N-Acetylcysteine in Depressive Symptoms and Functionality: A Systematic Review and Meta-Analysis

Brisa S. Fernandes, MD, PhD[a,b]; Olivia M. Dean, PhD[a]; Seetal Dodd, PhD[a]; Gin S. Malhi, MD, PhD[a,c,d]; and Michael Berk, MD, PhD[a,e,*]

ABSTRACT

Objective: To assess the utility of *N*-acetylcysteine administration for depressive symptoms in subjects with psychiatric conditions using a systematic review and meta-analysis.

Data Sources: A computerized literature search was conducted in MEDLINE, Embase, the Cochrane Library, SciELO, PsycINFO, Scopus, and Web of Knowledge. No year or country restrictions were used. The Boolean terms used for the electronic database search were (NAC OR *N*-acetylcysteine OR acetylcysteine) AND (depression OR depressive OR depressed) AND (trial). The last search was performed in November 2014.

Study Selection: The literature was searched for double-blind, randomized, placebo-controlled trials using *N*-acetylcysteine for depressive symptoms regardless of the main psychiatric condition. Using keywords and cross-referenced bibliographies, 38 studies were identified and examined in depth. Of those, 33 articles were rejected because inclusion criteria were not met. Finally, 5 studies were included.

Data Extraction: Data were extracted independently by 2 investigators. The primary outcome measure was change in depressive symptoms. Functionality, quality of life, and manic and anxiety symptoms were also examined. A full review and meta-analysis were performed. Standardized mean differences (SMDs) and odds ratios (ORs) with 95% CIs were calculated.

Results: Five studies fulfilled our inclusion criteria for the meta-analysis, providing data on 574 participants, of whom 291 were randomized to receive *N*-acetylcysteine and 283 to placebo. The follow-up varied from 12 to 24 weeks. Two studies included subjects with bipolar disorder and current depressive symptoms, 1 included subjects with MDD in a current depressive episode, and 2 included subjects with depressive symptoms in the context of other psychiatric conditions (1 trichotillomania and 1 heavy smoking). Treatment with *N*-acetylcysteine improved depressive symptoms as assessed by Montgomery-Asberg Depression Rating Scale and Hamilton Depression Rating Scale when compared to placebo (SMD = 0.37; 95% CI = 0.19 to 0.55; $P < .001$). Subjects receiving *N*-acetylcysteine had better depressive symptoms scores on the Clinical Global Impressions-Severity of Illness scale at follow-up than subjects on placebo (SMD = 0.22; 95% CI = 0.03 to 0.41; $P < .001$). In addition, global functionality was better in *N*-acetylcysteine than in placebo conditions. There were no changes in quality of life. With regard to adverse events, only minor adverse events were associated with *N*-acetylcysteine (OR = 1.61; 95% CI = 1.01 to 2.59; $P = .049$).

Conclusions: Administration of *N*-acetylcysteine ameliorates depressive symptoms, improves functionality, and shows good tolerability.

J Clin Psychiatry 2016;77(4):e457–e466
dx.doi.org/10.4088/JCP.15r09984

[a]IMPACT Strategic Research Centre, Deakin University, School of Medicine, and Barwon Health, Geelong, Australia
[b]Laboratory of Calcium Binding Proteins in the Central Nervous System, Department of Biochemistry, Federal University of Rio Grande do Sul, Porto Alegre, Brazil
[c]Discipline of Psychiatry, Sydney Medical School, University of Sydney, Australia
[d]CADE Clinic, Department of Psychiatry, Royal North Shore Hospital, St Leonards, Australia
[e]Florey Institute for Neuroscience and Mental Health, Department of Psychiatry and Orygen, The National Centre of Excellence in Youth Mental Health, University of Melbourne, Parkville, Australia
**Corresponding author:* Michael Berk, MD, PhD, Deakin University, School of Medicine, Barwon Health, 285-295 Ryrie Street, Kitchener House, 3220 Geelong, Victoria, Australia (mikebe@barwonhealth.org.au).

Depressive symptoms are pervasive in a manifold of psychiatric conditions and often are a challenge to treat. Bipolar disorder and major depressive disorder (MDD) are 2 prevalent conditions, both associated with depression. Major depressive disorder is the most prevalent psychiatric disorder, and its course is typically recurrent and chronic. Remission of depressive symptoms in bipolar disorder, MDD, and other comorbid psychiatric disorders may present formidable difficulties, and full remission is only achieved by a small population of persons with these conditions and usually after several courses of treatment. This situation is aggravated by the lack of developments of new interventions capable of ameliorating depressive symptoms.[1]

One new and promising target for treating depressive symptoms is oxidative stress.[2] Both bipolar disorder and MDD have been associated with a prooxidative balance and consequent brain neurotoxicity.[3,4] Glutathione, the primary endogenous antioxidant in the brain, is vulnerable to depletion in oxidative stress states. It is synthesized from the precursor amino acids L-glutamate, L-glycine, and L-cysteine in 2 enzymatic steps. Enhancing L-cysteine supply, the rate-limiting factor in glutathione synthesis via a nutraceutical precursor, *N*-acetylcysteine, leads to a rise in brain glutathione.[5] *N*-acetylcysteine is capable of crossing the blood-brain barrier. Moreover, *N*-acetylcysteine protects against oxidative stress, chelates heavy metals, impacts glutamate neurotransmission, reduces markers of inflammation, protects against multiple models of mitochondrial dysfunction, inhibits apoptosis, enhances neurogenesis, and promotes neuronal survival in a variety of neurodegenerative preclinical models—all of which are implicated in depression.[6]

In defiance of its auspicious attributes and promising results from preclinical studies, clinical data regarding efficacy of *N*-acetylcysteine for management of

Clinical Points

- *N*-acetylcysteine has emerged as a promising adjunctive treatment for depressive symptoms, but results from different studies are conflicting.
- A meta-analysis of all double-blind, randomized controlled trials of *N*-acetylcysteine compared to placebo was performed.
- *N*-acetylcysteine successfully improved severity of depressive symptoms and functionality and can be considered as an adjunctive treatment for patients with depressive symptoms.

