bias was assessed using a funnel plot, as shown in Fig. 2. An Egger's test could not be conducted as a minimum of ten studies is required for this analysis (28).

Pooled antidepressant effect of anti-inflammatory agents

The pooled effect size was based on a total of 312 participants, including studies assessing omega-3s (n = 140), NSAIDs (n = 53), NAC (n = 76), and

Table 1. Summary of study characteristics, demographics, efficacy, and side effects[a]

Study	Study length, weeks	Diagnostic criteria	Adjunctive[a] agent and dosage, n	Gender, female, n (%)	Age, years, mean ± SD	Outcome measure	Effect, p-value	adverse effects
Omega 3 fatty acids								
Frangou et al., 2006 (32)	12	DSM-IV (research) BD-I or BD-II and >10 on HDRS-17	Paraffin oil (n = 26)	16 (61.45)	46.5 ± 10.3	HDRS-17 YMRS	0.03 NS	NS difference between groups
			EPA 1 g/day (n = 24)	19 (79.17)	49.2 ± 11.2	CGI	0.04	Mostly include GI: loose stools, upset stomach, flatulence
			EPA 2 g/day (n = 25)	22 (88.00)	45.5 ± 9.6			
Frangou et al., 2007 (33)	12	DSM-IV BD-I and >10 on HDRS-17, female, lithium for past 12 weeks	Paraffin oil (n = 7)	7 (100)	41.5 ± 8.6	HDRS-17	NS	Not reported
			EPA 2 g/day (n = 7)	7 (100)	41.8 ± 8.6			
Hirashima et al., 2004 (30)	4	DSM-IV BD-I, female, unknown phase of illness	Placebo (n = 9)	9 (100)	26.7 ± 6.2	HDRS-23 YMRS	NS NS	Not reported
			EPA 5 g + DHA 3 + 1.7 g other (n = 6)					
			EPA 1.3 g + DHA 0.7 g (n = 6)	12 (100)	39.5 ± 13.8			
Keck et al., 2006 (31)	16	DSM-IV BD-I, BD-II, or BD-NOS	Paraffin (n = 29)	31 (54.4)	49 ± 13	IDS-C	NS	NS difference between groups
			EPA 6 g/day (n = 28)	25 (42.4)	46 ± 11			Mostly included mood/anxiety and GI symptoms
	16	DSM-IV rapid cycling BD	Paraffin (n = 28)	17 (61)	42 ± 12			
			EPA 6 g/day (n = 31)	13 (42)	44 ± 12			
Murphy et al., 2012 (50)	16	DSM-IV BD-I with mood episode in last year	Placebo (n = 15)	9 (60)	40.0 ± 10.3	MADRS YMRS GAF	NS NS NS	NS difference between groups No severe effects, mild GI discomfort
			O3FA EPA 3 g/day (n = 15)	3 (20)	40.0 ± 9.6			
			O3FA EPA 3 g/day + CYT 2 g/day (n = 15)	7 (46.7)	45.0 ± 9.8			
Stoll et al., 1999 (29)	16	DSM-IV BD-I, mood episode within past year	Olive oil (n = 16)	11 (68.6)	44.6 ± 10.4	HDRS YMRS GAS CGI	0.002 NS NS <0.001	NS difference between groups Mild GI discomfort
			EPA 6.2 g/day + DHA 3.2 g/day (n = 14)	9 (64.3)	41.4 ± 6.8			

Table 1. (Continued)

