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Regular Article

Effects of N-acetyl cysteine on cognitive function in bipolar disorder

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Aims: Bipolar disorder is characterized by progressive changes in cognition with declines in executive functioning, memory and sustained attention. Current pharmacotherapies for bipolar disorder target mood symptoms but have not addressed these cognitive changes resulting in euthymic individuals who still experience cognitive deficits. N-acetyl cysteine (NAC) has been shown to have effects on antioxidant status, glutamate transmission, inflammation and neurogenesis. Adjunctive treatment with NAC improves the symptoms experienced by those with bipolar disorder, particularly depression, and it was hypothesized that cognition may also be improved following NAC treatment.

Methods: As part of a larger randomized, double-blind, placebo-controlled trial, participants in the current report were tested at baseline and 6 months to assess changes in cognitive function following either 2000 mg of NAC daily or placebo.

Results: This study failed to find changes in cognitive function following treatment with NAC compared to placebo.

Conclusions: While an important pilot study, this study had a small sample size and included a limited battery of cognitive tests. Further investigations on the effects of NAC on cognitive performance in bipolar disorder are required.

Key words: bipolar disorder, clinical trial, cognition, N-acetyl cysteine, oxidative.

BIPOLAR DISORDER (BD) is typically characterized by fluctuations in mood states (mania and depression), however those with BD also experience alterations in cognitive function. Evidence suggests that cognitive deficits appear early in the course of BD and that altered cognitive function is present throughout the course of the disorder.[1] Even those experiencing euthymia have been shown to have residual cognitive deficits.[2]

Recent evidence has suggested that bipolar disorder involves a complex interaction of many factors, including changes in oxidative stress, inflammation and neurogenesis in addition to the traditional evidence of altered neurotransmission.[3] Current pharmacological treatments are believed to target some of these aspects but often leave individuals with suboptimal outcomes, including residual cognitive deficits. If an agent targets the core components of the process of neuroprogression, it could potentially impact the structural and cognitive changes seen in the disorder. Novel treatments specifically focusing on these processes are warranted. N-acetyl cysteine (NAC) is one

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such treatment having already shown promise as an adjunctive therapy for the symptoms of schizophrenia and bipolar disorder.[4,5] N-acetyl cysteine has been shown to increase the levels of the brain's primary antioxidant, glutathione, decrease pro-inflammatory cytokines and enhance neurogenesis.[6] The current study aimed to explore the benefits of 2000 mg of NAC (compared with placebo) treatment on cognitive function in bipolar disorder in addition to treatment as usual. This study was part of a larger study investigating change in symptoms, functioning, quality of life and cognitive function. The results of the other components of the study have been published previously.[5] The aim of the current study was to determine if NAC could improve cognitive function in participants over 6 months of treatment.

METHOD

Participants and procedure

Complete details of the methodology for the complete randomized, double-blind, placebo-controlled trial are presented elsewhere.[5] In summary, participants were recruited at three sites in Victoria, Australia and were randomized sequentially to receive either 2000 mg/day of NAC or placebo in addition to any existing treatments. Participants took part in the treatment phase for 6 months and cognitive testing (digit span, word learning, trail making, and verbal fluency) at baseline and 6 months. A total of 75 participants were recruited for the larger study. The current analyses include only those who provided complete cognitive data (NAC: $n = 21$; placebo: $n = 25$). Twenty-nine participants were not included in this analysis as they did not complete 6 months of trial treatment and therefore did not attend the second cognitive testing session. There was no difference between the numbers of non-completers in the NAC ($n = 16$) or placebo ($n = 13$) groups ($P = 0.577$). The trial was approved by the relevant Human Research and Ethics Committees. All participants included in the study provided written informed consent.

Statistical analysis

Repeated-measures ANCOVA was used to investigate the differences between NAC and placebo groups comparing baseline to end-point (month 6). The effects of age, sex and medication use (including antipsychotic, antidepressant and mood stabilizers) were explored as confounding variables. For non-parametric and frequency data, χ^2 was employed. Baseline differences were explored using two-samples *t*-test (two-tailed). Results were considered statistically significant at an alpha level of ≤ 0.05.

