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

Running head: Anti-inflammatory agents for BD

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Abstract

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 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 (SMD) compared to standard therapy alone.

Results: Ten RCTs were identified for qualitative review. Eight RCTs (n = 312) assessing adjunctive non-steroidal 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 inclusion criteria for quantitative analysis. The overall effect size of adjunctive anti-inflammatories 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. 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 to 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.

Key words: aspirin – bipolar disorder – depression – inflammation – infliximab – minocycline – N-acetylcysteine (NAC) – non-steroidal anti-inflammatory drugs (NSAIDs) – omega 3 polyunsaturated fatty acids – pioglitazone

Bipolar disorder (BD) is a chronic illness associated with high levels of morbidity and mortality (1, 2). Current psychopharmacologic 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 pro-inflammatory cytokines interleukin (IL)-4, tumor necrosis factor alpha (TNF-α), soluble IL-2 receptor (sIL-2R), IL-1β, IL-6, soluble receptor of TNF-alpha type 1 (STNFR1) and C-reactive protein (CRP) have been consistently shown to be elevated in subjects with BD compared to 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 extensively reviewed 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 were identified (n = 6,262) investigating the antidepressant effects of cytokine inhibitors and adjuvant non-steroidal anti-inflammatories drugs (NSAIDs) (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), a naturally occurring agent with some anti-inflammatory properties. Omega-3s have been extensively investigated for their antidepressant effects yielding mixed results (23, 24). Further, aspirin as one of the oldest agents in medicine, was highlighted in a recent review as a potential new therapy for a range of neuropsychiatric disorders due 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 anti-depressant effects of adjunctive anti-inflammatory agents in the treatment of BD. A recent systematic review qualitatively evaluated the effects of N-acetylcysteine (NAC), NSAIDs and omega-3s in BD (26); however, the overall anti-depressant effect size of anti-inflammatory agents in BD has yet to be quantified. Therefore, the primary objective of the current review was to systematically (in accordance with PRISMA), qualitatively and quantitatively evaluate the anti-depressant effects of anti-inflammatory agents in BD. In addition, the current review aims to systematically 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 will also be reviewed.

Methods

Search methods for identification of trials

PubMed, PsycInfo, Cochrane, and Embase databases were searched from inception to 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* non-steroidal anti-inflammatory drugs *or* NSAIDS *or* NAC *or* N-acetylcysteine *or* omega-3 polyunsaturated fatty acids *or* pioglitazone *or* infliximab *or* tumor necrosis factor (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, N-acetylcysteine (NAC), NSAID, omega-3, creatine, and clinical trial. Reference lists from identified articles were manually searched 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

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 (BD-NOS) as defined by Diagnostic and Statistical Manual (DSM) or International Classification of Disease (ICD) criteria (no restrictions on edition used) in any phase of illness except for acute mania.
ii. Randomized clinical trials of adjunctive anti-inflammatory agents (e.g., conventional therapy plus adjunctive anti-inflammatory agent) compared to adjunctive placebo (e.g., conventional therapy plus adjunctive placebo).
iii. Depression severity was assessed and reported using standardized and validated scales.

iv. Data was provided to allow for calculation of effect size, namely, change in depression scores from baseline to primary endpoint for both treatment and placebo-control groups. Where data was not provided, authors were contacted to obtain necessary data. If the authors could not provide the necessary data, the trial was excluded from quantitative analysis.

Exclusion criteria

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 study was included to prevent overweighting of one data set).
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 was extracted from included studies by two independent reviewers (JR and RK) to systematically 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 pre-specified primary outcome was the pooled effect size of change in depression severity of adjunctive anti-inflammatory agents compared to adjunctive placebo (e.g., conventional therapy plus adjunctive placebo) in BD. A pre-specified 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 standard mean difference (SMD) of change in depression scores for placebo-controlled trials. A random effects model was used. Samples were not sub-grouped into responders and non-responders as an insufficient number of studies reported responder sub-grouped analysis.

