Letter to the Editor

Benefits of adjunctive *N*-acetylcysteine in a sub-group of clozapine-treated individuals diagnosed with schizophrenia

To the Editors:

Schizophrenia is a chronic and often debilitating disorder. While newer and better tolerated second generation antipsychotics are useful, there are still a proportion of individuals who require clozapine treatment to improve their symptoms. Despite clozapine treatment, there is often a shortfall in recovery between treatment response and symptom remission, and full functional recovery. As such, adjunctive therapies should be considered as part of the treatment of schizophrenia. Adjunctive *N*-acetylcysteine (NAC) has given signals of therapeutic benefit in a wide range of psychiatric disorders, and is safe and well-tolerated (Dean et al., 2011). We have previously reported the efficacy of 2000 mg/day of NAC as an add-on treatment (in addition to all usual treatments) for schizophrenia (Berk et al., 2008) and found that improvements were seen in the overall symptoms (based on the Positive and Negative Syndrome Scale, PANSS) and in the negative symptom domain. This has since been replicated by Farokhnia et al. (2013) in a study exploring people who were treated with risperidone. Our trial sample contained approximately 40% of participants who were administered primarily clozapine. Thus, we decided to do a post hoc analysis to explore those participants who were taking clozapine as their primary treatment to explore efficacy in this particular subgroup. As expected, we saw similar demographic variables (e.g, age) between those primarily administered clozapine and those given another antipsychotic but slightly longer duration of illness (average 16.4 years compared with 8.6 years) and number of admissions (median admission=1 compared with 2) in the clozapine group. There was no difference between clozapine-treated and non-clozapine-treated participants in regards to baseline PANSS score.

We examined the PANSS scores for the Total, General, Positive and Negative subscales using a similar analysis to that reported in the original publication (Berk et al., 2008). For the clozapine subgroup ($N_{Placebo}$=27 and N_{NAC}=28), analysis of covariance (ANCOVA) was used to compare differences between treatment means in changes from baseline to endpoint (both week 8 and week 24) for PANSS scores. The ANCOVA model included the fixed, continuous covariate of baseline score as well as the categorical fixed effects of treatment, investigator, and treatment-by-investigator interaction, as was conducted in the analysis of the overall trial. All tests were two-tailed ($p < 0.05$). The effect size (Cohen's *d*) was calculated as the adjusted mean change from baseline to endpoint scores after adjusting for baseline score, investigator, treatment, and treatment-by-investigator interaction. The primary outcome of the main study was change at week 24 (Berk et al., 2008). In the current analysis, we did not find a significant improvement between groups at week 24 (see Supplementary Table 1). At week 8, however, the NAC group (mean=59.59 ± 10.74 (SD) had significantly lower PANSS Total scores compared with the placebo group (mean=64.57 ± 10.67 (SD), *d*=0.47). This pattern was also seen at week 8 in PANSS Negative scores (NAC: mean 15.83 ± 4.08 (SD), placebo: mean 17.05 ± 4.04 (SD), *d*=0.30) and PANSS General scores (NAC: mean 31.24 ± 5.85 (SD) placebo: mean 29.01 ± 5.89 (SD), *d*=0.38). The benefit of NAC was seen at week 8 and not week 24 in the clozapine sub-group, in contrast to the pattern seen in the primary analysis (of the larger trial) in which statistically significant improvements in PANSS scores were seen at 24 but not 8 weeks (Berk et al., 2008). The apparent earlier treatment effect in those primarily treated with clozapine that dissipated in the latter stages of the trial may reflect the small sample size of the subgroup (i.e., the negative finding at week 24 is a type 2 error, yet it is equally possible in post hoc analyses that the positive effect of NAC at week 8 is a type 1 error); however, there are still similar patterns of improvement: benefit in total and negative domains but no effect on positive symptoms. This is an exploratory post hoc analysis and further research is required to determine specific effects of NAC and specific antipsychotics, particularly clozapine as a management strategy in treatment-refractory individuals.

Acknowledgments

Appendix A. Supplementary materials

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.psychres.2015.10.037.

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