Study	Study length, weeks	Diagnostic criteria	Adjunctive[a] agent and dosage, n	Gender, female, n (%)	Age, years, mean ± SD	Outcome measure	Effect, p-value	adverse effects
***N*-acetylcysteine**								
Berk et al., 2008 (36)	24	DSM-IV BD-I or BD-II, mood episode within past 6 months	Placebo (n = 37) NAC 2 g/day (n = 38)	22 (56.6) 23 (60.5)	46.6 ± 13.8 44.6 ± 11.2	MADRS BDRS CGI-S-BP CGI-S-D CGI-S-M CGI-I-BP CGI-I-D CGI-I-M YMRS Q-LES-Q LIFE-RIFT SLICE/LIFE GAF SOFAS	0.002 0.012 0.026 NS NS NS NS NS NS 0.006 0.002 0.009 0.030 0.025	NS difference between groups Mostly change in energy, headaches, heartburn, and joint pain
Berk et al., 2012 (37)	24	DSM IV BD-I or BD-II	Placebo (n = 73) NAC 2 g/day (n = 76)	41 (56.2) 60 (78.9)	44.4 ± 11.8 47.1 ± 10.9	MADRS, BDRS, CGI-S-BP, CGI-S-D, CGI-S-M, CGI-I-BP, CGI-I-D, CGI-I-M, YMRS, Q-LES-Q, LIFE-RIFT, SLICE/LIFE, GAF, SOFAS	NS differences on all outcome measures	Not reported
NSAIDs and aspirin								
Nery et al., 2008 (34)	6	DSM-IV BD-I or BD-II, HDRS of >18 current depressed, treated for 1 month prior with standard	Placebo (n = 11) Celecoxib 400 mg/day (n = 12)	9 (64.3) 7 (50)	41.1 ± 9.5 42.3 ± 10.4	HDRS YMRS	NS NS	NS difference between groups Mild rash
Saroukhani et al., 2012 (35)	6	DSM-IV-TR BAD, married men age 20–45 years, lithium therapy and YMRS <12 (stable)	Placebo (n = 15) Aspirin 240 mg/day (n = 15)	15 (100) 15 (100)	39.6 ± 9.7 35.6 ± 9.0	HDRS YMRS	NS NS	NS difference between groups Mostly increased appetite, drowsiness, nervousness, and constipation

Table 1. (Continued)

Study	Study length, weeks	Diagnostic criteria	Adjunctive[a] agent and dosage, n	Gender, female, n (%)	Age, years, mean ± SD	Outcome measure	Effect, p-value	adverse effects
Pioglitazone								
Zeinoddini et al., 2015 (38)	6	DSM-IV-TR BD-I with current depression, age 18–50 years, HDRS-17 > 20, YMRS <8 at randomization	Placebo (n = 22) Pioglitazone 15 mg for 1 week then increased to 30 mg for 5 weeks (n = 22)	8 (36.4) 7 (31.8)	31.8 ± 5.6 33.6 ± 5.5	HDRS YMRS	0.006 NS	NS difference between groups No serious side effects reported

BAD = bipolar affective disorder; BD = bipolar disorder; BD-I = bipolar I disorder; BD-II = bipolar II disorder; BD-NOS = bipolar disorder not otherwise specified; BDRS = Bipolar Depression Rating Scale; CGI = Clinical Global Impressions Scale; CGI-I-BP = Clinical Global Impressions Scale–Improvement–Bipolar; CGI-I-D = Clinical Global Impressions Scale–Improvement–Depression; CGI-I-M = Clinical Global Impressions Scale–Improvement–Mania; CGI-S-BP = Clinical Global Impressions Scale–Severity–Bipolar; CGI-S-D = Clinical Global Impressions Scale–Severity–Depression; CGI-S-M = Clinical Global Impressions Scale–Severity–Mania; CYT = cytidine; DHA = docosahexaenoic acid; DSM = diagnostic and statistical manual of mental disorders; EPA = eicosapentaenoic acid; GAF = Global Assessment of Functioning; GI = gastrointestinal; HDRS = Hamilton Depression Rating Scale; IDS-C = Inventory of Depressive Symptomatology–Clinical Rating Scale; LIFE-RIFT = Longitudinal Interval Follow-up Evaluation–Range of Impaired Function Tool; MADRS = Montgomery–Åsberg Depression Rating Scale; NAC = *N*-acetylcysteine; NS = non-significant; NSAIDs = non-steroidal anti-inflammatory drugs; O3FA = omega-3 fatty acid; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Scale; SD = standard deviation; SLICE/LIFE = Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Follow-up Evaluation; SOFAS = Social and Occupational Functioning Assessment Scale; YMRS = Young Mania Rating Scale.

[a]All anti-inflammatory treatments were an adjunct to conventional guideline-based bipolar disorder pharmacotherapy. Placebo groups received conventional guideline-based pharmacotherapy with adjunct placebo.

