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

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Abstract

Objectives: Previous studies and meta-analyses suggested that N-acetylcysteine (NAC) was superior to placebo in improving depression in bipolar disorder. However, more recent data, including two larger trials, found that NAC was no more effective than placebo. We conducted a meta-analysis to appraise the possible efficacy of NAC in treating bipolar depression.

Methods: A systematic review and meta-analysis of double-blind, placebo-controlled trials of NAC as a treatment augmentation strategy for bipolar depression was carried out in PubMed (1966–2020). We utilized random-effect analysis to evaluate improvement in depressive symptoms from baseline to endpoint as the primary efficacy measure.

Results: Six trials including 248 patients were included. Treatment augmentation with NAC showed a moderate effect size favoring NAC over placebo (d = 0.45, 95% C.I.: 0.06–0.84). There was substantial heterogeneity (I^2 = 49%). Meta-regression analyses did not identify any moderator that might explain variation in heterogeneity, including baseline depressive symptom scores, mean NAC dose, or duration of study.

Conclusions: Results from six clinical trials suggest that treatment augmentation with NAC for bipolar depression appears to be superior to placebo, with a moderate effect size, but a large confidence interval. Larger clinical trials, investigating possible moderating factors, such as NAC dose, treatment duration, baseline depression severity, or chronicity of illness, are warranted.

KEYWORDS
bipolar disorder, depression, meta-analysis, N-acetylcysteine, randomized clinical trials, systematic review

1 | INTRODUCTION

Bipolar depression is the most common mood state in bipolar disorder.[1] Long-term studies show that patients with bipolar disorder spend up to 50% of time with mood symptoms, and of those, up to 80% of time is on depressive mood state, rather than in mania or hypomania.[2–4] Bipolar depression is associated with increased disability and suicidality.[5,6] Unfortunately, very few treatment options exist for treatment of bipolar depression, and current available treatments are often not enough to provide relief or remission of symptoms.[7] For instance, in the U.S., only four options are FDA-approved to treat bipolar depression (quetiapine, olanzapine plus fluoxetine

combination, lurasidone, and cariprazine). Moreover, although widely used in clinical practice, there is a lack of evidence for the efficacy of antidepressants used to treat bipolar disorder, and some controversial evidence that their use in bipolar disorder may in fact be deleterious, increasing the risk of suicidal behavior and switch to mania.[8] Therefore, there is an urgent need to develop better treatment strategies, and to find agents that may treat bipolar depression without increasing the risk of manic switch.

One potential pharmacological agent to treat depressive symptoms in patients with bipolar disorder is N-acetylcysteine (NAC). NAC is a dietary supplement and glutathione precursor, widely used in pediatric and adult populations as a mucolytic and antidote for acetaminophen overdose, well tolerated, and with a very well-known safety profile.[9] Increasing interest exists in studying the efficacy and tolerability of NAC in the treatment of psychiatric disorders, given its putative mechanism of action as a glutamate neurotransmitter modulator, and its effect as a potent antioxidant and possible neuroprotective effect.[9–11] On the other hand, increasing evidence suggest that patients with bipolar disorder exhibit disturbances in the glutamate neurotransmitter system and biomarkers of oxidative stress, supporting the interest of evaluating the efficacy of NAC on depressive symptoms in bipolar disorder.[12–14] NAC also holds other potential benefits in bipolar disorder. For instance, although tested only in animal studies, it may protect the kidneys from lithium-induced renal failure.[15]

Early studies in adults with bipolar depression suggested that treatment augmentation with NAC was efficacious in improving depressive symptoms in bipolar disorder when compared with placebo augmentation.[16–18] Two previous meta-analyses have reported positive findings regarding the effects of NAC on depressive symptoms in general, regardless of main psychiatric condition or whether the reported effects of NAC on depressive symptoms were reported as secondary outcomes or not.[19,20] Analyses focusing on studies of NAC in bipolar disorder found that NAC was ineffective to treat bipolar depression.[10,21] However, none of these previous meta-analyses included three recent original studies of NAC for bipolar depression, of which two reported negative[22,23] and one positive[24] findings. Another recent meta-analysis of NAC for depressive symptoms in mood disorders, although including these recent studies, did not evaluate bipolar disorder separated from major depressive disorder.[25] Therefore, the possible beneficial effect of NAC on bipolar depression remains unclear. To further investigate the global effect of NAC on bipolar depression, we proposed here to conduct a systematic review and meta-analysis of published double-blind, placebo-controlled studies of NAC as an augmenting agent for the treatment of bipolar depression.

