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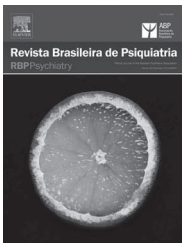

ORIGINAL ARTICLE

N-acetylcysteine for major depressive episodes in bipolar disorder

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DESCRIPTORS
Bipolar disorder;
Depression;
Acetylcysteine;
Antioxidants;
Oxidative stress.

Abstract
Objective: In this report, we aimed to evaluate the effect of add-on N-acetylcysteine (NAC) on depressive symptoms and functional outcomes in bipolar disorder. To that end, we conducted a secondary analysis of all patients meeting full criteria for a depressive episode in a placebo-controlled trial of adjunctive NAC for bipolar disorder. *Method*: Twenty-four week randomised clinical trial comparing adjunctive NAC and placebo in individuals with bipolar disorder experiencing major depressive episodes. Symptomatic and functional outcome data were collected over the study period. *Results*: Seventeen participants were available for this report. Very large effect sizes in favor of NAC were found for depressive symptoms and functional outcomes at endpoint. Eight of the ten participants on NAC had a treatment response at endpoint; the same was true for only one of the seven participants allocated to placebo. *Discussion*: These results indicate that adjunctive NAC may be useful for major depressive episodes in bipolar disorder. Further studies designed to confirm this hypothesis are necessary.

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DESCRITORES
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N-acetilcisteína para o tratamento de episódios de depressão maior no transtorno bipolar

Resumo
Objetivo: Neste relato, avaliamos o efeito da N-acetilcisteína (NAC) adjuvante em sintomas depressivos e desfechos funcionais no transtorno bipolar. Para isso, conduzimos uma análise secundária de todos os pacientes com critérios diagnósticos para um episódio depressivo em um ensaio clínico randomizado comparando NAC adjuvante com placebo no transtorno bipolar. *Método*: Ensaio clínico randomizado comparando NAC adjuvante com placebo para episódios depressivos no transtorno bipolar durante 24 semanas. Desfechos funcionais e sintomáticos foram coletados no período. *Resultados*: Dezessete participantes estavam disponíveis para esta análise. Tamanhos de efeito grandes foram encontrados para sintomas depressivos e desfechos funcionais. Oito dos dez participantes no grupo da NAC tiveram resposta clínica ao fim do tratamento. O mesmo ocorreu em apenas um dos sete que receberam placebo. *Discussão*: Esses resultados indicam que a NAC adjuvante pode ser útil para episódios de depressão maior no transtorno bipolar. Estudos desenhados para confirmar esta hipótese são necessários.

Introduction

There are few effective agents for depressive episodes in bipolar disorder.[1,2] This poses a problem, as depressive symptoms clearly predominate in the course of illness.[3] They are three times more frequent than mania, and hence the majority of the disability and costs associated with bipolar disorder are attributable to the depressive phase.[4,5]

The use of substances with mechanisms of action that target the pathways implicated in pathophysiology is an attractive development in the treatment of this disorder[6]. Among several promising alternatives, recent evidence points to the relevance of systemic inflammation and oxidative damage as current targets in bipolar disorder.[7-11] In addition to being related to illness activity, these pathways are thought to mediate the negative outcomes associated with illness progression.[8,11]

In this respect, N-acetylcysteine (NAC) has shown preclinical and clinical evidence of mitigating oxidative stress and modulating inflammation.[12-14] NAC has been demonstrated to replenish brain glutathione levels.[15,16] Glutathione, in turn, is the brain's major antioxidant, and recent post-mortem and genetic data support its involvement in the pathophysiology of bipolar disorder.[17,18] NAC also has demonstrable anti-inflammatory activity as well as direct effects on glutamatergic and dopaminergic neurotransmission.[13]

As previously reported, add-on NAC significantly improved depressive symptoms and functional outcomes in bipolar disorder in a double blind, randomized, placebo controlled--trial with large effect sizes.[19-21] Here, we report a secondary exploratory analysis on the effects of this compound in the subset of participants who met full diagnostic criteria for a major depressive episode at baseline. This analysis may indicate the treatment effect size for this particular population, which could be useful for planning future studies.

