# Moderating Role of Cigarette Smoking on the Effect of N-acetylcysteine on Frontal Glutamate Levels in Co-occurring Bipolar and Alcohol Use Disorders

Courtland Woods, B.S., William Mellick, Ph.D, Kaiya Brand, B.S., Sara Hix, B.S., and James J. Prisciandaro, Ph.D.
Bipolar Disorder Research Program, Department of Psychiatry and Behavioral Sciences
Medical University of South Carolina, Charleston, SC

## BACKGROUND

- N-acetylcysteine (NAC) has been shown to block reinstatement/relapse to substance use, including alcohol and nicotine, by decreasing extracellular glutamate levels.
- Dr. Prisciandaro and his team recently completed a randomized, double-blind, placebo-controlled crossover trial of NAC and gabapentin for individuals with co-occurring bipolar disorder and alcohol use disorder (BD+AUD) to see whether NAC would reduce drinking in this population by reducing frontal glutamate levels.
- Preliminary findings showed that NAC (2400mg/day for 1 week) significantly reduced glutamate+glutamine (Glx) levels in the dorsal anterior cingulate cortex (dACC) of individuals with BD+AUD (Fig. 1), and that this treatment effect was stronger among cigarette smokers (F=4.15, p=0.045).
- This research project aimed to better understand the moderating role of cigarette smoking on NAC effects on Glx in BD+AUD, by comparing Glx levels and baseline participant characteristics in smoking vs. non-smoking participants during the placebo (PBO) condition (i.e., faux-baseline).

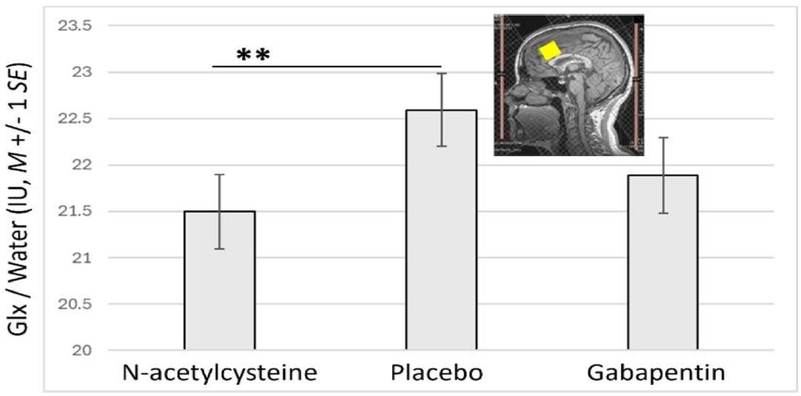


**FIGURE 1.** Preliminary findings of NAC on Glx levels across smokers and non-smokers. dACC indicated by voxel. NAC had a mean and standard deviation (M[SD]=21.50[2.55]) and PBO (M[SD]=22.59[2.56]) show an association with significant difference (p=0.003).

## METHODS

- Forty-two individuals with BD+AUD were divided by smoking status, with smoking defined as ≥10 cigarettes/day (smokers, *n* = 15; non-smokers, *n* = 27).
- Smokers and non-smokers were compared on their PBO Glx levels, acquired via proton MR spectroscopy ($^1$H-MRS) adjusted for within-voxel tissue fractions calculated through automated segmentation, along with their baseline clinical characteristics, including BD-subtype, manic and depressive symptoms, and drinking data acquired via the 90-day Timeline Followback method (e.g., percent heavy-drinking days [%HDD-90] and number of drinks/day). Clinical characteristics that significantly differed between groups were then correlated with Glx levels in smokers and non-smokers separately.
- Independent samples *t*-tests (for dimensional variables, including Glx) and chi-square tests of independence (for binary variables) were performed to examine potential group differences. Pearson correlation coefficients were calculated to explore bivariate associations between variables. Across analyses, a nominal $p < 0.05$ was used to determine statistical significance.

## RESULTS

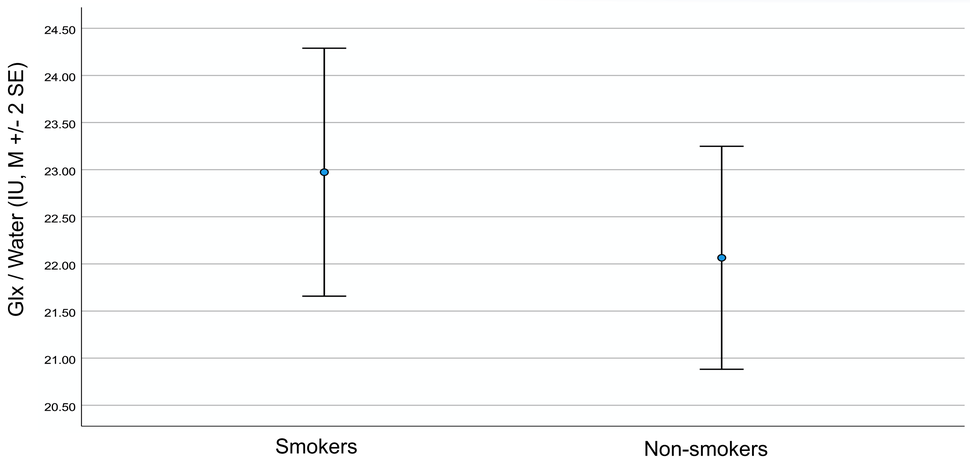


**FIGURE 2.** Glx levels between smokers and non-smokers following the placebo condition.

- Groups did not significantly differ on PBO Glx levels (M[SD] smokers = 22.07[2.29], non-smokers 22.97[3.42]; $p$ = 0.364). See *Fig. 2* above.