Pooled effect sizes (SMD) were sub-grouped based on anti-inflammatory agent tested and then pooled to calculate 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 description of randomization), allocation concealment, blinding of outcome assessors, intention-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. An Egger's test could not be conducted as a minimum of ten studies is required (28) and the current analysis only identified eight studies meeting 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 analysis. Ten completed randomized controlled trials (RCTs) met inclusion criteria for qualitative review including five studies of omega-3s (29-33), two of NSAID (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 accurately calculated. An RCT of NAC for maintenance 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 wash out period, and randomization occurred in stabilized largely non-depressed 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 S1* (NCT01403662, NCT01514422, NCT01429272, NCT01797575, NCT01479829, NCT02363738, NCT02294591).

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, intention-to-treat, for-profit bias and adverse events

bias. The results are summarized in Table 2. Notably, three studies had high risk for bias for inadequate reporting of adverse events (30, 33, 36). Two studies were found to have high risk of bias in several categories for inadequate reporting of sequence generation, concealment, blinded outcome analysis and adequate intention-to-treat analysis (30, 38). Publication bias was assessed using a funnel plot as shown in Figure 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 pioglitazone (n = 44). As shown in Figure 3, the overall SMD of adjunctive anti-inflammatory agents compared to conventional therapy alone was -0.40 (95% CI: -0.14 to -0.65, p = 0.002), indicative of a statistically significant moderate antidepressant effect. 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 the placebo group (Table 1). As well, as summarized in Table 1, there was no induction of manic/hypomanic episodes or a significant increase in manic symptoms 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 (i) anti-inflammatory agents do not appear to induce manic/hypomanic episodes and (ii) the observed decrease in depression severity is unlikely to be secondary to manic/hypomanic induction.

Antidepressant effects of omega-3s in BD

Five RCTs were identified assessing the antidepressant effects of adjunctive omega-3s in patients with BD (29-33). Of these studies, only two reported a significant reduction in depressive symptom severity compared to placebo (29, 32). The other three identified studies found no significant difference in 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 (YMRS) or Hamilton Depression Rating Scale

(HDRS) scores compared to 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 change in depression scores were not reported and thus effect size could not be calculated (only odds ratios of recurrence were reported; 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 EPA 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 statistical significance (p = 0.051). 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 were identified using adjunctive NSAIDs in the treatment of BD (34, 35). Nery et al (34) conducted a six-week RCT with adjunctive celecoxib 400 mg oral 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 change in depression symptom severity was not significantly different from the placebo group by the study endpoint (i.e., Week 6). Saroukhani (35) assessed the effect of adjunct aspirin 80 mg oral 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 reveals 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 oral twice daily compared to 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 to 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 criteria for a current major depressive episode (MDE) at baseline. This analysis showed that 8/10 participants in the NAC group demonstrated a 50% reduction in MADRS during the trial compared to only one participant in the placebo group. Magalhaes 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, significant reduction in depressive symptoms were 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 was identified investigating the effects of pioglitazone, a PPAR-gamma agonist with potent anti-inflammatory and anti-hyperglycemic effects (38). Zeinoddini et al. (38) conducted a six-week double-blind RCT comparing the effects of adjunctive pioglitazone 30 mg oral daily versus adjunctive placebo (both groups received lithium titrated to serum level of 0.6–0.8 mEq/L) in 48 outpatients with BD-I with a current MDE. A significantly greater reduction of HDRS scores was observed in the pioglitazone group compared to 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 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 to 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 to 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 to independently have a statistically significant antidepressant effect; however, the effect size was based only on a single study rather than a pooled sample. This finding is 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, however, no specific agent may be recommended as the pooled effects for each specific 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-inflammatories in BD have been completed, several ongoing studies are currently underway assessing the effects of aspirin (48), celecoxib (NCT01479829), NAC (NCT01797575, NCT02294591), infliximab (NCT02363738), and minocycline (NCT01403662, NCT01514422, NCT01429272). Compared to the recent meta-analysis of anti-inflammatory agents for MDD by Kohler et al. (22) (n = 6262), the results of the current meta-analysis are significantly 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 exclusion of studies. Phase of illness at 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 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 due to inadequate reporting of 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 be overestimating 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 did include 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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Figure legends

Fig. 1. PRISMA study selection flow diagram. RCTs = randomized controlled trials.

Fig. 2. Funnel-plot to assess for publication bias. SE = standard error; SMD = standard mean difference; O3FA = omega-3 polyunsaturated fatty acids; NSAIDS = non-steroidal anti-inflammatory drugs; NAC = N-acetylcysteine.