2 | MATERIAL AND METHODS

We searched the databases PubMed (http://www.ncbi.nih.gov/pubmed), Embase, Cochrane Library, and ClinicalTrials.gov for all double-blind, placebo-controlled studies using NAC for treatment of bipolar depression published between 1966 and September 2020. We used the following keywords: bipolar disorder AND depression AND N-acetylcysteine AND double blind AND placebo-controlled.

TABLE 1 Double-blind, placebo-controlled, randomized clinical trials using NAC as treatment augmentation in bipolar depression

	Sample size, n		Age, mean (SD)		Sex (females), n (%)		Design	Duration
Study	NAC	PCB	NAC	PCB	NAC	PCB		
Berk et al (2008)[a]	14	13	44.2 (13.7)	42.7 (11.6)	9 (64.3)	8 (61.5)	NAC vs. PCB	24 weeks
Hu et al (2012)	28	22	30.11 (6.14)	29.2 (9.36)	19 (67.9)	16 (72.7)	NAC vs. PCB	10 weeks
Porcu et al (2018)[a]	15	14	45.7 (11.3)	39.8 (12.3)	12 (80)	11 (78)	NAC vs. PCB	12 weeks
Bauer et al (2018)	8	8	36.38 (7.05)	39.13 (9.99)	6 (75)	5 (62.5)	NAC vs. aspirin vs. NAC+aspirin vs. PCB	16 weeks
Berk et al (2019)	59	61	44.9 (12.5)	45.4 (11.9)	36 (61)	40 (65.6)	NAC vs. NAC+CT vs. PCB	16 weeks
Ellegaard et al (2019)	40	40	43.7 (10)	43 (10.2)	26 (65)	21 (52.5)	NAC vs. PCB	20 weeks

Abbreviations: CT, nutraceutical compound; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery Asberg Depression Rating Scale; MDD, major depressive disorder; NAC, N-acetylcysteine; PCB, placebo.

[a]Subset of participants with bipolar depression. Please refer to Supporting Information for original sample characteristics.

We manually checked the reference list of the selected original articles, or systematic reviews or meta-analyses for additional clinical trials. The searches were independently conducted by two authors (FGN and JAW), who selected the articles included for analyses, and discussed discrepancies or presence of exclusion criteria. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement,[26] and we provided a checklist in Supporting Material.

We included all studies that were original papers published in peer-reviewed articles that were prospective, randomized, placebo-controlled trials evaluating the efficacy and safety of NAC for bipolar depression, and used a validated rating scale to measure the severity of depressive symptoms (Table 1). We excluded studies that were (a) systematic reviews or meta-analyses; (b) used an open-label design; (c) were not placebo-controlled; (d) investigated other disease states (e.g., post-traumatic stress disorder); (e) studies with overlapping samples (e.g., from same institution or authors, in which case, the study with the large dataset was included); and (f) protocol descriptions without original data. A summary of our search is shown as a PRISMA flowchart in Figure 1.[27]

We extracted data into an Excel (Microsoft, Redmond, WA) spreadsheet. We selected mean change from baseline to endpoint between NAC-treated and placebo-treated groups as the outcome measurement. We also collected data on tolerability (dosage, duration of trial, other measures, and dropout rates) for each study. We contacted the authors of original studies with mixed samples to request data on subsets of patients with bipolar depression.

We required data on change from baseline to a follow-up point to be available either as a direct report of mean changes with standard deviations of change scores, or for mean and standard deviations (SD) of absolute scale values to be reported separately at baseline and follow-up, or as an estimate of the standardized effect size (i.e., between-group difference in mean changes divided by standard deviation of change). For studies meeting these analytic criteria, standardized effect sizes were estimated from the change in Montgomery–Asberg Depression Rating Scale (MADRS) or HAMD scores at baseline and maximum follow-up, with sample sizes taken to be the reported N at the follow-up time. Where SDs of change scores were not stated, we considered two alternate ways to estimate them: (a) from the SDs at baseline and follow-up, assuming baseline and endpoint scores to have a pre–post correlation of $r = 0.5$; and (b) imputing the median value of the SD of change scores from studies where it was reported. We used the Cochrane Risk of Bias Assessment Tool to assess individual risk of bias.[28]

