PANSS erratic changes are associated with greater placebo response in schizophrenia negative symptom trial – a post hoc analysis

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Methodological Question Being Addressed

Is the presence of erratic changes in Marder Negative Factor score associated with placebo response in a schizophrenia negative symptom trial?

Introduction: Erratic changes represent unusually large changes in symptom severity across consecutive visits in opposite directions, e.g. large improvement is followed by large worsening. They may be a sign of a poor rating quality. In the current post-hoc analysis of unblinded data of a single clinical trial in schizophrenia focused on negative symptoms we investigated the effect of the presence of erratic changes as measured by the PANSS Marder negative factor score on the magnitude of placebo response.

Methods: Placebo arm data from a phase 3, randomized, placebo controlled, negative symptom schizophrenia trial were used to model the placebo response. We defined changes as erratic if the PANSS Marder negative factor score score changed by at least 20% from visit to visit across a minimum of three consecutive visits and the changes occurred in opposite directions. Using MMRM modelling we assessed the PANSS Marder negative factor score difference in placebo response between subjects with and subjects without erratic changes present.

Results: Data from 512 subjects (162 on placebo) were analyzed. In 73 subjects (20 on placebo) we identified the presence of at least one occurrence of erratic change. The least square mean placebo change from baseline at the end of treatment in these subjects was -9.13 (SE = 1.03) PANSS Marder negative factor points vs. -6.56 (SE=0.39) in the non-affected subjects, the difference between these 2 groups was highly statistically different (-2.56, p = 0.0042).

Discussion: In this post-hoc analysis subjects with the presence of erratic changes in the Marder negative factor had a significantly higher response to placebo than non-affected subjects. We used a rather conservative definition of erratic changes where we required the change to be of at least 20% of the Marder negative factor score and it is therefore surprising that there were more than 12% of subjects affected by erratic changes in this negative symptom trial. Erratic changes in symptom severity may be caused by true symptom severity variations but that is rather unlikely to happen in such a magnitude in the intended trial population. We hypothesize that other reasons such as interviewing and rating sloppiness, relative ratings (ratings against prior visit and not according to current symptom severity), data tampering or data fabrication are at play. Further research is needed to better understand the factors affecting the presence of erratic changes.