depressive symptoms have been mixed.[7–10] The first double-blind, randomized, placebo-controlled trial[8] of *N*-acetylcysteine was published in 2008, and it found benefits of *N*-acetylcysteine for depressive symptoms and functionality in the maintenance phase of bipolar depression. This relatively small preliminary study was followed by a larger, more substantive study,[9] which included an open-label phase for acute bipolar depression and found marked improvement of depressive symptomatology, overall functionality, and quality of life. However, in the double-blind, placebo-controlled phase of the study[10] of maintenance treatment in bipolar depression, once the participants' depressive symptoms in the open-label *N*-acetylcysteine phase had improved, they remained low in both the *N*-acetylcysteine and placebo arms. In another study[11] addressing the acute phase of MDD, *N*-acetylcysteine failed to differentiate from placebo in terms of impact on depressive symptoms at the week 12 primary end point, but it was significant at the week 16 postdiscontinuation time point. Notably, *N*-acetylcysteine showed superiority over placebo in terms of global functionality.[11] Assessing psychiatric disorders other than bipolar disorder and MDD, a study[12] that examined the efficacy of *N*-acetylcysteine in trichotillomania found no effect of *N*-acetylcysteine on depressive symptoms or functionality, while another[13] investigating heavy smokers found a marked advantage in favor of *N*-acetylcysteine over placebo for depressive symptoms. Although strictly depressive measures were not used in a very rigorous study[14] of *N*-acetylcysteine for idiopathic pulmonary fibrosis, the study found no benefits on pulmonary measures but noted improvements in *N*-acetylcysteine–treated individuals on quality of life, as assessed by the EuroQoL visual-analog scale and the 36-Item Short-Form Health Survey mental health score. Similarly, in a study[15] of *N*-acetylcysteine for epistaxis, while only minor effects were seen on epistaxis, there were improvements in work-related quality of life. It should be noted that, in all negative studies outlined above, all end points regarding depressive symptoms and functionality were numerically better in *N*-acetylcysteine than in placebo, albeit not statistically significant.

Three of the studies[8,10,11] mentioned above used *N*-acetylcysteine as an adjunctive therapy to treatment as usual.[9] This highlights a paradigm problem because gaining additional benefits on top of an already established treatment is considerably harder than providing benefit as monotherapy. This may be translated as *N*-acetylcysteine possessing, at best, a small to moderate advantage to what, in turn, would require a large and powerful sample size in order to accurately avoid false-negative results. Therefore, the potentially better profile of *N*-acetylcysteine, with a lack of statistical significance in some studies, may reflect this issue.

In order to clarify this point, we performed a systematic review and meta-analysis of all double-blind, randomized, placebo-controlled trials of *N*-acetylcysteine in depressive symptoms, irrespective of the primary pathology, to simulate real-world patients.

METHODS

This study comprised a between-group meta-analysis comparing *N*-acetylcysteine and placebo in randomized controlled trials of persons with depressive symptoms, regardless of the main psychiatric diagnosis. We adhered to the recommended guidelines for systematic reviews and meta-analyses of interventional studies statement (PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses]) and the Cochrane Collaboration.[16] Two of the authors performed the literature search, made decisions on inclusion, extracted data, and assessed quality control independently.

Search Strategy

We conducted a systematic search for all possibly eligible English and non-English peer-reviewed articles to avoid language publication bias[17] using MEDLINE, Embase, the Cochrane Library, SciELO, PsycINFO, Scopus, and Web of Knowledge. No year or country restrictions were used.[16] The Boolean terms used for the electronic database search were (NAC OR *N*-acetylcysteine OR acetylcysteine) AND (depression OR depressive OR depressed) AND (trial). The last search was performed in November 2014. We then manually checked the reference sections of the publications found through our electronic search to identify additional studies that may have been missed, and we also contacted potential authors in order to verify the existence of unpublished results. Study selection eligibility and exclusion criteria were prespecified.

Study Selection

Inclusion criteria were (1) adult subjects with presence of depressive symptoms, meeting or not meeting criteria for a full depressive episode, as defined by American Psychiatric Association; (2) double-blind, randomized controlled trials (RCTs) of *N*-acetylcysteine versus placebo; (3) studies assessing end points related to depressive or manic symptoms, functionality, or quality of life; and (4) studies with intention-to-treat, on treatment, or as per protocol analysis. Exclusion criteria were (1) duplicate reports; (2) studies conducted in subjects aged less than 18 years; (3) lack of a placebo arm; or (4) studies regarding subjects without depressive symptoms (Figure 1). The decision of whether to include studies in the meta-analysis was made based on the above criteria,

and a consensus was reached among the authors on those decisions.

Data Extraction

To avoid potential errors, 2 reviewers independently extracted data (n and mean [SD]).[16] We extracted the following data: sample size, sex, age, length of illness, body mass index (BMI), medication in use, adverse events, and design of the study. Depression scores were assessed by the Hamilton Depression Rating Scale (HDRS) or Montgomery-Asberg Depression Rating Scale (MADRS), anxiety scores by the Hamilton Anxiety Rating Scale (HARS), and mania scores by the Young Mania Rating Scale (YMRS). Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales were also collected for overall, depressive, and manic symptoms. Regarding functionality, we extracted data for Global Assessment of Functioning (GAF), Longitudinal Interval Follow-Up Evaluation-Range of Impaired Functioning Tool (LIFE-RIFT), Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interview Follow-up Evaluation (SLICE-LIFE), and Social and Occupational Functioning Assessment Scale (SOFAS). Quality of life was assessed using the Quality of Life Inventory. Scores for all scales were assessed both at baseline and at follow-up. According to information available in the studies, we performed subgroup analyses according to the outcome measured. Discrepancies in data entry were double-checked by the reviewers with the original published data, and consensus was reached.[16] When the necessary data were not available from the published article, we contacted the authors and requested the necessary information. Whenever multiple reports pertained to the same groups of patients, we retained only the original report for the meta-analytic calculations to avoid duplication of information.[16] Most of the included studies included data regarding more than 1 selected outcome. Whenever 1 study possessed more than 1 end point of interest, we extracted and analyzed them all.

Risk of Bias Assessment

We assessed the risk of bias in all included studies as suggested by the Cochrane Collaboration.[16] The potential biases analyzed were selection, performance, detection, attrition, and report bias, and these were considered as high, low, or unclear. In general, the risk of bias was low for all studies, with the exception of the risk of attrition bias, which was high for all studies, particularly Prado et al.[13]

Publication Bias

Studies with negative results are less likely to be published than studies with positive results.[16] To account for significant publication bias, we analyzed the funnel plot graph, a scatter plot of the standardized mean difference (SMD) against a measure of study size, and the Egger test.[18,19] In addition, the Orwin fail-safe N test (file drawer statistic) was used to quantify the number of possible negative omitted studies that would be required to make our results nonsignificant ($P > .05$).[20]