Method

A thorough description of recruitment and evaluation procedures of the study has been published elsewhere.[19,21] Briefly, individuals were randomized to receive double-blind NAC or placebo in addition to treatment as usual. They had to meet DSM-IV criteria for bipolar disorder I or II disorder, and be on stable therapy for at least one month prior to randomization. For this report we only included those with a depressive episode at baseline. All participants provided written informed consent. The trial was approved by the Research Ethics Committees of participating institutions. The study was registered with the Australian and New Zealand Clinical Trials Registry (Registration number: 12605000362695).

The trial was conducted in an outpatient setting. Participants received two NAC (500 mg) capsules twice daily or matching placebo. A diagnosis of bipolar disorder ascertained with the Mini-International Neuropsychiatric Interview was required for inclusion.[22] For this report, we included only those with a major depressive episode at baseline. Exclusion criteria were kept to a minimum to make this study as naturalistic and generalisable as possible, and included systemic medical disorders, pregnant or lactating women, current use of NAC (500 mg/day), selenium (200 ug/day) or vitamin E (500 IU/day), and previous known intolerance or contraindication to NAC.

Interviewers assessed mood and functional outcomes at baseline and at weeks 2, 4, 8, 12, 16, 20, and 24. Interviewers assessed mood using the Bipolar Depression Rating Scale (BDRS),[23,24] Montgomery-Asberg Rating Scale (MADRS),[25] and Young Mania Rating Scale (YMRS).[26] The Clinical Global Impression[27] (CGI) was obtained as a measure of overall illness severity. Functioning was assessed with the Longitudinal Interval Follow-up Evaluation – Range of Impairment Functioning Tool[28] (LIFE-RIFT), and quality of life was assessed using the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).[29]

All analyses are based on the intention-to-treat population (for results on the whole sample, as well as original sample size estimation, please see Berk et al.[19]). Categorical definitions of response and remission were defined as a 50% reduction in MADRS scores and a MADRS score of 7 or less, in accordance with published guidelines; likewise, we used the International

Society for Bipolar Disorder taskforce's recommendation of an YMRS score of 9 or more as a possible manic switch.[30]

Group differences in categorical outcomes were tested with chi-squared tests and odds ratios. T-tests with bootstrap bias-corrected accelerated confidence intervals with 2,000 re-samples were used to compare groups regarding continuous measures. These are more accurate when the theoretical distribution of the statistic is unknown and is more reliable when the sample size is small.[31] Possible confounding from antidepressant drugs used was controlled for using analysis of covariance. We express endpoint differences between groups as effect sizes using Hedges g, which is more reliable with smaller sample sizes.[32]

Results

Seventeen participants were available for this report, 10 in the NAC group and seven in the placebo group (see Table 1). Participants were moderately ill, with a median CGI of 4 in both groups.

At endpoint, the NAC group showed significant improvement on measures of symptom severity, functioning, and quality of life (Table 2). Effect sizes on the MADRS (2.33), BDRS (1.44), GAF (1.04), RIFT (1.92), and Q-LES-Q (1.11) were consistently large. Adjusting for the concomitant use of antidepressants, participants on NAC had lower MADRS ($F = 21.45$, $p < 0.001$), BDRS ($F = 8.92$, $p = 0.011$) and RIFT ($F = 17.32$, $p = 0.001$) scores and higher Q-LES-Q ($F = 5.03$, $p = 0.043$) scores than those on placebo at endpoint.

Eight of the 10 participants in NAC group had a treatment response (50% reduction in MADRS scores), while only one in the placebo group had the same outcome (OR = 24.00, 95%CI 1.74–330.80, $p = 0.015$, NNT = 2). Full remission (a MADRS score of 7 or less) was also more common in the NAC (40%) than in the placebo group (0%), but it did not reach statistical significance ($p = 0.103$).

One participant in the placebo group (due to non-adherence) and one in the NAC group (withdrew consent) failed to complete all assessments. Three participants in the NAC group (vs. 0 in the placebo group; $p = 0.228$) had transient elevations in YMRS scores meeting possible affective switch criteria. Side effects were mild; three patients on NAC complained of headache, and two of abdominal pain and diarrhea. One patient on placebo complained of palpitations and one of diarrhea.