Standardized effect sizes (Cohen's *d*, hereafter abbreviated *d*) were combined using a random effects model, estimated by maximum likelihood using the *rma* function in the *metafor* package in R (v3.5.3 for Windows). We reported confidence interval (95%) estimates of mean *d* (the average effect in a population of potentially heterogeneous effects), interval estimates for a typical effect size (the range where 95% of true effects in this population might be expected to lie), and I^2, the proportion of observed variance estimated to be attributable to heterogeneity beyond what would be expected due to sampling error (i.e., variance not explainable by limited sample

Dose	Primary outcome measure	Results	Baseline depressive scores, mean (SD)		Endpoint depressive scores, mean (SD)	
			NAC	PCB	NAC	PCB
2000 mg/d	MADRS	Larger improvement in depressive symptoms in NAC-treated group than in PCB-treated group	24.1 (12.1)	20.4 (9.3)	10.8 (9.6)	17 (12.0)
1200 mg/d	HAMD	Lower depression scores in weeks 8 and 10 in NAC-treated group vs. PCB-treated group	26.3 (3.4)	26.1 (3.1)	1.4 (2.0)	4.1 (3.7)
1800 mg/d	HAMD	Larger improvement in NAC-treated group than in PCB-treated group	11.7 (7.0)	9.1 (5.0)	4.2 (4.1)	6.1 (5.4)
1000 mg/d	MADRS	Patients treated with NAC had higher probability of response than placebo	22.9 (4.1)	19.4 (4.9)	13.6 (13.8)	11.4 (10.4)
2000 mg/d	MADRS	Depressive symptoms improved in both groups, no significant differences between groups	29.4 (5.6)	28.8 (5.2)	15.0 (10.0)	15.8 (10.5)
3000 mg/d	MADRS	Depressive symptoms improved in both groups, with no statistical differences between groups differences in depressive scores between NAC-treated and PCB-treated groups at end of study	30.1 (7.9)	28.8 (7.1)	16.3 (2.1)	15.6 (2.4)

