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

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METHODOLOGICAL QUESTION

- 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

- Intent-to-treat data was obtained from two identically designed phase 3, multicenter, randomized, double blind, placebo controlled (NCT01393613 and NCT01396421) with brexpiprazole in the treatment of adults with acute schizophrenia (Kane et al, 2015; Correll et al, 2015)
- PANSS data 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) of the PANSS scores collected throughout the trial and identified subjects with their WPV above 95th percentile as subjects with high WPV
- Using Fisher's exact test we identified 2 groups of sites: Outlying sites (sites with statistically ($p<=.05$) outlying numbers of subjects having high WPV compared to the remaining study data) and Non-outlying sites
- The LSmean change from baseline was derived from a mixed model repeated measures (MMRM) analysis with fixed effect of treatment, visit, treatment visit interaction, baseline value, and baseline visit interaction as covariate or each treatment arm and site group
- Using MMRM analysis with fixed effect of treatment, visit, treatment visit interaction, baseline value, subgroup treatment visit three-way interaction, subgroup treatment visit two-way interactions and baseline visit interaction as covariate, and with a compound-symmetry variance-covariance matrix structure the LSmean difference between the outlying and non-outlying sites for placebo arm and drug placebo difference was computed

RESULTS

- Data from 1076 subjects (358 on placebo) were analyzed
- Using Fisher's exact test we identified 4 out of 123 (3.25%) sites to be statistically significantly different compared to the study in the proportion of subjects with high WPV
- The least square mean placebo change from baseline at week 6 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($p<0.0001$) (Figure 1)
- 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 ($p<0.02$) (Figure 2)

Figure 1: Placebo (N=358) LSmean change from baseline in PANSS Total at week 6 for Outlying and Non-outlying sites on high within person variance (WPV)

