Title: Nonparametric methods for analyzing cognitive test data where missing values may reflect cognitive impairment: Another look at PEARL III.

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Methodological Question being Addressed: What is the utility of applying rank ANCOVA (Koch et al., 1990) to account for missing/incomplete cognitive data in a short-term phase 3 study.

Introduction: Results from a 6-week, double-blind, placebo-controlled study demonstrated that patients treated with lurasidone 160 mg/day performed significantly better at study endpoint on a measure of cognitive function (computerized CogState Schizophrenia Battery (CSB)) than patients receiving placebo (p=0.038) or quetiapine XR 600 mg/day (p=0.018). Patients treated with lurasidone 80 mg/day did not significantly differ from placebo or quetiapine XR groups. (Harvey et al, 2013). However, this finding was only observed in a subset (n=267) of patients in the intent to treat (ITT) population (n=482) whose cognitive testing was determined to be evaluable at both baseline and Week 6 based on prespecified criteria. This has raised concerns that the finding might not be generalizable to the full sample. While a subsequent study introduced adaptations to CSB administration that have improved its acceptability in acutely ill patients (Citrome et al, 2016), there is evidence in the present study to suggest that greater impairment in the non-evaluable sample may have contributed to their difficulty in completing the tests. For example subjects with evaluable compared to non-evaluable cognition scores had significantly lower mean PANSS total scores at baseline (p<0.001) (Harvey et al, 2013).

Methods: In order to address the issue of incomplete data from the non-evaluable sample, an analysis based on the full ITT sample was conducted using rank ANCOVA, in which non-evaluable or missing scores at baseline and/or week-6, and/or early dropouts were assigned the lowest possible rank score (=0). Tied ranks were resolved by standard averaging methods. Accordingly, positive or negative change in rank reflects respectively improvement or worsening in position relative to the whole sample. This method allowed for missing or partial data from all patients to inform the analysis, and assumes that missing data reflects the lowest performance level.

Results: The results from the full ITT data sample were comparable to previous analyses using the evaluable subgroups. Patients treated with lurasidone 160 mg/day improved in rank between baseline and 6 weeks by 10.2 rank points, whereas those on placebo experienced an average drop in rank of -16.8 points, a difference which was statistically significant (p<0.05). Patients in the lurasidone 80 mg/day group improved by 6 rank points (p=0.08) and the quetiapine XR 600 mg/day group did not differ from

placebo.

Conclusion: In this post-hoc analysis, a nonparametric approach was employed to permit the inclusion of missing cognitive data from patients who failed the evaluability criteria. Using this technique, results from the full patient ITT sample, including those with significant cognitive impairment at the time of testing due to severe psychiatric illness, were shown to be consistent with a subsample of evaluable patients. Informed by this experience, CSB administration was modified to permit rest periods if needed, as is routine with paper and pencil cognitive testing, and the test sequence was altered. Using this modified presentation of the identical tests, Citrome et al (2016) achieved 100% evaluable data on the CSB in an acute schizophrenia sample.

References

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