Statistical Analysis

Comprehensive Meta-Analysis, version 2.0 software (Biostat, Inc) was employed in all analyses. Because studies used different measurement methods, SMD was used as the main effect. The SMD is a summary statistic used in meta-analysis when all the studies assess the same outcome but measure it in a variety of ways, such as was done, for instance, for our outcome "depression scores," where the studies measured depression but used different psychometric scales (in this case, MADRS and HDRS).[16] The SMD expresses the size of the intervention effect in each study relative to the variability observed in that study. The 95% CI of the SMD was also computed. An SMD of 0.2 is considered an indication of a low effect, meaning a small difference between *N*-acetylcysteine and placebo, an SMD of 0.5 a moderate effect, and an SMD of 0.8 a large effect.[16] Although all included studies were randomized, there were some small differences in the values of the scales analyzed in the baseline, probably due to "unlucky randomization" secondary to small sample size. This could lead to a regression to the mean effect, with the arm with higher baseline scores more prone to change regardless of the true effect of the intervention. In order to take this phenomenon into account, we adjusted each meta-analysis to its baseline scores, as suggested by the Cochrane Collaboration.[16] For adverse events, we extracted the absolute number of events and performed the meta-analysis employing the odds ratio (OR) of the occurrence.[16]

We assessed heterogeneity across studies using the Cochran *Q* test, a weighted sum of the squares of the deviations of individual study SMD estimates from the overall estimate, and a *P* value of $< .10$ was considered significant (ie, showing heterogeneity).[21,22] Inconsistency across studies was then quantified with the I^2 metric. It can be interpreted as the percentage of total variation across several studies due to heterogeneity, and it is considered substantial when greater than 50%.[23] Since the analyses showed that the studies were heterogeneous for some outcomes, we pooled the SMD results from different studies weighted according to the inverse variance method of accounting for random effects, which allows population-level inferences and is more stringent than fixed-effects models. Random-effects modeling assumes a genuine diversity in the results of various studies and incorporates a between-study variance into the calculations, resulting in a more conservative analysis.[16] The direction of the SMD values was positive if subjects showed an improvement in the outcomes with *N*-acetylcysteine and was negative if they showed improvement with placebo. Studies were weighted such that the studies with the most precise parameters, quantified by the sample size and 95% CI, had more influence in the analyses.[16]

The meta-analyses consisted of 2 steps. First, we performed the overall analysis for each outcome of the meta-analysis. Second, sensitivity analyses were conducted to ascertain whether the results of our analyses were strongly influenced by any single study or studies sharing some characteristic. The overall significance was recomputed after each study or group of studies with a common feature was deleted from

the analysis. The level of significance for the SMD estimates was set at $P < .05$.

RESULTS

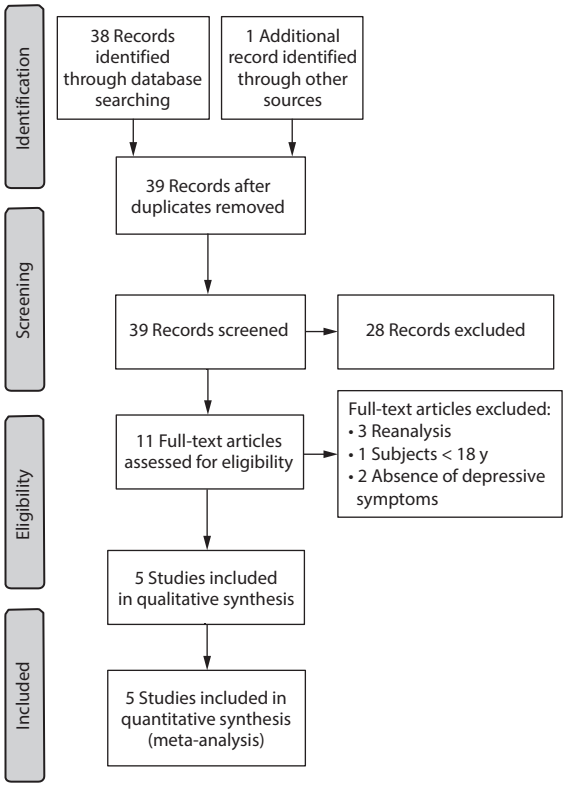
We identified 38 studies, after excluding duplicates, through electronic searches, all of which had an English abstract. Of those, 28 were excluded on the basis of title and abstract, leaving 10 studies for further evaluation. Three RCTs were excluded, 2 because they did not include subjects with depressive symptoms[7,14] and 1 because it addressed childhood.[24] Three studies were duplicates and were also excluded.[25–27] One additional epub-ahead-of-print study was included.[13] In total, 5 studies fulfilled our inclusion criteria for the meta-analysis, providing data on 574 participants, of whom 291 were randomized to receive *N*-acetylcysteine as an add-on treatment and 283 to placebo (Figure 1). Of those, 2 studies[8,10] included subjects with bipolar disorder and current depressive symptoms; 1 study,[11] subjects with MDD in a current depressive episode; and 2 studies, subjects with depressive symptoms in the context of other psychiatric condition (1 trichotillomania[12] and 1 heavy smoking[13]). We included all studies examining persons with depressive symptoms, meaning it was not necessary to fulfill criteria for a full depressive episode. Two studies[11,12] provided data for anxiety symptoms, 2 studies[8,10] for depressive symptoms on the CGI-I, 2 studies[8,10] for manic symptoms on the CGI-I, 2 studies[8,10] for the CGI-I overall, 3 studies[8,10,11] for depressive symptoms on the CGI-S, 2 studies[8,10] for manic symptoms on the CGI-S, 2 studies[8,10] for the CGI-S overall, 5 studies[8,10–13] for depressive symptoms as assessed by HDRS or MADRS, 3 studies[8,10,11] for GAF, 3 studies[8,10,11] for LIFE-RIFT, 2 studies[8,10] for manic symptoms as assessed by YMRS, 4 studies[8,10–12] for quality of life, 3 studies[8,10,11] for the SLICE-LIFE, and 3 studies[8,10,11] for the SOFAS. All studies except one[13] provided more than 1 pairwise comparison.

Table 1 summarizes the included studies. The studies were published from 2008 to 2015 and varied in sample size (from 31 to 269). The dose of *N*-acetylcysteine employed ranged from 2 to 3 grams daily. The mean participant age varied from 32.7 to 50.7 years. All 5 studies were double-blind RCTs. Three[8,10,11] used *N*-acetylcysteine as an add-on to treatment as usual compared to a placebo arm, and 2 studies[12,13] used *N*-acetylcysteine as the main psychiatric medication. Four of the studies[8,10–12] used intention-to-treat analysis, and 1 study[13] employed per protocol analysis.