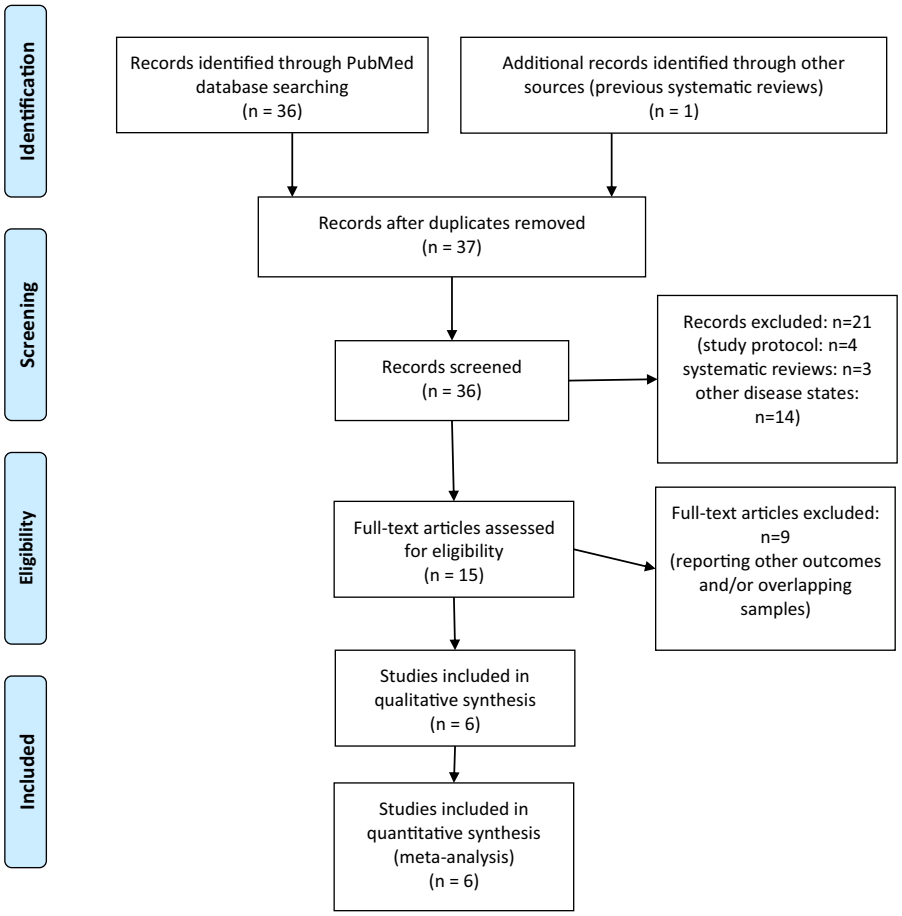

FIGURE 1 PRISMA flow diagram for studies of N-acetylcysteine treatment augmentation for bipolar depression

size). We used sensitivity analysis to address issues with individual studies by performing leave-one-out estimation (computing six meta-analytic estimates, with each study omitted in turn, and noting how these differ among themselves and from the estimate base on all six studies).

Meta-regression analyses were performed to identify moderators that could explain variation between studies, including mean NAC daily dose, study duration, or mean baseline MADRS scores. We converted HAMD scores to MADRS scores via the equipercentile method [29].

3 | RESULTS

Our original search in PubMed yielded 36 studies. After reading the abstracts, we excluded one duplicate citation, and 21 articles due to specified exclusion criteria (i.e., four study protocols, three systematic reviews, and 14 on disease states other than bipolar disorder). We added one article[30] from the reference list of one previous meta-analysis.[21] We then selected 15 articles for full-text reading. After evaluation of full text, we further excluded nine studies due to either reporting outcomes other than depressive symptoms (e.g., cognition and mania) or studies from the same group with overlapping samples (Figure 1). Our additional searches in Embase, Cochrane Library, and ClinicalTrials.gov did not identify any other study to be included. Details of these additional searches are available as Supporting Material.

We finally included six studies in our systematic review and meta-analysis.[16,22–24,30,31] Three studies were in bipolar depression,[22,23,30] one in bipolar disorder in different mood states,[16] one in depressed or mixed states of bipolar disorder,[24] and one with a mixed sample of bipolar disorder and major depressive disorder.[31] We contacted the authors of two studies including different mood states[16] and major depressive disorder,[31] and obtained original data for the subset of patients with bipolar depression. One study was published in China and was translated from Chinese by one of the co-authors of this meta-analysis (WL).[30]

3.1 | Systematic review

Berk et al (2008) were the first to study the effects of NAC treatment augmentation on depressive symptoms in bipolar disorder.[16] Thirty-eight participants, in a mixed sample of depressed, euthymic, or manic states, were randomized to NAC 2000 mg daily and 37 participants to placebo, added to their standard mood stabilizer

regimen, and followed over 24 weeks. NAC treatment augmentation was associated with a significant reduction in depressive symptoms at week 20 compared with placebo. A subset of this sample, restricting the analysis to 17 participants meeting criteria for a major depressive episode (10 received NAC and seven received placebo), reported that NAC had a large effect on depressive symptoms compared with placebo, with a calculated effect size of 2.3.[32] There was no difference in adverse events in NAC group compared with placebo.

Hu et al treated 28 patients with bipolar depression with NAC 1200 mg daily and 22 participants with placebo for over 10 weeks.[30] In this trial, patients were required to be experiencing a current major depressive episode (HAMD-17>17), and were randomized to receive NAC 1200 mg daily (n = 28) or placebo (n = 22), in addition to their routine treatment with valproate and paroxetine, during 10 weeks. Participants treated with NAC showed significantly lower HAMD scores in weeks 8 and 10 compared with participants treated with placebo. There was no significant difference in the incidence of adverse symptoms using a treatment emergent symptom scale (TESS).

Porcu et al (2018) studied the efficacy of NAC augmentation in a mixed sample of 67 patients with bipolar depression or major depressive disorder, divided in four groups by their baseline high-sensitivity C-reactive protein (hs-CRP) levels.[31] Participants were randomly allocated to receive either NAC 1800 mg daily or placebo augmentation over 12 weeks. NAC augmentation treatment was superior to placebo augmentation only among participants with higher baseline hs-CRP, but not among those with lower baseline hs-CRP. NAC was well tolerated, and about 60% of each group did not suffer from adverse events.