Table 2. Summary of study bias

Study	Sequence generation	Concealment	Blinded outcome assessment	Intent-to-treat analysis	Adverse events bias	For-profit bias
Omega-3 fatty acids						
Frangou et al. 2006 (32)	Low	Low	Low	Low	Low	High
Frangou et al. 2007 (33)	Low	Low	Low	Low	High	Low
Hirashima et al. 2004 (30)	High	High	High	Low	High	Low
Keck et al. 2006 (31)	Low	Low	Low	High	Low	High
Murphy et al. 2012 (50)	Low	Low	Low	Low	Low	Low
Stoll et al. 1999 (29)	Low	Low	Low	Low	Low	Low
***N*-acetylcysteine**						
Berk et al. 2008 (36)	Low	Low	Low	High	High	Low
Berk et al. 2012 (37)	Low	Low	Low	Low	Low	Low
Non-steroidal anti-inflammatory drugs and aspirin						
Nery et al. 2008 (34)	Low	Low	Low	Low	Low	Low
Saroukhani et al. 2012 (35)	Low	Low	Low	Low	Low	Low
Pioglitazone						
Zeinoddini et al. 2015 (38)	Low	High	High	High	Low	Low

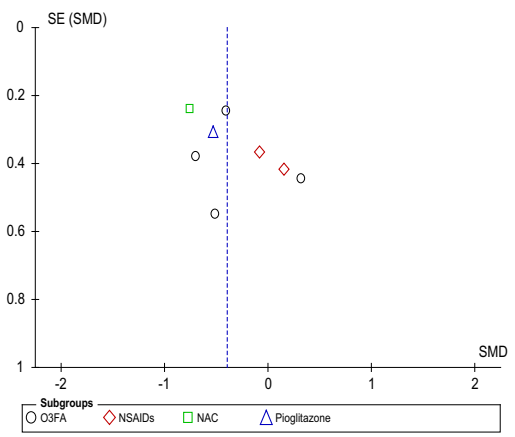

Fig. 2. Funnel plot to assess for publication bias. NAC = *N*-acetylcysteine; NSAIDs = non-steroidal anti-inflammatory drugs; O3FA = omega-3 polyunsaturated fatty acids; SE = standard error; SMD = standard mean difference; dotted line represents pooled SMD (-0.40).

pioglitazone (n = 44). As shown in Fig. 3, the overall SMD of adjunctive anti-inflammatory agents compared with conventional therapy alone was −0.40 (95% CI: −0.14 to −0.65, p = 0.002), indicative of a statistically significant moderate antidepressant effect. The heterogeneity of the pooled sample was found to be low ($\chi^2 = 8.17$, df = 7, p = 0.32, $I^2 = 14\%$). Of the included studies, no serious adverse events were observed and side effect profiles were comparable to those of the placebo group (Table 1). In addition, as summarized in Table 1, there was no induction of manic/hypomanic episodes or significant increase in manic symptom severity scores with administration of anti-inflammatory agents in any of the identified studies. The lack of change in mania rating scales or induction of manic/hypomanic episodes suggests that anti-inflammatory agents do not appear to induce manic/hypomanic episodes, and that the observed decrease in depression severity is unlikely to be secondary to manic/hypomanic induction.

Antidepressant effects of omega-3s in BD

Five RCTs assessing the antidepressant effects of adjunctive omega-3s in patients with BD (29–33) were identified. Of these studies, only two reported a significant reduction in depressive symptom severity compared with placebo (29, 32). The other three identified studies found no significant difference in the reduction of depressive symptom severity (30, 31, 33). Chiu et al. (39) evaluated the effects of omega-3s in acutely manic inpatients with BD in a four-week RCT and found no difference in Young Mania Rating Scale or Hamilton Depression Rating Scale (HDRS) scores compared with placebo. No serious adverse events were observed in any of these trials.