N-Acetylcysteine Improves Depressive Symptoms With No Changes in Manic and Anxiety Symptoms

Overall, random-effects meta-analysis showed that, when compared to placebo, add-on treatment with *N*-acetylcysteine moderately improved depressive symptoms as assessed by MADRS and HDRS (SMD = 0.37, 95% CI = 0.19 to 0.55, $P < .001$; 5 between-group comparisons, n = 574). Subjects receiving *N*-acetylcysteine consistently presented better scores regarding depressive symptoms on the CGI-S at the follow-up than subjects on placebo

Figure 1. PRISMA Flow Diagram of the Systematic Review Showing the Study Inclusion and Exclusion Process



Abbreviation: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

(SMD = 0.22, 95% CI = 0.03 to 0.41, $P < .001$; 3 between-group comparisons, n = 493). When analyzing depressive symptoms on the CGI-I, there were no significant differences between *N*-acetylcysteine and placebo, although there was a trend in favor of *N*-acetylcysteine (SMD = 0.17, 95% CI = −0.09 to 0.43, $P = .199$; 2 between-group comparisons, n = 224). This last analysis may be underpowered, since it consisted of only 2 studies, and the 95% CI was consequently large, reflecting the imprecision of the analysis (Figure 2, Table 2).

When we carried out the analyses regarding severity of manic and anxiety symptoms, we found no effect of *N*-acetylcysteine over placebo on manic symptoms as assessed by the YMRS, CGI-S, CGI-I, and on anxiety symptoms as measured by HARS. In addition, there were no differences on the CGI-S overall and on the CGI-I overall (Figure 2, Table 2). However, it is worthwhile to point out that each one of the analyses above consisted of only 2 studies and that, since the inclusion criteria was subjects with depressive symptoms, the scores regarding manic symptoms were very low at baseline and consequently less prone to change.

N-Acetylcysteine Improves Functionality in Subjects With Depressive Symptoms Without Changes in Quality of Life

Another important outcome in the studies analyzed was functionality. Three of the studies included data regarding

Table 1. Demographic Characteristics of Randomized Controlled Trials Included in the Meta-Analysis of *N*-Acetylcysteine Versus Placebo for Subjects With Depressive Symptoms

Study	Subjects	Design	Intervention	Follow-Up, wk	Treatment	n	Dropout (%)	Male/Female Gender, n/n	Age, Mean, y	Smoking, n (%)	Primary and Secondary Outcomes	Outcomes Scores Included in the Meta-Analysis[a]	Psychiatric Medication at Baseline
Berk et al, 2008[8]	Bipolar disorder, current depressive state	Double-blind, RCT, ITT analysis	*N*-acetylcysteine 1 g twice daily add-on to treatment as usual	24	*N*-acetylcysteine Placebo	38 37	13 (35.0) 14 (39.0)	15/23 15/25	44.6 46.6	15 (39.5) 19 (51.4)	Changes in mood symptoms, functioning, and quality of life	CGI-S depression, CGI-S mania, CGI-S overall, CGI-I depression, CGI-I mania, CGI-I overall, MADRS (used for the depressive score), GAF, LIFE-RIFT, YMRS (used for the mania score), Quality of Life Inventory, SLICE-LIFE, SOFAS	Mood stabilizers, antipsychotics, antidepressants, lamotrigine, benzodiazepines
Berk et al, 2012[10]	Bipolar disorder, residual depressive symptoms	Double-blind, RCT, ITT analysis	*N*-acetylcysteine 1 g twice daily add-on to treatment as usual	24	*N*-acetylcysteine Placebo	76 73	17 (22.4) 11 (15.1)	16/60 32/41	47.1 44.4	20 (30.8) 29 (43.3)	Changes in mood symptoms, functioning, and quality of life	CGI-S depression, CGI-S mania, CGI-S overall, CGI-I depression, CGI-I mania, CGI-I overall, MADRS (used for the depressive score), GAF, LIFE-RIFT, YMRS (used for the mania score), Quality of Life Inventory, SLICE-LIFE, SOFAS	Mood stabilizers, antipsychotics, antidepressants, lamotrigine, benzodiazepines
Berk et al, 2014[11]	MDD, current depressive episode	Double-blind, RCT, ITT analysis	*N*-acetylcysteine 1 g twice daily add-on to treatment as usual	12	*N*-acetylcysteine Placebo	135 134	27 (20.0) 36 (26.1)	50/84 60/75	49.9 50.5	22 (16.3) 25 (18.7)	Changes in mood symptoms, functioning, and quality of life	CGI-S depression, MADRS (used for the depressive score), GAF, LIFE-RIFT, YMRS (used for the mania score), Quality of Life Inventory, SLICE-LIFE, SOFAS, HARS (used for the anxiety score)	Drug-free, mood stabilizers, antipsychotics, antidepressants, benzodiazepines
Grant et al, 2009[12]	MDD or depressive symptoms in trichotillomania	Double-blind, RCT, ITT analysis	*N*-acetylcysteine 1.2 g twice daily add-on to treatment as usual	12	*N*-acetylcysteine Placebo	25 25	03 (12.0) 03 (12.0)	01/24 04/21	32.7 35.8	NA	Changes in mood symptoms, trichotillomania habits, and quality of life	HDRS (used for the depressive score), Quality of Life Inventory, HARS (used for the anxiety score)	Drug-free, antidepressants
Prado et al, 2015[13]	MDD or depressive symptoms in smokers	Double-blind, RCT, PP analysis	*N*-acetylcysteine 1.5 g twice daily add-on to treatment as usual	12	*N*-acetylcysteine Placebo	17 14	06 (35.3) 10 (71.4)	07/10 02/12	51.9 50.7	17 (100.0) 17 (100.0)	Changes in cigarettes use and in depressive symptoms	HDRS (used for the depressive score)	NA

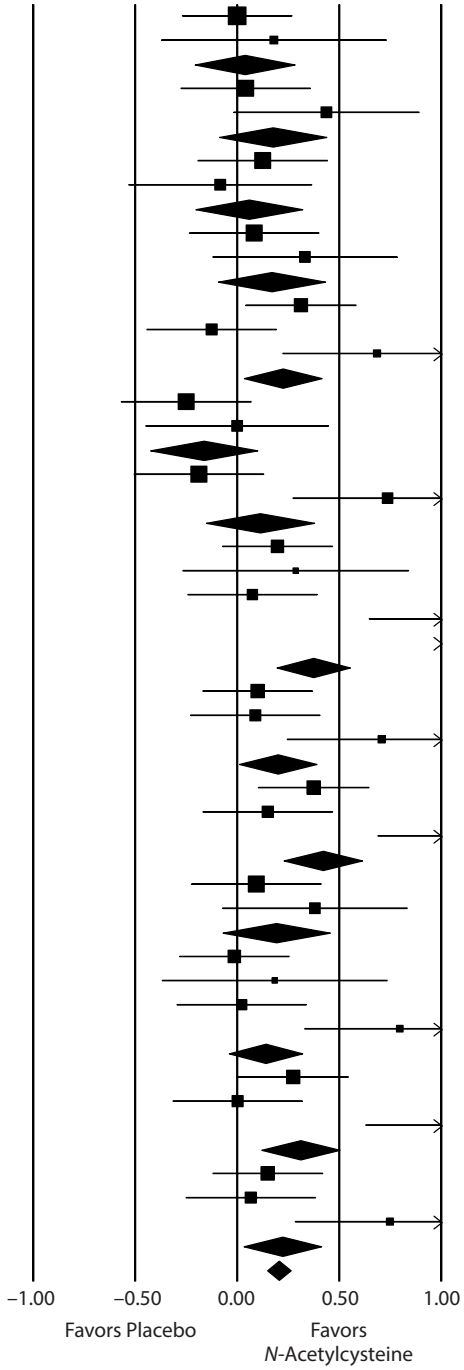
[a]Depression scores were assessed by Hamilton Depression Rating Scale (HDRS) or Montgomery-Asberg Depression Rating Scale (MADRS); anxiety scores, by the Hamilton Anxiety Rating Scale (HARS); and mania scores, by the Young Mania rating Scale (YMRS).