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; NSAIDS = non-steroidal anti-inflammatory drugs; NAC = N-acetylcysteine.

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

Study	Study length, weeks	Diagnostic criteria	Adjunctive[a] agent and dosage, n	Sex, female, n (%)	Age, years, mean ± SD	Outcome measure	Effect, p-value	Side 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 CGI	0.03 NS 0.04	NS difference between groups Mostly include GI: loose stools, upset stomach, flatulence
			EPA 1 g/day (n = 24)	19 (79.17)	49.2 ± 11.2			
			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	Placebo (n = 9) EPA 5 g + DHA	9 (100)	26.7 ± 6.2	HDRS-23 YMRS	NS NS	Not reported

		phase of illness	3 g + 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 Mostly included, mood/anxiety and GI symptoms
			EPA 6 g/day (n = 28)	25 (42.4)	46 ± 11			
	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 +	7 (46.7)	45.0 ± 9.8			

			CYT 2 g/day (n = 15)					
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			
N-acetylcysteine								
Berk at al. 2008 (36)	24	DSM-IV BD-I or BD-II, mood episode within past 6 months	Placebo (n = 37)	22 (56.6)	46.6 ± 13.8	MADRS BDRS CGI-S-BP CGI-S-D CGI-S-M CGI-I-BP CGI-I-D CGI-I-M YMRS Q-LES-Q	0.002 0.012 0.026 NS NS NS NS NS NS 0.006	NS difference between groups Mostly change in energy, headaches, heartburn and joint pain
			NAC 2 g/day (n = 38)	23 (60.5)	44.6 ± 11.2			

						LIFE-RIFT SLICE/LIFE GAF SOFAS	0.002 0.009 0.030 0.025	
Berk et al. 2012 (37)	24	DSM IV BD-I or BD-II	Placebo (n = 73)	41 (56.2)	44.4 ± 11.8	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
			NAC 2 g/day (n = 76)	60 (78.9)	47.1 ± 10.9			
NSAIDS and aspirin								
Nery et al. 2008 (34)	6	DSM-IV BD-I or BD-II, HDRS of	Placebo (n = 11)	9 (64.3)	41.1 ± 9.5	HDRS YMRS	NS NS	NS difference between groups

		> 18 current depressed, treated for one month prior with standard	Celecoxib 400 mg/day (n = 12)	7 (50)	42.3 ± 10.4			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)	15 (100)	39.6 ± 9.7	HDRS YMRS	NS NS	NS difference between groups Mostly increased appetite, drowsiness, nervousness, and constipation
			Aspirin 240 mg/day (n = 15)	15 (100)	35.6 ± 9.0			
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	Placebo (n = 22)	8 (36.4)	31.8 ± 5.6	HDRS YMRS	0.006 NS	NS difference between groups No serious side effects reported
			Pioglitazone 15 mg for 1 week then increased to 30 mg for 5	7 (31.8)	33.6 ± 5.5			

		randomization	weeks (n = 22)					

DSM = Diagnostic and Statistical Manual of Mental Disorders; BD = bipolar disorder; BD-I = bipolar I disorder; BD-II = bipolar II disorder; BD-NOS = bipolar disorder not otherwise specified; BAD = bipolar affective disorder; HDRS = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; O3FA = omega-3 fatty acid; CYT = cytidine; NAC = N-acetylcysteine; NSAIDS = non-steroidal anti-inflammatory drugs; CGI = Clinical Global Impressions Scale; IDS-C = Inventory of Depressive Symptomatology–Clinical Rating Scale; MADRS = Montgomery–Åsberg Depression Rating Scale; GAF = Global Assessment of Functioning; BDRS = Bipolar Depression Rating Scale; 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; 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; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Scale; LIFE-RIFT = Longitudinal Interval Follow-up Evaluation–Range of Impaired Function Tool; SLICE/LIFE = Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Follow-up Evaluation; SOFAS = Social and Occupational Functioning Assessment Scale; NS = non-significant; GI = gastrointestional.