For the quantitative analysis, four RCTs were included (n = 140). Of note, an RCT of omega-3s by Keck et al. (31) was excluded as the change in depression scores was not reported and thus effect size could not be calculated (only odds ratios of recurrence were reported; the authors were not able to provide original data to allow for SMD calculations, *personal communication*). Notably, this trial found no significant antidepressant effect of omega-3s after a six-week trial of eicosapentaenoic acid 6 g/day (n = 121). The remaining four RCTs were pooled, revealing an SMD of −0.36 (95% CI: −0.73 to 0.01); however, the effect failed to reach

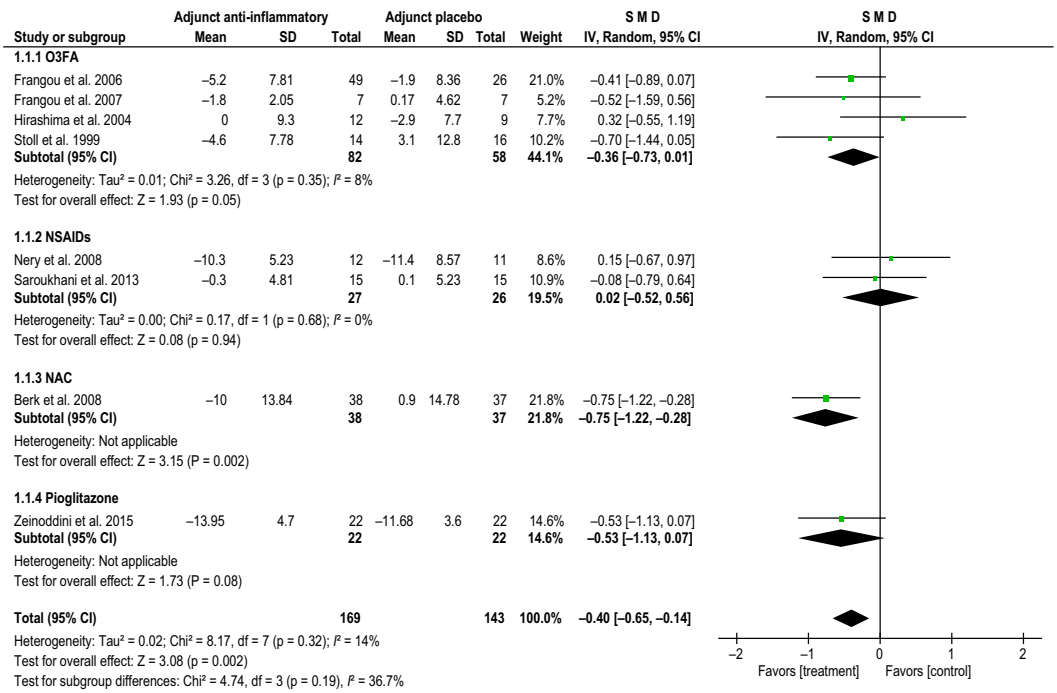

Fig. 3. Forest plot of pooled effect sizes of adjunctive anti-inflammatory agents for bipolar depression. SD = standard deviation; CI = confidence interval; O3FA = omega-3 polyunsaturated fatty acids; NAC = *N*-acetylcysteine; NSAIDs = non-steroidal anti-inflammatory drugs; SMD = standard mean difference.

statistical significance (p = 0.051). The heterogeneity of the pooled sample was low ($\chi^2 = 3.26$, df = 3, p = 0.35, $I^2 = 8\%$).

Antidepressant effect of NSAIDs and aspirin in BD

Two studies using adjunctive NSAIDs in the treatment of BD were identified (34, 35). Nery et al. (34) conducted a six-week RCT with adjunctive celecoxib 400 mg orally daily versus conventional therapy alone in 28 patients with BD-I or BD-II in a current depressive or mixed episode. Adjunctive celecoxib lowered HDRS by week 1; however, the primary outcome was negative as the change in depression symptom severity was not significantly different from that in the placebo group by the study endpoint (i.e., week 6). Saroukhani et al (35) assessed the effect of adjunct aspirin 80 mg orally three times daily in 32 married male euthymic subjects with BD and found no significant difference between treatment and placebo groups by the end of the six-week RCT. Curiously, these authors reported that aspirin reduced lithium-induced sexual side effects. No serious adverse events were observed in either trial. Pooling of effect sizes for these two RCTs revealed an SMD of 0.02 (95% CI: −0.52 to 0.56), indicative of no statistical difference between adjunctive NSAIDs and conventional therapy alone. Pooling of results had low heterogeneity ($\chi^2 = 0.17$, df = 1, p = 0.68, $I^2 = 0\%$).