Abbreviations: CGI-I = Clinical Global Impression-Improvement scale, CGI-S = Clinical Global Impression-Severity of Illness scale, GAF = Global Assessment of Functioning, ITT = intention to treat, LIFE-RIFT = Longitudinal Interval Follow-Up Evaluation-Range of Impaired Functioning Tool, MDD = major depressive disorder, NA = not available, PP = per protocol, RCT = randomized controlled trial, SLICE-LIFE = Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interview Follow-up Evaluation, SOFAS = Social and Occupational Functioning Assessment Scale.

It is illegal to post this copyrighted PDF on any website.

Figure 2. Forest Plot for Random Effects Meta-Analysis of Randomized Controlled Trials of *N*-Acetylcysteine Versus Placebo for Depressive Symptoms for Outcomes Related to Depressive, Manic, and Anxiety Symptoms and to Functionality and Quality of Life[a]

Study	Outcome	SMD	*P*
Berk et al, 2014[11]	Anxiety scores	0.00	1.00
Grant et al, 2009[12]	Anxiety scores	0.18	.53
		0.03	.78
Berk et al, 2012[10]	CGI-I depression	0.04	.80
Berk et al, 2008[8]	CGI-I depression	0.44	.06
		0.17	.20
Berk et al, 2012[10]	CGI-I mania	0.13	.45
Berk et al, 2008[8]	CGI-I mania	−0.08	.72
		0.06	.68
Berk et al, 2012[10]	CGI-I overall	0.08	.61
Berk et al, 2008[8]	CGI-I overall	0.33	.15
		0.17	.22
Berk et al, 2014[11]	CGI-S depression	0.31	.03
Berk et al, 2012[10]	CGI-S depression	−0.13	.45
Berk et al, 2008[8]	CGI-S depression	0.69	.00
		0.22	.02
Berk et al, 2012[10]	CGI-S mania	−0.25	.13
Berk et al, 2008[8]	CGI-S mania	0.00	1.00
		−0.17	.22
Berk et al, 2012[10]	CGI-S overall	−0.19	.25
Berk et al, 2008[8]	CGI-S overall	0.74	.00
		0.11	.42
Berk et al, 2014[11]	Depression scores	0.20	.16
Grant et al, 2009[12]	Depression scores	0.29	.31
Berk et al, 2012[10]	Depression scores	0.08	.65
Berk et al, 2008[8]	Depression scores	1.13	.00
Prado et al, 2015[13]	Depression scores	5.00	.00
		0.37	.00
Berk et al, 2014[11]	GAF	0.10	.47
Berk et al, 2012[10]	GAF	0.09	.59
Berk et al, 2008[8]	GAF	0.71	.00
		0.20	.04
Berk et al, 2014[11]	LIFE-RIFT	0.38	.01
Berk et al, 2012[10]	LIFE-RIFT	0.15	.36
Berk et al, 2008[8]	LIFE-RIFT	1.18	.00
		0.42	.00
Berk et al, 2012[10]	Mania scores	0.09	.57
Berk et al, 2008[8]	Mania scores	0.38	.10
		0.19	.16
Berk et al, 2014[11]	Quality of Life Inventory	−0.01	.92
Grant et al, 2009[12]	Quality of Life Inventory	0.18	.52
Berk et al, 2012[10]	Quality of Life Inventory	0.02	.89
Berk et al, 2008[8]	Quality of Life Inventory	0.80	.00
		0.14	.14
Berk et al, 2014[11]	SLICE-LIFE	0.28	.05
Berk et al, 2012[10]	SLICE-LIFE	0.00	.99
Berk et al, 2008[8]	SLICE-LIFE	1.11	.00
		0.31	.00
Berk et al, 2014[11]	SOFAS	0.15	.28
Berk et al, 2012[10]	SOFAS	0.07	.68
Berk et al, 2008[8]	SOFAS	0.75	.00
		0.22	.02
Overall		0.20	.00



[a]The sizes of the squares are proportional to sample size. A total of 5 studies were included, comprising 574 subjects, 291 being allocated to *N*-acetylcysteine and 283 to placebo. The diamonds represent the effect size, and the horizontal lines represent the 95% CI.

Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, GAF = Global Assessment of Functioning, LIFE-RIFT = Longitudinal Interval Follow-Up Evaluation-Range of Impaired Functioning, SLICE-LIFE = Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interview Follow-up Evaluation, SMD = standardized mean difference, SOFAS = Social and Occupational Functioning Assessment Scale.

Table 2. Statistics on the Meta-Analyses Regarding Double-Blind Randomized Clinical Trials of *N*-Acetylcysteine Versus Placebo in Persons With Depressive Symptoms

Groupwise Outcome[a]	No. of Pairwise Comparisons	*N*-Acetylcysteine, n	Placebo, n	Meta-Analysis				Heterogeneity		
				SMD	95% CI		*P*	I^2	*Q*	*P*
Depression scores	5	291	283	0.37	0.19	0.55	**.001***	92.64	54.38	.001
Anxiety scores	2	160	159	0.03	−0.21	0.28	.779	0.00	0.32	.568
Mania scores	2	114	110	0.05	−0.20	0.31	.680	0.01	0.77	.378
CGI-S depression	3	249	244	0.22	0.03	0.41	**.023***	77.01	8.69	.013
CGI-S mania	2	114	110	−0.16	−0.42	0.09	.216	0.00	0.77	.378
CGI-S overall	2	114	110	0.11	−0.15	0.37	.418	90.18	10.19	.001
CGI-I depression	2	114	110	0.17	−0.09	0.43	.199	47.99	1.92	.568
CGI-I mania	2	114	110	0.05	−0.20	0.31	.680	0.00	0.54	.463
CGI-I overall	2	114	110	0.16	−0.09	0.42	.215	0.00	0.76	.382
GAF	3	249	244	0.19	0.01	0.39	**.042***	63.81	5.52	.063
LIFE-RIFT	3	249	244	0.42	0.23	0.61	**.001***	83.26	11.45	.003
SLICE-LIFE	3	249	244	0.31	0.12	0.50	**.002***	85.76	14.04	.001
SOFAS	3	249	244	0.22	0.03	0.41	**.024***	66.84	6.03	.049
Quality of Life Inventory	4	274	269	0.14	−0.04	0.32	.136	67.60	9.26	.026