Bauer et al (2018) compared the efficacy of NAC augmentation with placebo augmentation and a combination of NAC and aspirin augmentation on 24 patients with bipolar depression.[24] Patients were randomized to receive NAC (1000 mg daily), aspirin (1000 mg daily), combined NAC and aspirin (same doses), or placebo, as adjunctive to their treatment as usual, and followed over 16 weeks. Depressive symptom scores improved over time in the four groups and there were no statistical differences among groups. No information is provided on tolerability or rate of adverse events on this trial.

Berk et al (2019) evaluated 81 participants with bipolar depression, randomized to receive treatment augmentation with NAC (n = 59), placebo augmentation (n = 61), or a combination of NAC and a nutraceutical compound (n = 61) treated over 16 weeks.[23] The nutraceutical compound was comprised of acetyl-L-carnitine, ubiquinone, magnesium, vitamin D, vitamin E, complex B vitamins, coenzyme Q10, and alpha-lipoic acid. All groups significantly improved their depressive symptom scores over the duration of the trial, and there were no significant differences between groups. Adverse events were more frequent in the NAC group compared with placebo group, and were mostly gastrointestinal, such as heartburn/indigestion, diarrhea, and nausea/vomiting.

Finally, Ellegard et al (2019) studied the efficacy of NAC augmentation in a sample of 80 participants with bipolar depression, randomized into receiving NAC augmentation (3000 mg daily) or placebo augmentation[22] over 80 weeks. The improvement in depressive symptom was comparable in both groups, and was not statistically significant at any visit. After 4 weeks of discontinuing the study medication, the placebo-treated group had an increase in its depressive symptoms while the NAC-treated group had a decline. There was no difference in terms of adverse events between groups, and the most common side effects were headache, diarrhea, nausea, dizziness, and reflux.

Details of each study are displayed in Table 1 and in Supporting Information.

3.2 | Meta-analysis

The six studies discussed above met our analytic criteria for the meta-analysis. The total combined population in the meta-analysis was 248 participants (n = 125 for NAC, n = 123 for placebo, with mean ages ranging between 30.1 and 45.7 for NAC and 29.2 and 45.4 years old for placebo). The sample size from individual studies included in the meta-analysis varied between 16 and 120

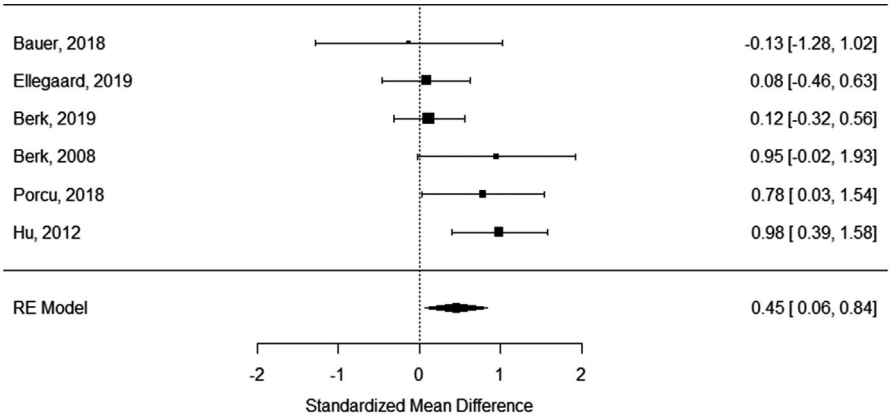

FIGURE 2 2Forest plot for studies of N-acetylcysteine treatment augmentation for bipolar depression. Abbreviations: NAC, N-acetylcysteine

participants. In the included studies, the dose of NAC used in the studies ranged from 1000 to 3000 mg/d, the range of duration was 10 to 24 weeks, and the instrument used was either the Hamilton Depression Rating Scale (HAMD) or the Montgomery–Asberg Depression Rating Scale (MADRS). Table 1 summarizes the included studies.