Of note, in addition to these completed and ongoing RCTs, Stolk et al. (40) conducted a retrospective chart review of 5,145 patients with BD, finding that low-dose aspirin produced a statistically significant reduction in the relative risk of clinical deterioration in patients on lithium, whereas other NSAIDs and glucocorticoids did not have any effect.

Antidepressant effect of NAC in BD

Two RCTs assessing the antidepressant effects of NAC in BD were identified for qualitative review (36, 37). In a 24-week RCT, Berk et al. (36) studied 75 subjects with BD-I or BD-II with at least one depressed, mixed, or manic episode in the last six months. Subjects were randomized to adjunctive NAC 1,000 mg orally twice daily compared with conventional therapy alone. Adjunctive NAC lowered depression symptom severity, as measured by Montgomery–Åsberg Depression Rating Scale (MADRS) scores, throughout the trial, with a statistically significant difference compared with the placebo group by the primary endpoint (i.e., 24 weeks). No serious adverse events were observed with NAC treatment. The calculated effect size was −0.75 (95% CI: −1.22 to −0.28), indicative of a large and statistically significant effect size. Of note, Magalhaes et al. (41) conducted a *post hoc* analysis of 17 subjects

from this sample who met the criteria for a current major depressive episode at baseline. This analysis showed that 8/10 participants in the NAC group demonstrated a 50% reduction in MADRS scores during the trial compared with only one participant in the placebo group. Magalhaes et al. additionally noted reductions in manic symptoms in a *post hoc* analysis and in BD-II (41–43).

Berk et al. (37) conducted an additional study assessing adjunctive NAC for maintenance therapy in an RCT of 149 subjects with BD. This trial was excluded from quantitative analysis as both placebo and treatment groups initially received an eight-week open-label trial of adjunctive NAC prior to entering the 24-week RCT, without a washout period. During the eight-week open-label trial of NAC, a significant reduction in depressive symptoms was noted (44); however, during the subsequent double-blind RCT phase, there was minimal further change in depression severity, with scores remaining low (37). As such, from this low phase II baseline depression score, there were no statistically significant differences in recurrence, clinical functioning, or quality of life measures between NAC and placebo groups.

Antidepressant effect of pioglitazone

One RCT investigating the effects of pioglitazone, a peroxisome proliferator-activated receptor-gamma agonist with potent anti-inflammatory and antihyperglycaemic effects, was identified (38). Zeinoddini et al. (38) conducted a six-week double-blind RCT comparing the effects of adjunctive pioglitazone 30 mg orally daily versus adjunctive placebo (both groups received lithium titrated to a serum level of 0.6–0.8 mEq/L) in 48 outpatients with BD-I with a current major depressive episode. A significantly greater reduction in HDRS scores was observed in the pioglitazone group compared with the placebo group at weeks 2, 4, and 6. No serious adverse events were observed. The calculated effect size was −0.54 (95% CI: −1.14 to 0.06, p = 0.08).

Antidepressant effect of TNF-α inhibitors in BD

No completed trials of TNF-α inhibitors for BD were identified. However, one notable trial assessed infliximab in treatment-resistant depression (n = 60) and included subjects with BD (n = 9) in their sample. While overall the antidepressant effect was negative for this study, a significant antidepressant effect was observed for a subgroup of subjects – namely, those with elevated blood levels of CRP and TNF-α (45). No significant adverse events were reported.

Discussion

In summary, the current analysis suggests that adjunctive anti-inflammatory agents have a significant antidepressant effect in BD when compared with placebo (as measured by change in depressive symptom severity). Of note, the reduction in depressive symptom severity is not an epiphenomenon of hypomanic induction, as indicated by no significant change in mania rating scales or observed induction of manic/hypomanic episodes in any of the studies identified. The effect size was found to be moderate (SMD = −0.40), with low heterogeneity of the pooled sample (I^2 = 14%). Of note, this effect size is comparable with the antidepressant effect size of olanzapine (SMD = −0.52), quetiapine (SMD = −0.29), lurasidone (SMD = −0.36), and olanzapine + fluoxetine (SMD = −0.45), as indicated by a recent meta-analysis (46).