[a]Depression scores were assessed by Hamilton Depression Rating Scale (HDRS) or Montgomery-Asberg Depression Rating Scale (MADRS); anxiety scores, by the Hamilton Anxiety Rating Scale (HARS); and mania scores, by the Young Mania Rating Scale (YMRS).
*$P < .05$.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impression-Severity of Illness scale, GAF = Global Assessment of Functioning, LIFE-RIFT = Longitudinal Interval Follow-Up Evaluation-Range of Impaired Functioning Tool, SLICE-LIFE = Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interview Follow-up Evaluation, SMD = standardized mean difference, SOFAS = Social and Occupational Functioning Assessment Scale.

this domain. The scales considered in the studies were GAF, LIFE-RIFT, SLICE-LIFE, and SOFAS. In general, there was a consistent benefit of treatment with *N*-acetylcysteine over placebo in all functionality scales considered above (Figure 2, Table 2). However, when considering quality of life as assessed by the Quality of Life Inventory, we found no benefit of *N*-acetylcysteine over placebo (Figure 2, Table 2).

Sensitivity Analyses

The heterogeneity for the analyses was moderate or high. We verified that the high heterogeneity was mostly due to the study of MDD.[11] Thereafter, we conducted a sensitivity analysis in all meta-analyses, excluding studies one at a time to determine the robustness of the analyses and to verify whether a particular study was responsible for the high heterogeneity. No single study thoroughly explained the heterogeneity, and the results remained significant in all cases, with the exception of the analyses regarding the SLICE-LIFE and SOFAS, where, when the study by Berk et al,[8] was excluded, the significance was lost. In order to ascertain the risk of bias in the studies included, we also reran the analysis regarding depressive symptoms, excluding the study by Prado et al,[13] which was the only one that employed a per protocol in lieu of an intention-to-treat analysis and that presented a particularly high risk for attrition bias. Again, the results remained significant, although there was a discrete decrease in the SMD from 0.37 (SMD = 0.37, 95% CI = 0.19 to 0.55, $P < .001$) to 0.32 (SMD = 0.32, 95% CI = 0.12 to 0.45, $P = 0.001$), showing that the positive result regarding improvement of depressive symptoms with *N*-acetylcysteine was not due to the inclusion of a study with a less strict methodology.

Safety Profile of *N*-Acetylcysteine

N-acetylcysteine was not associated with more severe adverse events (OR = 1.04, 95% CI = 0.43 to 2.51, $P = .920$; 5 between-group comparisons, n = 574). Severe adverse events were only presented in 3 of the studies,[8,10,11] with 2 of the studies[12,13] presenting only minor adverse events. Most severe adverse events were hospitalizations due to deteriorations in mental state.

Regarding minor adverse events, the most common reported were gastrointestinal complaints such as nausea and heartburn and musculoskeletal complaints such as back and joint pain. Additional reports included decreased energy and headaches. In general, *N*-acetylcysteine was associated with an increase in minor adverse events (OR = 1.61, 95% CI = 1.01 to 2.59, $P = .049$; 5 between-group comparisons, n = 574).

Publication Bias and Sample Power

We found no evidence of publication bias in the funnel plot, and the Egger test was not significant ($P = .19$). The Duval and Tweedie trim and fill method found no negative missing studies. Moreover, the Orwin fail-safe N test yielded 49 studies as the number of negative studies necessary to turn our positive results into negative ones.

In addition, we calculated the numbers of subjects that were needed to detect differences with a power of 0.80 with an α of .05 (2-sided), considering the SMD of 0.37 for depressive symptoms as the "true" magnitude difference for *N*-acetylcysteine and placebo. The calculations suggested that 48 subjects in each group would be necessary to reliably detect differences between *N*-acetylcysteine and placebo when considering depressive symptoms. Based on this, just 2 of the included studies were sufficiently powered to reliably detect differences in this outcome.

DISCUSSION

This meta-analysis of *N*-acetylcysteine compared to placebo in subjects with depressive symptoms included a

total of 5 double-blind, RCTs, with a total of 574 participants. It shows that *N*-acetylcysteine has a moderate effect over placebo in decreasing depressive symptoms and improving functionality over a follow-up of 12 to 24 weeks. However, treatment with *N*-acetylcysteine did not improve quality of life over the same period and was associated with a small increase in minor adverse events.

If *N*-acetylcysteine has efficacy for depression, this raises the question as to why this might be. *N*-acetylcysteine impacts a wide array of pathways and systems known to be dysregulated in depression, including inflammation,[28–31] heavy metal chelation, glutathione and oxidative stress,[32–36] glutamate and dopamine neurotransmission,[37] mitochondrial biogenesis, apoptosis, and neurogenesis.[1] Determining which of these is the predominant operative pathway is the next challenge for the field.[6]

Nevertheless, oxidative stress was the underpinning hypothesis leading to exploration of the role of *N*-acetylcysteine.[6] Data confirming the role of redox dysregulation in mood disorders derive from 4 main areas: (1) evidence of dysregulated oxidative defenses[38]; (2) data on effects of oxidative stress on cellular constituents, particularly lipids, proteins, and DNA[38]; (3) evidence that known mood disorder treatments influence oxidative processes[6]; and (4) structural evidence of a neuroprogressive process. Additionally, glutamate has been implicated in mood disorders and can be modulated by *N*-acetylcysteine via its effects on cystine glutamate exchange.[5] *N*-acetylcysteine has putative anti-inflammatory effects that are again concordant with an emerging role of inflammatory processes in depression. Finally, and in keeping with the actions of almost all accepted antidepressants, *N*-acetylcysteine administration in the forced swim test results in a significant decrease in the immobility time in male Wistar rats.[39] All of these factors in conjunction with the findings in our study are concordant with an acute antidepressant action for *N*-acetylcysteine.[6]

Interestingly, we found positive results for global functionality in addition to the benefits on depression. This is a particularly clinically meaningful outcome and may suggest that the usefulness of *N*-acetylcysteine extends beyond improvement of symptoms of depression and that it can ameliorate some of the functional consequences that result from depression.

