Analysis of the Impact of Family History Subgroups on Drug Placebo Separation and Placebo Response on Tandem Rater and Computer Outcomes in RCTS

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ABSTRACT

INTRODUCTION: High placebo response is associated with clinical trial failure. Family history is considered a validator of psychiatric diagnosis, and one factor to examine when researching placebo response in clinical trials.

METHODS: We have examined patterns of placebo response in multi-center depression (MDD and bipolar) studies to explore hypotheses regarding the failure of double-blind, RCT trials. We also included tandem assessments of the primary outcome measure (MADRS or HAMD) administered by site-based raters (MADRS or HAMD) and independently assessed by computer (MADRScomp or HAMDcomp). Placebo response was compared for subgroups reporting no family history of mood disorder (FHx(-)) and subjects reporting at least one first or second family member with a mood disorder (FHx(+)).

RESULTS: In each trial, no significant differences were found between the placebo group and active treatment groups for both the rater and computer tandem assessments on any of the efficacy measures. Among FHx(-) subjects the Active vs. placebo difference (AP∆) favored placebo in all four trials across all treatment groups. This difference reached statistical significance based on MADRScomp but not MADRS in two of the four trials examined.

In all studies, the computer scores demonstrated a greater difference between the FHx (+) and FHx (-) subgroups than the corresponding SBR scores.

In all studies reviewed, placebo response based on the computer scores was numerically higher in the FHx(+) groups than in the FHx(-) groups. This difference reached statistical significance based on HAMDcomp scores in one study. In three of the four studies reviewed, placebo response based on the SBR scores was numerically higher in the FHx(+) groups than in the FHx(-) groups. None reached statistical significance.

CONCLUSION: Our review of four recent failed clinical trials, including one conducted outside the US, suggests high rates of placebo response in subjects reporting no family history of mood disorder may be a causal factor in failure of these efficacy studies. Further studies are needed to clarify which correlates of the FHx(+) subject status may be associated with high placebo response (e.g. diagnostic validity or enrollment rate).

REFERENCES:

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