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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High placebo response is associated with clinical trial failure, and is a common problem in mood disorder treatment studies. We previously (Sachs et al, in press) reported higher placebo response in subjects with low confidence diagnosis compared to those with higher confidence diagnosis. Family history is considered a validator of psychiatric diagnosis and prior studies suggest the majority of subjects in a depression study could be expected to have a positive family history of mood disorder (Perlis 2006). Previous research (included in this poster) indicated that family history did have an impact on the placebo response in a trial conducted in Russia. Therefore, we now compare the signal for drug-placebo difference and placebo response for subjects based on their reported family history of mood in four recent failed clinical trials.

RESULTS

None of the studies found statistically significant differences between the placebo group and active treatment groups for the SBR or computer tandem assessments on any of the efficacy measures. In the three US only studies, the FHx(-) group represented 58% of the subjects randomized. Among FHx(-) subjects Active vs. placebo difference (AP∆) favored placebo in all four trials across all treatment groups. This difference reached statistical significance based on MADRS by not HAM(D) in two of the four trials examined.

METHODS

We have examined patterns of placebo response to explore hypotheses regarding the failure of double-blind, RCT trials. We reviewed two failed MDD and two failed bipolar depression trials for analysis. Each was an early phase study of an investigational compound. Each trial included tandem assessments for diagnosis. A computer diagnostic assessment that included questions about the subjects family history of psychiatric conditions was administered to subjects in each study, and eight raters administered a MINI or SCID diagnosis instrument to determine the primary diagnosis required for inclusion.

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

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 factor in failure of these efficacy studies. Further studies are needed to clarify which correlates of the FHx(-) status may be associated with high placebo response (e.g., diagnostic validity of enrolments), further studies are also needed to understand whether FHx(-) can be a consistently useful apart of diagnostic criteria in cultures where mood disorders may have a lower rate of recognition and social acceptance.

REFERENCES