

Effect of High within Subject Variance at Research Sites on Placebo Response and Drug Placebo Separation in Acute Schizophrenia Trials – A Post Hoc Analysis

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Methodological Question Being Addressed

Is the presence of accumulated extreme symptom instability at sites associated with increased placebo response and decreased drug-placebo separation in acute schizophrenia trials?

Introduction: We have previously identified a number of markers of rater and subject behavior that predict subsequent data quality (Kott et al, 2017). The objective of this analysis was to evaluate the relationship between variability in symptom severity at the site level and measures of data quality (e.g., placebo response and drug-placebo separation) in acute schizophrenia clinical trials.

Methods: Data from two identically designed phase 3, randomized, placebo controlled, acute schizophrenia trials (NCT01393613 and NCT01396421) were used to model the placebo response and drug placebo differences. For each subject we calculated the within person variance WPV (Jahng et al, 2008) and identified subjects with their WPV above 95th percentile as subjects with high WPV . Utilizing Fisher's exact test we then identified research sites with significantly higher number of subjects having high WPV (outlying sites). Using MMRM modelling we assessed both the difference in placebo response and the drug placebo differences between the outlying and non-outlying sites from baseline to end of treatment.

Results: Data from 1076 subjects (358 on placebo) were analyzed. We have identified 4 out of 123 sites to be significantly different compared to the study in the proportion of subjects with high WPV. The least square mean placebo change from baseline at the sites identified as outlying was -42.55 (SE = 5.31) points while at the non-outlying sites the LSmean change was -14.74(SE = 0.77), the difference between these 2 groups was -25.26(p<0.0001). The drug placebo difference for the outlying sites was 5.3 favoring placebo, while in the non-outlying sites was -5.81 favoring active treatment, the difference in drug placebo separation between the sites was estimated to be 11.47 points (p<0.02).

Conclusions: High within-person variance represents extreme symptom instability characterized by numerous either uni- or bi-directional dramatic changes from visit to visit. While clinically possible in individual cases, an accumulation of subjects with extreme instability at a site may be an indicator of instability in interview or rating methodology and should be investigated by review of recorded interviews or worksheets, if available and remediated if appropriate. We have recently identified a significant effect of erratic (bidirectional) changes on placebo response in a trial in schizophrenia with predominant negative symptoms (Kott et al, 2017). The current results expand on our previous findings and validate the utility of within person variance in ongoing data quality monitoring programs as a risk indicator.

References:

Jahng, Seungmin; Wood, Phillip K.; Trull, Timothy J. (2008): Analysis of affective instability in ecological momentary assessment: Indices using successive difference and group comparison via multilevel modeling. In *Psychological Methods* 13 (4), pp. 354–375. DOI: 10.1037/a0014173.

Kott, Alan; Umbricht, Daniel; Wang, Xingmei; Daniel, David (2017): Erratic Changes in the PANSS are Associated with Greater Placebo Response in a Schizophrenia Negative Symptom Trial – A Post hoc Analysis. Poster presentation at the 2017 International Society for CNS Clinical Trials and Methodology (ISCTM) 13th Annual Scientific Meeting, 21-23 February 2017, Washington DC, USA

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