

Effects of *N*-Acetyl Cysteine on Suicidal Ideation in Bipolar Depression

To the Editor: Suicide is the leading cause of death in young adults, and the lifetime risk of suicide for people with bipolar disorder is 15%. A meta-analysis of 15 studies¹ determined prevalence rates of attempted suicide as high as 36.3% in bipolar I disorder and 32.4% in bipolar II disorder. A recent review² on suicide in bipolar disorder emphasized the need for further research into how suicidality is generated and how to avert this outcome. Of the available psychotropic agents, only lithium has an evidence base for efficacy in suicide prevention. Effective therapies, including novel therapies, for suicide prevention in bipolar disorder are therefore a clinical imperative.

N-Acetyl cysteine (NAC) has a diversity of actions, including on glutamate, glutathione, oxidative stress, inflammation, and mitochondrial dysfunction, that as a group represent dysregulated pathways in bipolar disorder.³ Glutamate dysregulation in particular has been implicated in suicide attempts. A recent study⁴ reported increased levels of quinolinic acid (an agonist of the glutamatergic *N*-methyl-D-aspartate receptor) in the cerebrospinal fluid of 64 medication-free suicide attempters compared to 36 controls. This study emphasized the importance of inflammation and glutamate neurotransmission in the pathophysiology of suicidal behavior, which has implications for the detection and treatment of suicidal patients. However, no studies have been reported on the reduction of suicidality by NAC to date. NAC is a relatively safe, available, and well-tolerated agent, with efficacy signals in a number of neuropsychiatric disorders.⁵

Method and results. In this light, we conducted a post hoc analysis of the effects of NAC on suicidal ideation in a sample of individuals diagnosed with *DSM-IV* bipolar depression. The data included in this analysis are from a previously conducted 24-week randomized, multicenter, double-blind, placebo-controlled trial⁶ ($N = 75$) of NAC (2 gpp daily) for bipolar depression. The unadjusted Montgomery-Asberg Depression Rating Scale⁷ (MADRS) mean (SD) score of item 10 (Suicidality) at baseline was 0.78 (1.3) for placebo and 1.21 (1.5) for the NAC treatment group. At 24 weeks, the MADRS mean score of item 10 was 0.92 (1.4) for placebo and 0.22 (0.52) for NAC. The unadjusted Bipolar Depression Rating Scale⁸ (BDRS) mean (SD) score of item 13 (Suicidality) at baseline was 0.41 (0.76) for placebo and 0.55 (0.92) for the NAC treatment group. At 24 weeks, the BDRS mean score of item 13 was 0.44 (0.65) for placebo and 0.04 (0.21) for NAC. These results indicate there was a reduction in suicidal ideation for those taking NAC compared to those taking placebo. Using an intention-to-treat, mixed-effects model, repeated-measures approach (SPSS version 21; IBM, Inc) correcting for the MADRS total score at the start of the trial, we analyzed weeks 0, 4, 8, 12, 16, 20, and 24 of the MADRS suicidality item 10 and found a statistically significant difference in suicidal ideation between NAC and placebo ($P = .039$, $CI = -0.476$ to -0.013). This result was replicated with BDRS item 13 ($P = .024$, $CI = -0.308$ to -0.022). This statistically significant difference in suicidal ideation still persisted after adjusting for age and sex.

Conclusion/discussion. In summary, we found a suggestive signal for the reduction of suicidal ideation associated with the use of NAC in a study of bipolar depression. NAC has been shown to be beneficial for bipolar depression, and this study provides a preliminary indication that it might reduce suicidal ideation in this population as an adjunctive therapy. Because this analysis is post hoc, the sample size is limited for the investigation of suicidal

ideation. As such, these data are preliminary and can only be taken as directions for future study. Nevertheless, given the severity of the problem of suicide in bipolar disorder,^{1,9} the paucity of therapeutic options, and the benign nature of the intervention, use of NAC in this population is a lead worth following.

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