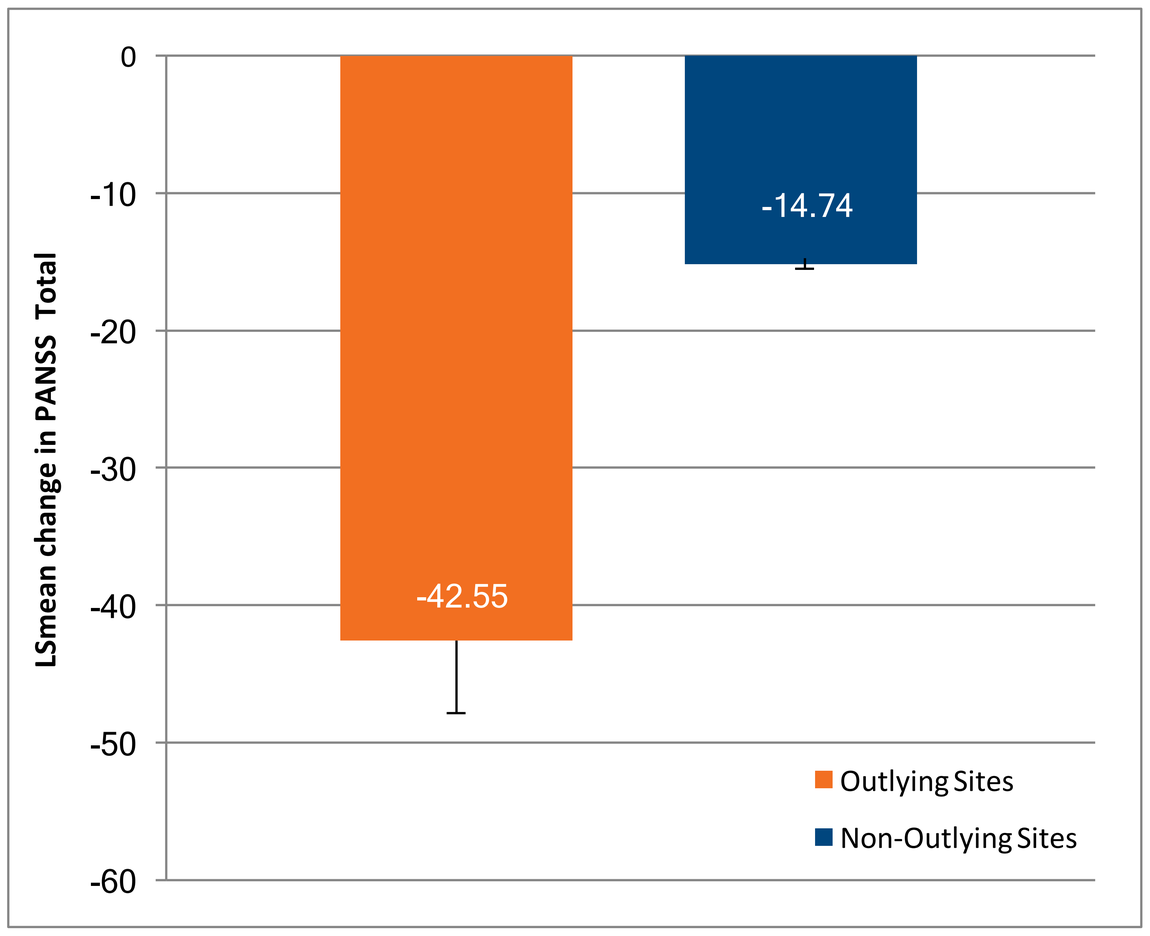
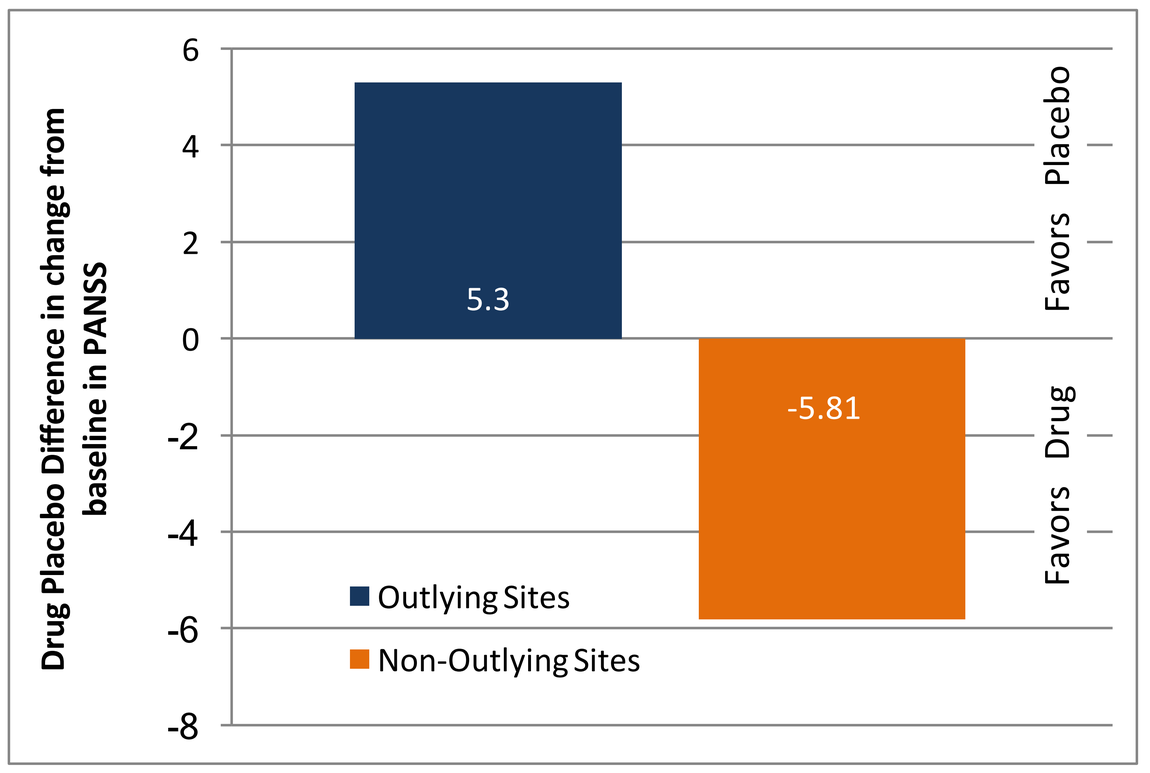


Figure 2: Drug placebo difference in PANSS Total at week 6 for Outlying and Non-outlying sites on high within person variance (WPV)



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, data analytics 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

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