[a]All anti-inflammatory treatments were 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	Intention-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 at 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

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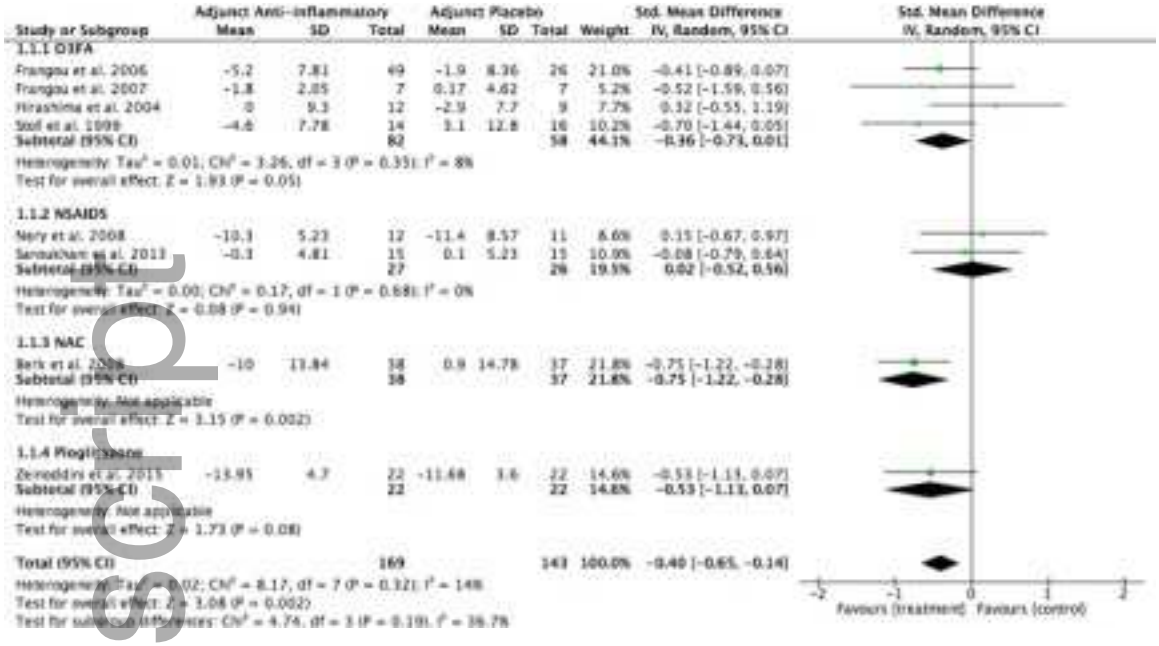

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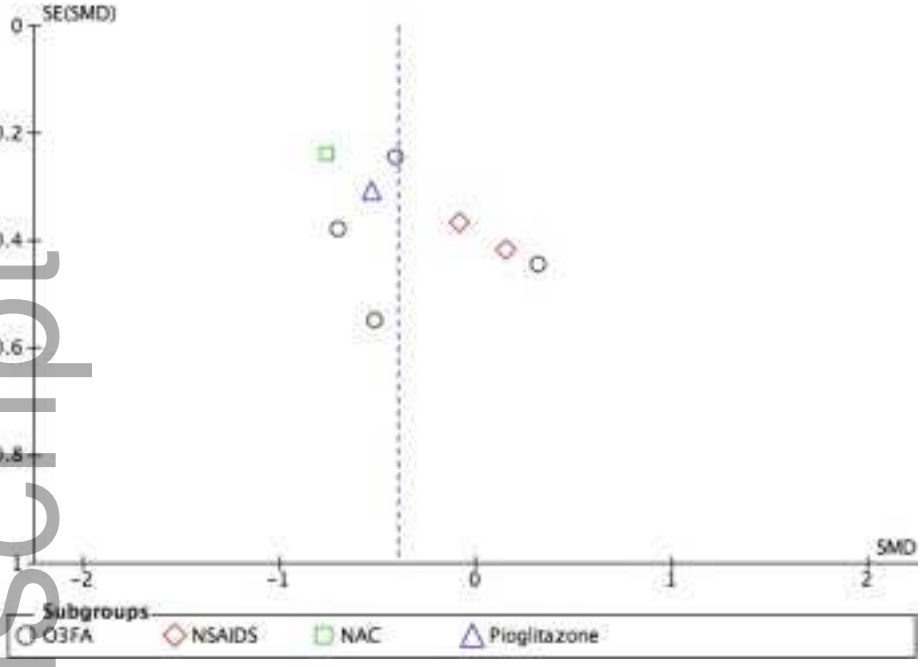

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