Table 1 Demographical, clinical, and treatment characteristics of the study sample at baseline

Characteristic	NAC (n = 10)	Placebo (n = 7)
Mean age (SD)	43.00 (15.39)	42.86 (15.39)
Female sex	50%	57%
Treated in the private sector	40%	57%
Bipolar I disorder	80%	71%
Medication		
Lithium	25%	29%
Other mood stabilizers	50%	57%
Atypical antipsychotics	25%	29%
Antidepressants	50%	43%
Benzodiazepines	38%	29%

Discussion

Adjunctive N-acetylcysteine (NAC) showed promising efficacy for participants with a syndromal diagnosis of bipolar depression in this exploratory analysis. Effect sizes for endpoint comparisons with placebo were large for depressive symptoms, functioning, and quality of life. Effect sizes in this subgroup were larger than those in the primary study, where most participants had subsyndromal symptoms. Furthermore, response rates in NAC group were strikingly different from the placebo group.

Basic and clinical research indicate that NAC affects several targets of interest in bipolar disorder.[13] These include redox modulation and actions on neurogenesis, inflammatory and glutamatergic pathways.[12,13] Since antioxidants differ considerably in their intracellular mechanisms of action,[14] these results should be seen as supporting NAC specifically, not antioxidants in general. Limitations of this secondary analysis include the small sample size and the fact that the original study was not designed as an acute bipolar depression

Table 2 Baseline and endpoint rating scale scores according to intervention group and between-group endpoint effect size with corresponding p value

Scale	NAC (n = 10)		Placebo (n = 7)		Effect size	p value
	Baseline	Endpoint	Baseline	Endpoint		
MADRS	27.80 (10.00)	9.60 (5.50)	24.29 (4.61)	23.57 (5.97)	2.33	0.008
BDRS	23.90 (15.08)	11.20 (6.30)	21.00 (5.80)	19.86 (4.63)	1.44	0.008
YMRS	4.10 (4.48)	4.40 (4.03)	2.29 (2.43)	2.71 (2.50)		NS
GAF	52.40 (11.40)	62.70 (9.51)	53.86 (10.43)	53.00 (7.72)	1.04	0.034
RIFT	16.30 (3.59)	10.50 (2.92)	15.29 (2.50)	15.86 (2.19)	1.92	0.001
Q-LES-Q	42.20 (8.65)	53.40 (10.63)	41.14 (8.65)	43.29 (3.99)	1.11	0.021

[a] Results are shown as mean (SD). Effect sizes shown are for differences between groups at endpoint. MADRS: Montgomery-Asberg Rating Scale; YMRS: Young Mania Rating Scale; BDRS: Bipolar Depression Rating Scale; GAF: Global Assessment of Functioning; SOFAS: Social and Occupational Functioning Assessment Scale; SLICE-LIFE: Streamlined Longitudinal Interview Clinical Evaluation for the Longitudinal Interval Follow-up Evaluation; LIFE-RIFT: Longitudinal Interval Follow-up Evaluation – Range of Impairment Functioning Tool; Q-LES-Q: Quality of life Enjoyment and Satisfaction Questionnaire.

trial. As such, illness severity at baseline was largely mild to moderate. We are also unable to control for changes in baseline medication, although baseline use of antidepressants had no impact on results. Of note, there has been little exploration of how modulation of oxidative biology and antioxidants affect outcomes in bipolar disorder, and this was the rationale for the secondary analysis presented here. One possible exception is pramipexole, a drug with redox modulation and dopaminergic properties,[33] that has been studied in two small positive trials.[34,35]

These data suggest that a definitive trial of adjunctive NAC for bipolar depression is necessary. Further randomized trials should be able to more reliably determine the treatment effect size. Another interesting possibility would be to measure biomarkers related to its mechanisms of action; this would allow examination of changes in the biomarker targets associated with improvements following NAC treatment. The understanding of mechanisms of action of novel agents could ultimately be useful to guide further pathophysiologically based treatment discoveries, and a more individually tailored psychopharmacology.

Disclosures

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* Modest
** Significant
*** Significant: Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.

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