Standardized effect sizes *d* and estimated 95% confidence interval (C.I.) for each study are shown in Figure 2. Sample sizes were generally small, and considerable heterogeneity was apparent, with three quite large estimated effects,[16,30,31] and three very small estimates.[22–24] As estimated by I^2, among-study heterogeneity was substantial (49%), and a model of homogeneity did not fit well (Cochran's Q = 9.7, $p = 0.09$). The mean value of *d* was estimated as 0.45 (95% C.I.: 0.06–0.84). As the standard deviation of *d* in the population (the degree to which studies meeting the inclusion criteria might be expected to differ among themselves) was estimated as 0.33, we estimate that 95% of effect sizes of comparable studies might lie in the range of 1.01 (an extremely large beneficial effect) to −0.21 (a rather small harmful effect).

Individual risk of bias assessment yielded low concerns for three studies,[16,22,23] some concerns for two studies,[24,31] and high concerns for one study.[30] As expected, leave-one-study-out validation yielded smaller and variable estimates of efficacy, with a mean *d* about 0.51, and the remaining leave-one-out estimates for *d* in the range of 0.27 to 0.56. Sensitivity analysis did not show any substantial decrease in heterogeneity from any individual study, except from Hu et al (2012).[30] The leave-one-study-out estimates for I^2 ranged from 44% to 55%, with the exception of Hu et al (2012). When Hu et al (2012) was omitted from the analyses, there was a decrease in average effect size: $d = 0.27$ (0.03–0.58, $p = 0.08$), and substantial decrease in heterogeneity, with $I^2 = 8\%$. When Bauer et al (2018) was omitted, there was a slight increase in moderate average effect size: $d = 0.51$ (0.09–0.93), and in heterogeneity ($I^2 = 55\%$).

We also noted in the case of Hu et al (2012) that the reported mean changes and stated *t*-statistic (3.47 on 42 degrees of freedom) would imply a rather small value for the SD of HAMD changes (<3).[30] In interpreting the NAC effect size of this study, this fact should be noted along with the massive improvement reported for patients in both groups of this study, with baseline HAMD scores dropping from about 26 to only 4.1 in the placebo group and 1.4 in the NAC group. Therefore, although the resulting effect size is quite large, this obscures the fact that both groups appeared to improve nearly to the floor of the scale.

We noted by visual inspection of the forest plot and respective *d*s that three studies had large effect sizes and three had small effect sizes. Post hoc analysis showed that when these studies were aggregated as a function of large or small effect sizes, heterogeneity for each subgroup of studies was 0 (for the larger effect size subgroup, mean $d = 0.91$, 95% C.I.: 0.50–1.34; $p < 0.001$, and $I^2 = 0$; for the smaller effect size subgroup, mean $d = 0.09$, 95% C.I.: −0.21–0.41; $p = 0.607$, $I^2 = 0$).

Results were insensitive to methods of estimating missing change score standard deviations.

Meta-regression analyses did not identify any moderators that might explain this variation, including mean NAC dose, study duration, and mean baseline depressive symptom scores.

We did not assess publication bias because there were an inadequate number of included trials to properly assess a funnel plot or more advanced regression-based assessments.

4 | DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis of double-blind, placebo-controlled clinical trials evaluating the effects of NAC augmentation for bipolar depression.

Our systematic review yielded six double-blind, placebo-controlled trials that used NAC as an adjunctive agent to treat depression associated with bipolar disorder. Three of these studies were in bipolar depression, and three in mixed samples including, but not exclusively, bipolar depression. Despite some encouraging positive results from the first trials, the most recent and larger trials showed no benefits of NAC compared with placebo. Therefore, a meta-analytic summary of these contradictory results was necessary to help balance the results.

Different from previous meta-analyses,[19,20,25] which included only two studies of NAC for bipolar depression or did not evaluate this condition separated from unipolar depression, we included here data from six clinical trials and patient-level data specific to bipolar depression thus, our meta-analysis is better powered to evaluate the effects of NAC on bipolar depression. Our results suggest that treatment augmentation with NAC for bipolar depression appears to be superior to placebo, with a moderate effect size, but a large confidence interval. We found a summary effect size of 0.45, favoring NAC over placebo, which is in the range of mild to moderate. The 95% C.I. was wide though, meaning that the estimated true effect size of NAC could be as very small or negligible or very large for the doses and treatment durations included in this meta-analysis.