Our study relied on a moderate sample size considering the field (5 studies with a total of 574 participants), which permitted us to draw results through meta-analysis technique. Our results are unlikely to be caused by publication bias, since the funnel plot was symmetrical,[18] and a very large amount of negative unpublished studies would be necessary to shift these positive results into nonsignificance. In addition, through a series of sensitivity and subgroup analyses, we were able to rule out the possibility that the results were biased due to a unique outlier. The above-mentioned approach also allowed us to investigate and rule out any single study as the sole source of the moderate or high heterogeneity found in most of the analyses. Furthermore, the paucity of exclusion criteria in addition to the examination of depressive symptoms and the broad range of pathologies associated with depressive symptoms—in this case, MDD, bipolar disorder, trichotillomania, and heavy smoking—reinforces the translational validity of these data into clinical practice.

Notwithstanding its strengths, our article has some inherent limitations due to its design and statistical methods employed. First, meta-analysis is retrospective research in nature, affected by the methodological rigor of the studies included, comprehensiveness of search strategies, and possibility of publication bias.[16] We tried to keep the probability of bias to a minimum by doing a thorough search for published and unpublished data and by using explicit criteria for study selection, data collection, and data analysis. Therefore, 3 notable studies[7,14,24] were not eligible for our meta-analysis for legitimate reasons. We believe that we have been robust in our approach and that the results and conclusions can, therefore, provide reliable recommendations for clinical practice.

Second, as with other meta-analyses, our results should be interpreted with caution because individual studies varied greatly with respect to the demographic characteristics of participants, pathology responsible for the depressive symptoms, and duration of follow-up. Therefore, our report can provide information only about whether *N*-acetylcysteine 2 to 3 grams daily is effective for reduction of depressive symptoms in general and for reinforcing benefits in functionality over placebo as an adjunctive therapy. The study cannot provide evidence of efficacy of *N*-acetylcysteine in monotherapy or superiority of *N*-acetylcysteine over other treatments approved for depressive symptoms, such as, for instance, classical antidepressants for MDD or lithium and lamotrigine for bipolar depression. However, it is worth pointing out that *N*-acetylcysteine is considered a nutraceutical with a benign, low-risk profile. This was also confirmed in this study, with *N*-acetylcysteine being associated only with minor adverse events, most commonly gastrointestinal and musculoskeletal symptoms, and not with severe adverse outcomes.

Third, as previously stated, moderate to high heterogeneity was pinpointed across most of the analyses. Although we tried to investigate the source of heterogeneity through a series of statistical techniques, it could not be clarified without access to individual participant data.

Fourth, sufficient data were not available to reliably analyze effects of *N*-acetylcysteine on quality of life and manic symptoms. These particular meta-analyses may have failed to achieve statistical significance due to a lack of power, giving us a false-negative result. This may particularly be the case in the quality of life analysis, where we found no benefit of *N*-acetylcysteine over placebo, regardless of the improvement in functionality. The follow-up also varied from 12 to 24 weeks, so it is not possible to extrapolate these positive results in depressive symptoms and functionality over a longer period. It is also worth mentioning that the absence of benefit of *N*-acetylcysteine in the quality of life domain may be due to the short follow-up, since we

might speculate that improvement in quality of life would consequently follow improvement of functionality in the long term. This would be in line with the glutathione deficit hypothesis, since some length of time would be necessary for *N*-acetylcysteine to restore glutathione levels and exert an effect.[6] It is also worth noting that none of the studies reported assessment of glutathione, glutamate, or oxidative stress; thus, we cannot assess whether changes in their levels modulate the effect of *N*-acetylcysteine.

Our meta-analytic findings substantiate the use of *N*-acetylcysteine for the treatment of depressive symptoms in psychiatric clinical practice. If the benefits of *N*-acetylcysteine for depressive symptoms and functionality are germane to diverse disorders, data regarding which of its many pharmacodynamic mechanisms are most critical and whether its beneficial effects last beyond 24 weeks of treatment remain to be confirmed in larger and longer randomized, placebo-controlled clinical trials.

Submitted: March 23, 2015; accepted May 18, 2015.

Drug names: lamotrigine (Lamictal and others), lithium (Lithobid and others).

Potential conflicts of interest: **Dr Berk** has received grant/research support from National Institutes of Health, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, National Health and Medical Research Council (NHMRC), Beyond Blue, Rotary Health, Geelong Medical Research Foundation, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Meat and Livestock Board, Organon, Novartis, Mayne, Servier, and Woolworths; has been a speaker for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Merck, Pfizer, Sanofi Synthelabo, Servier, Solvay, and Wyeth; and has served as a consultant to AstraZeneca, Bioadvantex, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Merck, and Servier. He is also a co-inventor of provisional patents regarding the use of *N*-acetylcysteine and related compounds for psychiatric indications, which, while assigned to the Florey Institute for Neuroscience and Mental Health, could lead to a commercialization event. **Dr Dean** is a research fellow and has received grant support from the Brain and Behavior Foundation, Simons Autism Foundation, Australian Rotary Health, Stanley Medical Research Institute, Deakin University, Brazilian Society Mobility Program Lilly, NHMRC, and an Australasian Society for Bipolar and Depressive Disorders/Servier grant. She has also received in kind support from BioMedica Nutraceuticals, NutritionCare, and Bioceuticals. **Dr Dodd** has received grant funding from the Stanley Medical Research Institute, NHMRC, Beyond Blue, Australian Rotary Health Research Fund, Simons Foundation, Geelong Medical Research Foundation, Fondation FondaMental, Eli Lilly, GlaxoSmithKline, Organon, Mayne, and Servier; has received speaker's fees from Eli Lilly; has received advisory board fees from Eli Lilly and Novartis; and has received conference travel support from Servier. **Drs Fernandes** and **Malhi** report no conflicts of interest.

Funding/support: Dr Fernandes is supported by a scholarship from CNPq (National Council for Scientific and Technological Development), Brazil. Dr Berk is supported by a NHMRC Senior Principal Research Fellowship 1059660.