| Variables [x̄ (SD) or %] | Smokers (n=15) | Non-Smokers (n=27) | t/$\chi^2$ (*p*)* |
|---|---|---|---|
| Age (in years) | 41.20 (11.90) | 41.22 (12.65) | 0.01 *(0.996)* |
| % Female (*n*) | 60.00 (9) | 48.10 (13) | 0.583 *(0.704)* |
| %BD Type I (*n*) | 73.30 (11) | 44.40 (12) | 3.24 *(0.071)* |
| %Anxiety (*n*) | 66.70 (10) | 51.90 (14) | 0.86 *(0.353)* |
| %SUD (*n*) | 53.3 (8) | 25.90 (7) | 3.160(0.076) |
| #Drinks/day | 6.31(5.06) † | 6.69(5.05) † | 0.23(*0.816*) |
| %drinking days | 60.67(26.53) † | 76.91 (19.05) † | 2.09 (0.048) |
| MADRS | 7.73 (7.70) | 14.19 (11.17) | 2.20 *(0.034)* |
| %HDD-90 | 51.93(34.86) | 62.80(25.50) | *1.06(0.300)* |

**TABLE 1.** Participant characteristics. BD = bipolar disorder; Anxiety = current (past 3-month) anxiety disorder(s); SUD = current (past 3-month) substance use disorder(s), MADRS, Montgomery-Asberg Depression Rating Scale; #Drinks/day-90, number of drinks per day over the past 30 days, and %HDD-90, percent of past 90 days defined as heavy-drinking days (> 4 [men] or 3 [women] alcohol drinks/day) determined using the timeline followback method (TLFB). %HDD, heavy drinking days. †Past 90 days, per TLFB. Statistical significance= p<0.05.

- Smokers and non-smokers significantly differed on baseline %drinking days and depressive symptoms, the latter measured by the Montgomery-Asberg Depression Rating Scale (MADRS), but not other baseline characteristics. See *Table 1*, above.

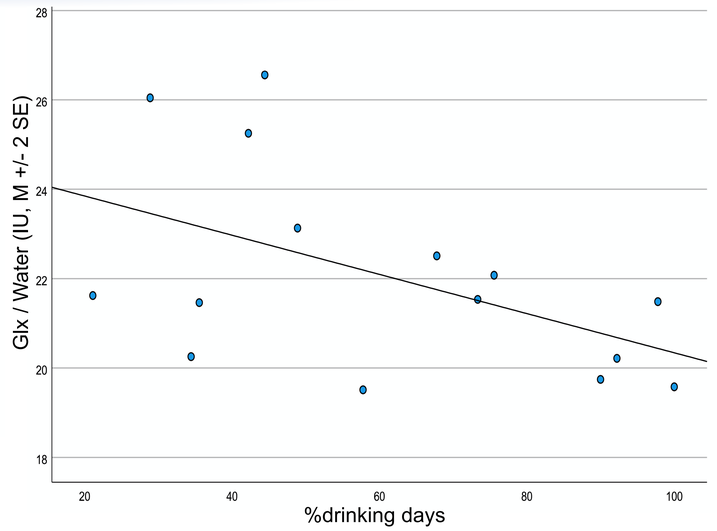


**FIGURE 3.** Negative association between Glx levels and %drinking days in smokers. Lower Glx levels were associated with greater drinks/day and greater %drinking days.

- Examining Pearson correlations within-groups demonstrated strong negative associations of PBO Glx levels and %drinking days ($r$ = -0.51, $p$ = 0.053, $R^2$ = 0.258; see *Fig. 3*) but not MADRS scores ($r$ = 0.04, $p$ = 0.877) in smokers. No strong negative association of PBO Glx levels and %drinking days ($r$ = -0.18, $p$ = 0.373) and MADRS scores ($r$ = -0.14, $p$ = 0.476) in non-smokers.

## REFERENCES

## CONCLUSION

- The findings suggest that the observed moderating effect of cigarette smoking on the effect of NAC on Glx levels in BD+AUD was not due to non-treatment ("baseline") differences on Glx levels between smokers and non-smokers. Instead, the effect of NAC on Glx appears to have been significantly stronger in smokers vs. non-smokers.
- Further exploration of baseline clinical characteristics found that smokers and non-smokers significantly differed on %drinking days and MADRS scores, with the former significantly correlated with Glx levels in the placebo ("baseline") condition. These results may indicate %drinking days as a potentially fruitful variable for better understanding the moderating role of smoking on associations of NAC treatment with Glx levels. These results may indicate %drinking days as a potential driver of the observed moderating effect of smoking on the effect of NAC on Glx levels in BD+AUD. Further exploration of these data are warranted to guide future investigative drug trials in BD+AUD.

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