Methodological approaches to outliers in cognitive assessment for schizophrenia: A post-hoc analysis of the EMERGENT-1 study

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SUBMISSION DETAILS

What is the Methodological Question Being Addressed? Methods exist to identify and remove (e.g., screen fail) participants that have unstable or potentially invalid scores on clinical outcome measures. However, to our knowledge, such approaches are not established for cognitive assessment. Here we present an approach that leverages the highly inter-related nature of cognitive ability to identify and censor outliers.

Introduction Computerized cognitive batteries (CCBs) provide an alternative to traditional neuropsychological assessment, achieving similar results to standard batteries but without the need for a trained neuropsychologist.1 However, CCBs may be more susceptible to task non-compliance or non-completion than traditional “pen and paper” assessments. In a recent schizophrenia treatment study using a CCB as an exploratory endpoint, greater than 20% of subjects had to be excluded due to excessive task errors or non-completion.2 This high rate of data loss increases variability and can bias results towards the null, making it challenging to detect changes in cognitive performance. Excluding data based on error rates, while effective, may artificially exclude meaningful data of individuals who are especially cognitively impaired. Here we present an alternative approach to current outlier management techniques that leverages the interrelated nature of cognitive functioning across subdomains to analyze data from a Phase 2 trial of KarXT in patients with schizophrenia.

Methods An abbreviated version of the Cogstate CCB was administered as part of EMERGENT-1, a Phase 2 randomized, double-blind, placebo-controlled, 5-week inpatient trial in adults (n=182) with acute exacerbation(s) of schizophrenia. The evaluable sample (n=125) included subjects who provided valid scores for all subtests of the Cogstate CCB at both baseline and week 5. Outliers were identified by applying the 1.5 inter-quartile range (IQR) rule to the intra-individual variability (IIV; standard deviation of each subject’s normalized subtest z-scores). Composite scores were created per subject by averaging across subtest z-scores. Statistical models assessing the effect of KarXT (vs. placebo) on change from baseline composite scores were performed both before and after IIV-driven outlier removal. Baseline PANSS scores were compared between included and IIV-excluded subjects.

Results Prior to removal of outliers, there was a non-significant treatment effect for KarXT (n=60) vs. placebo (n=65), with greater cognitive improvement in the KarXT arm (estimate = 0.18, SE =0.13, t=1.40, p=0.16, d=0.20). The average IIV at baseline was 1.28 ± 0.78, suggesting that within this sample a subject’s cognitive performance across subtests could be expected to vary by 1.28 SDs from their composite score. Eight subjects with excessive IIV on one or both CCB administrations were identified as outliers (IIV > 2.42 at baseline or 2.47 at week 5; the upper limit of 1.5 IQR) and removed from the analysis. Following outlier removal, a significant overall treatment effect of KarXT vs. placebo was found (KarXT [n=54], Placebo [n=63], estimate = 0.27,

SE =0.13, t=2.05, p=0.04, d=0.31). Baseline PANSS scores did not significantly differ between included (PANSS Total = 95.95 ± 7.60) vs. excluded subjects (PANSS Total = 97.5 ± 13.17), t=0.33, p=0.75.

Conclusion The identification and removal of outliers using IIV may be an effective tool for censoring CCB assessments that may not reflect true cognitive performance. The application of this approach, which is agnostic to performance within any single cognitive subdomain, may improve sensitivity to detect therapeutic change and could be prespecified prior to data analysis. Further examination of this method is warranted using different CCBs, and in comparison to traditional neuropsychological assessments.

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