REFERENCES

1. Berk M, Kapczinski F, Andreazza AC, et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. *Neurosci Biobehav Rev*. 2011;35(3):804–817.
2. Berk M, Williams LJ, Jacka FN, et al. So depression is an inflammatory disease, but where does the inflammation come from? *BMC Med*. 2013;11:200.
3. Brown NC, Andreazza AC, Young LT. An updated meta-analysis of oxidative stress markers in bipolar disorder. *Psychiatry Res*. 2014;218(1–2):61–68.
4. Palta P, Samuel LJ, Miller ER 3rd, et al. Depression and oxidative stress: results from a meta-analysis of observational studies. *Psychosom Med*. 2014;76(1):12–19.
5. Kau KS, Madayag A, Mantsch JR, et al. Blunted cystine-glutamate antiporter function in the nucleus accumbens promotes cocaine-induced drug seeking. *Neuroscience*. 2008;155(2):530–537.
6. Berk M, Malhi GS, Gray LJ, et al. The promise of N-acetylcysteine in neuropsychiatry. *Trends Pharmacol Sci*. 2013;34(3):167–177.
7. Berk M, Copolov D, Dean O, et al. N-acetyl cysteine as a glutathione precursor for schizophrenia—a double-blind, randomized, placebo-controlled trial. *Biol Psychiatry*. 2008;64(5):361–368.
8. Berk M, Copolov DL, Dean O, et al. N-acetyl cysteine for depressive symptoms in bipolar disorder—a double-blind randomized placebo-controlled trial. *Biol Psychiatry*. 2008;64(6):468–475.
9. Berk M, Dean O, Cotton SM, et al. The efficacy of N-acetylcysteine as an adjunctive treatment in bipolar depression: an open label trial. *J Affect Disord*. 2011;135(1–3):389–394.
10. Berk M, Dean OM, Cotton SM, et al. Maintenance N-acetyl cysteine treatment for bipolar disorder: a double-blind randomized placebo controlled trial. *BMC Med*. 2012;10(1):91.
11. Berk M, Dean OM, Cotton SM, et al. The efficacy of adjunctive N-acetylcysteine in major depressive disorder: a double-blind, randomized, placebo-controlled trial. *J Clin Psychiatry*. 2014;75(6):628–636.
12. Grant JE, Odlaug BL, Kim SW. N-acetylcysteine, a glutamate modulator, in the treatment of trichotillomania: a double-blind, placebo-controlled study. *Arch Gen Psychiatry*. 2009;66(7):756–763.
13. Prado E, Maes M, Piccoli LG, et al. N-acetylcysteine for therapy-resistant tobacco use disorder: a pilot study. *Redox Rep*. 2015;20(5):215–222.
14. Idiopathic Pulmonary Fibrosis Clinical Research Network, Martinez FJ, de Andrade JA, Anstrom KJ, et al. Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370(22):2093–2101.
15. de Gussem EM, Snijder RJ, Disch FJ, et al. The effect of N-acetylcysteine on epistaxis and quality of life in patients with HHT: a pilot study. *Rhinology*. 2009;47(1):85–88.
16. Higgins JPT, Green S, eds. *Handbook for Systematic Reviews of Interventions, Version 5.1.0*. London, UK: The Cochrane Collaboration; 2011.
17. Egger M, Zellweger-Zähner T, Schneider M, et al. Language bias in randomised controlled trials published in English and German. *Lancet*. 1997;350(9074):326–329.
18. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–634.
19. Soeken KL, Sripusanapan A. Assessing publication bias in meta-analysis. *Nurs Res*. 2003;52(1):57–60.
20. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56(2):455–463.
21. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–560.
22. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med*. 1997;127(9):820–826.
23. Bowden J, Tierney JF, Copas AJ, et al. Quantifying, displaying and accounting for heterogeneity in the meta-analysis of RCTs using standard and generalised Q statistics. *BMC Med Res Methodol*. 2011;11(1):41.
24. Bloch MH, Panza KE, Grant JE, et al. N-Acetylcysteine in the treatment of pediatric trichotillomania: a randomized, double-blind, placebo-controlled add-on trial. *J Am Acad Child Adolesc Psychiatry*. 2013;52(3):231–240.
25. Magalhães PV, Dean OM, Bush AI, et al. N-acetylcysteine for major depressive episodes in bipolar disorder. *Rev Bras Psiquiatr*. 2011;33(4):374–378.
26. Magalhães PV, Dean OM, Bush AI, et al. N-acetyl cysteine add-on treatment for bipolar II disorder: a subgroup analysis of a randomized placebo-controlled trial. *J Affect Disord*. 2011;129(1–3):317–320.
27. Magalhães PV, Dean OM, Bush AI, et al. A preliminary investigation on the efficacy of N-acetyl cysteine for mania or hypomania. *Aust N Z J Psychiatry*. 2013;47(6):564–568.
28. Beloosesky R, Weiner Z, Ginsberg Y, et al. Maternal N-acetyl-cysteine (NAC) protects the rat fetal brain from inflammatory cytokine responses to lipopolysaccharide (LPS). *J Matern Fetal Neonatal Med*. 2012;25(8):1324–1328.
29. Tsai GY, Cui JZ, Syed H, et al. Effect of N-acetylcysteine on the early expression of inflammatory markers in the retina and plasma of diabetic rats. *Clin Experiment Ophthalmol*. 2009;37(2):223–231.
30. Wang X, Svedin P, Nie C, et al. N-acetylcysteine reduces lipopolysaccharide-sensitized hypoxic-ischemic brain injury. *Ann Neurol*. 2007;61(3):263–271.
31. Brietzke E, Stertz L, Fernandes BS, et al. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. *J Affect Disord*. 2009;116(3):214–217.
32. Chen Y, Curran CP, Nebert DW, et al. Effect of chronic glutathione deficiency on the behavioral phenotype of Gclm–/– knockout mice. *Neurotoxicol Teratol*. 2012;34(4):450–457.
33. Choy KH, Dean O, Berk M, et al. Effects of N-acetyl-cysteine treatment on glutathione depletion and a short-term spatial memory deficit in 2-cyclohexene-1-one-treated rats. *Eur J Pharmacol*. 2010;649(1–3):224–228.
34. Dean O, Bush AI, Berk M, et al. Glutathione depletion in the brain disrupts short-term spatial memory in the Y-maze in rats and mice.

Behav Brain Res. 2009;198(1):258–262.
35. Konradi C, Eaton M, MacDonald ML, et al. Molecular evidence for mitochondrial dysfunction in bipolar disorder. *Arch Gen Psychiatry*. 2004;61(3):300–308.
36. Kulak A, Cuenod M, Do KQ. Behavioral phenotyping of glutathione-deficient mice: relevance to schizophrenia and bipolar disorder. *Behav Brain Res*. 2012;226(2):563–570.
37. Olive MF, Cleva RM, Kalivas PW, et al. Glutamatergic medications for the treatment of drug and behavioral addictions. *Pharmacol Biochem Behav*. 2012;100(4):801–810.
38. Andreazza AC, Kauer-Sant'anna M, Frey BN, et al. Oxidative stress markers in bipolar disorder: a meta-analysis. *J Affect Disord*. 2008;111(2–3):135–144.
39. Ferreira FR, Biojone C, Joca SR, et al. Antidepressant-like effects of N-acetyl-L-cysteine in rats. *Behav Pharmacol*. 2008;19(7):747–750.

It is illegal to post this copyrighted PDF on any website.