RESULTS

Table 1 shows the baseline age, sex and medication distribution and duration of illness of participants in this study. There were no significant between-group differences on these demographic factors. There were no significant differences at baseline between placebo and NAC groups on any of the cognitive measures (see Table 1). More importantly there were no significant differences between NAC or placebo groups following 6 months of treatment on any of the cognitive measures (digit span, word learning, trail making, and verbal fluency). These results were independent of age, sex and medication status (mood stabilizer, antipsychotic or antidepressant), which were used in combination as covariates. Furthermore, there was no within-group changes between baseline and 6 months of NAC treatment, nor was there a correlation between mood severity (based on Montgomery–Asberg Depression Rating Scale) and any cognitive domain included (data not shown).

DISCUSSION

N-acetyl cysteine (NAC) has been shown to improve depressive symptoms of bipolar disorder, functioning and quality of life, following 6 months of treatment.[5] However, on the tasks included in this study, no change in cognitive function following NAC treatment was found. The trial duration of 6 months may also have been insufficient to detect changes in cognitive function. Given the chronicity of illness and the associated changes, it may be plausible that a greater time may be required to correct cognitive deficits. The limited sample size is likely to be a significant contributor to this negative outcome. The cognitive testing was a secondary outcome in this study and not completed by all participants. Future studies may include a larger sample size and specifically target a broad neurocognitive battery to provide a more definitive picture of the effects of NAC on cognition.

While NAC has been shown to be an effective adjunctive therapy in bipolar disorder,[5] this study has

Table 1. Demographic information and cognitive outcome measures

	NAC Baseline		PLACEBO Baseline				
Demographic items	Mean/ frequency	SD	Mean/ frequency	SD			
Age	44.6	*12.5*	46.4	*13.1*			
Sex – No. of women	13		15				
Medication:							
Mood stabilizer	16		22				
Antipsychotic	6		12				
Antidepressant	11		18				
Duration of illness	7.9	*5.7*	11.5	*11.8*			
	Baseline		End-point		Baseline		End-point		
Outcome measures	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*P*-value
MADRS	15.9	*10.0*	6.0	*6.9*	13.2	*9.5*	14.0	*11.5*	
YMRS	3.8	*3.8*	2.2	*3.5*	4.6	*4.7*	3.7	*5.4*	
Digit span forward	9.8	*2.3*	9.4	*2.7*	10.2	*1.9*	10.1	*2.3*	0.383
Digit span backward	6.0	*1.7*	6.3	*2.1*	6.3	*2.7*	6.6	*3.0*	0.673
Digit span total	15.8	*3.6*	16.2	*3.5*	16.6	*4.1*	16.8	*4.8*	0.568
Word learning total	23.1	*6.7*	25.1	*7.3*	27.2	*8.9*	28.2	*7.7*	0.080
Trail Making A–No. of mistakes	0.0	*0.0*	0.0	*0.0*	0.12	*0.44*	0.08	*0.4*	0.120
Trail Making A – Time (s)	34.1	*52.1*	19.7	*4.7*	25.4	*15.2*	22.1	*10.3*	0.592
Trail Making B– No. of mistakes	1.4	*3.2*	0.43	*0.75*	2.4	*3.3*	1.6	*2.5*	0.079
Trail Making B – Time (s)	53.9	*25.1*	43.0	*15.9*	63.4	*44.5*	56.2	*32.6*	0.198
Trail Making Ratio B : A	2.2	*0.95*	2.2	*0.74*	2.6	*0.78*	2.6	*0.89*	0.126
Trail Making B–A	19.8	*54.7*	23.2	*14.5*	38.0	*32.0*	34.2	*25.8*	0.092
Verbal Fluency – total	35.0	*9.6*	37.9	*11.2*	38.8	*12.9*	42.6	*15.4*	0.225

There is no interaction with age; sex; or medication (mood stabilizer, antipsychotic, antidepressant).
NAC, N-acetyl cysteine Depression Rating Scale, MADRS, Montgomery–Asberg Depression Rating Scale; YMRS, Young Mania Rating Scale.

failed to show benefit of 2000 mg/day of NAC (in addition to treatment as usual) compared with placebo on cognitive domains in bipolar disorder. More data are required however to make definitive statements.

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