Subgroup analysis of NSAIDs, omega-3s, and pioglitazone, albeit underpowered, revealed effect sizes that were not statistically significant. Only adjunctive NAC was found independently to have a statistically significant antidepressant effect; however, the effect size was based only on a single study, rather than a pooled sample. This finding was mirrored by a meta-analysis of NAC in depression by Fernandes et al. (47), showing an aggregate positive effect. Therefore, the current study suggests that agents with anti-inflammatory effects may have antidepressant properties in BD, although no specific agent may be recommended as the pooled effects for each agent alone, with the exception of NAC, was not significant; statistical significance was only reached when pooling the effects of all mechanistically dissimilar agents together.

A major limitation of the current review and meta-analysis was the limited number of studies and small sample sizes, yielding a total of only 312 participants. While a limited number of studies evaluating the antidepressant effects of anti-inflammatory drugs in BD have been completed, several ongoing studies assessing the effects of aspirin (48), celecoxib (NCT01479829), NAC (NCT01797575, NCT02294591), infliximab (NCT02363738), and minocycline (NCT01403662, NCT01514422, NCT01429272) are currently under way. Compared with the recent meta-analysis of anti-inflammatory agents for MDD by Kohler et al. (n = 6,262) (22), the results of the current meta-analysis are considerably less robust. It is notable,

however, that the antidepressant effect size reported by Kohler et al. in MDD (SMD = −0.34; 95% CI: −0.11 to −0.57) was similar to the effect size in BD found in the current study (SMD = −0.40; 95% CI: −0.14 to −0.65).

In addition, given the small number of known studies of anti-inflammatory agents for BD, studies including subjects in any phase of illness (except for studies of acute mania as this would obscure depression rating scales) were included in the current analysis to minimize the exclusion of studies. Phase of illness at the time of randomization is summarized in Table 1. While the majority of studies randomized subjects during an acute depressive episode, some studies did not specify the phase of illness or stated that subjects had experienced a recent mood episode within the past six months to one year. Conceptually, measuring the change in depression severity scores for currently depressed versus euthymic patients would certainly vary; however, from a relapse prevention perspective, measuring relapse and change in depression severity with adjunctive anti-inflammatory agents versus conventional therapy alone would still be of interest.

Another limitation was the exclusion of one study assessing omega-3s from the quantitative analysis owing to inadequate reporting of the change in depression scores. In this study, Keck et al. (31) found no significant effect of omega-3s in depression severity in BD. Therefore, had this study been included, it may have decreased the overall effect size. As such, the reported pooled SMD may overestimate the effect of omega-3s. Notably, however, the calculated effect size for omega-3s in the current study (SMD = −0.36; 95% CI: −0.73 to 0.01) was similar to the effect size reported by Sarris et al. (49) in their meta-analysis of omega-3s for depressive symptoms in BD, which included the study by Keck et al. (SMD = −0.338; 95% CI: −0.035 to −0.641). The presence of potential bias in several of the included studies (Table 2) presents as another limitation of the current analysis.

Conclusions

Taken together, the current review suggests that adjunctive anti-inflammatory agents may potentially play a role in the future treatment of bipolar depression; however, currently, there is insufficient evidence to recommend the clinical use of any particular agent. This analysis may serve as a proof-of-concept of anti-inflammatory agents in BD, while not providing conclusive results on efficacy or safety. Therefore, further studies are merited to assess the efficacy, tolerability, and safety of anti-inflammatory agents in the treatment of BD. Clinical trials assessing inflammatory biomarkers may be of particular relevance. Ongoing clinical trials assessing the effects of minocycline, aspirin, NAC, infliximab, and NSAIDs may add to the therapeutic armamentarium and support the notion that inflammation is a core component of the pathophysiology of the disorder. Additionally, future studies may endeavor to identify the effect of anti-inflammatory agents on specific domains (e.g., anhedonia, cognition, etc.) of bipolar depression, which would have greater clinical relevance, as well as serve to improve the understanding of the role of inflammation in the pathophysiology of BD.

Author contributions

All authors contributed to the development of the research hypothesis and study design. JDR and RK conducted the search, data extraction, and data analysis. JDR wrote the first draft of the manuscript. All authors contributed to the interpretation of results and manuscript writing.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Summary of ongoing clinical trials from ClinicalTrials.gov.