As expected, the heterogeneity between studies was moderate to high. Sensitivity analysis showed that the heterogeneity was not better attributed to any individual study, with the exception of Hu et al (2012). This study had several differences compared with the others, including a per-protocol analysis (rather than intent-to-treat), the primary outcome (remission at baseline rather than percentage of improvement), and background medication (a stable combination of valproate and paroxetine, as opposed to standard mood-stabilizing treatment). There were concerns for high risk of bias in this study due to a lack of description of blinding and randomization procedures. It should be noted that, when omitting this study, the average effect size of NAC decreased, and only approached statistical significance. Regarding other studies, although Bauer et al (2018) included patients in mixed episodes, the omission of this study did not substantially change our results.

Visual inspection of the forest plot and respective *d*s showed that the studies were clustered together in terms of having either very small or very large effect sizes. Post hoc analyses showed that

heterogeneity changed substantially as functioning of this clustering. These findings suggest that differences in sample characteristics or in depression assessment instruments could be a source of heterogeneity between studies. For instance, the studies with the small effect sizes used MADRS and two of the three studies with large effect sizes used HAMD. Compared with the MADRS, the HAMD is considered less internally consistent, less able to detect differences between drug and placebo, and less suitable for outpatients.[33–35] The studies with the small effect sizes had patients with longer illness duration or higher number of lifetime depressive episodes,[22,23] while the studies with large effect sizes had patients with shorter illness duration or less lifetime depressive episodes.[16,30,31] Staging models of bipolar disorder have proposed that longer illness duration and higher number of mood episodes are associated with poorer treatment response due to progressive neurobiological brain changes.[36] Finally, a tendency for early trials to show more promising results than subsequent ones has been noted elsewhere.[37]

In our meta-regression analysis, we saw no evidence that average efficacy correlates with factors such as mean NAC dose, study duration, or baseline depressive symptoms. Of note, there could be a very high risk of false negative due to the limited number of trials. Our negative results on meta-regression do not exclude the possibility that relationships between mean NAC dose, baseline depressive symptom scores, or study duration might exist at the individual level, a question that can only be addressed from patient-level data. At least regarding study duration, preliminary evidence suggest that NAC beneficial effects on depressive symptoms might appear after a prolonged period of exposure.[16,23] Other additional factors not addressed by previous studies include the interaction between NAC and the antidepressant agent being augmented. At least in animal studies, antidepressant effect of NAC augmentation varies between different antidepressants and different NAC doses.[38] Therefore, future studies could examine whether a prolonged duration (e.g., > 20 weeks), different doses, or specific antidepressant agents being augmented could lead to better improvement in depression. Finally, changes in background medication were allowed in three of the studies included in this meta-analysis.[16,22,23] We have no ability to know if any potential change in background medication might have influenced response to NAC or placebo.

Although we did not assess publication bias by statistical methods, given the low number of studies, we believe that the risk is low. No study was sponsored by NAC manufacturers, all studies had good internal validity in terms of blindness and randomization, authors were inquired, and multiple sources of search were performed to look for unpublished data.

In summary, we report here the results of a meta-analysis of double-blind, placebo-controlled trials of NAC as a treatment augmentation strategy for bipolar depression. Our results suggest that treatment augmentation with NAC for bipolar depression appears to be superior to placebo, with a moderate effect size, but a large confidence interval. This means that NAC could be on average highly beneficial or not efficacious at all, depending on moderating factors that we are unable to identify. However, given that NAC is known to have a benign safety profile, even modest adjunctive effects could be clinically relevant. Consequently, we conclude that while there are some limited evidence that NAC may have meaningful efficacy, larger well-controlled studies are necessary. These should systematically account for plausible effect-moderating variables (e.g., NAC dose, baseline severity, treatment duration, chronicity of bipolar illness, and the primary agent(s) being augmented).

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CONFLICT OF INTEREST

Dr. Nery's spouse is an employee of Eli Lilly & Co. Dr. DelBello has received research support from Amylin, Eli Lilly, Pfizer, Otsuka, GlaxoSmithKline, Merck, Martek, Novartis, Lundbeck, Pfizer, Sunovion, and Shire. She has received Consulting/Advisory Board/Honoraria/Travel support from Pfizer, Lundbeck, Sunovion, Supernus, and Otsuka. The remaining authors reported no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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