Impact of Overzealous Patients and Raters on Drug-Placebo Separation in an MDD Trial: Analysis of Tandem Ratings
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INTRODUCTION

The inclusion criteria in the protocol required a MADRSCOMP ≥26 scored before the MADRSCOMP. The study was conducted at 23 sites in the United States, concluding in late 2011. The protocol included the administration of a selective serotonin and norepinephrine reuptake inhibitor approved for treatment of major depressive disorder. The database have concluded that treatment effect has declined and placebo response has increased over the past ten years, resulting in a larger difference favoring placebo than MADRSSBR at the overall study population level. The effect size (Cohen’s d) was calculated using the raw (unadjusted) mean difference from baseline and standard deviations. In the Concordant group, both the MADRSSBR and MADRSCOMP had a smaller effect size, ~2 larger than the effect sizes found in the overall study population. (Figure 3)

METHODS

The study was conducted at 23 sites in the United States, concluding in late 2011. The protocol included the administration of the MADRSCOMP at each study visit. The MADRSSBR was administered before the MADRSCOMP. The inclusion criteria in the protocol required a MADRSCOMP ≥26 and MADRSSBR, ≥30 at screening and baseline visits. We analyzed the MADRSCOMP change from baseline to end of treatment (Week 8) using MMRM, exploring associations of tandem (paired computer and clinician) ratings with drug-placebo separation in prior analyses into subset groups of the patient population. (Figure 1)

RESULTS

Table 1: Overall Study Results

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline Mean</th>
<th>Change Score (SE)</th>
<th>Change Score (95% CI)</th>
<th>Change Score</th>
<th>LSMD (SE)</th>
<th>LSMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>58.04 (6.09)</td>
<td>2.37 (1.26)</td>
<td>(0.99, 3.75)</td>
<td>2.37 (0.99, 3.75)</td>
<td>3.16 (0.10)</td>
<td>(2.95, 3.37)</td>
</tr>
<tr>
<td>Active</td>
<td>55.04 (6.09)</td>
<td>3.30 (1.26)</td>
<td>(1.99, 4.61)</td>
<td>3.30 (1.99, 4.61)</td>
<td>3.92 (0.10)</td>
<td>(3.72, 4.13)</td>
</tr>
</tbody>
</table>

By contrast, the difference favored placebo in the subset with discordant ratings (n = 87, approximately 20% of all patients).

The MADRSSBR favored placebo consistently across both the rater inflation and overzealous patient groups.

The Concordant baseline group (n = 429, approximately 80% of all patients) demonstrated over two points more drug-placebo separation than the overall study population; results were consistent for the MADRSSBR and MADRSCOMP.

The Concordant baseline group compared to the rater inflation group.

The effect size (Cohen’s d) was calculated using the raw (unadjusted) mean difference from baseline and standard deviations. In the Concordant group, both the MADRSSBR and MADRSCOMP had a smaller effect size, ~2 larger than the effect sizes found in the overall study population. (Figure 3)

CONCLUSIONS

Both MADRSSBR and MADRSCOMP achieved statistically significant drug-placebo separation in the study and showed similar patterns of treatment effect and placebo response across the analyses.

The subset of patients with Concordant baseline tandem ratings (~80% of the population) demonstrated significant drug-placebo separation in favor of LVM on both the MADRSSBR and MADRSCOMP while discordant baseline tandem ratings (~20% of the population) significantly favored placebo on both outcomes.

The discordant group was divided evenly between the rater- and patient-inflated scores.

“Overzealous patients” demonstrated a larger difference favoring placebo on MADRSSBR whereas inflated rater scores and overzealous patients favored placebo at about the same rate on MADRSCOMP.

These results suggest that incorporation of tandem ratings into the inclusion criteria for studies of mood disorders would allow for greater power and to increase the probability of a positive outcome study.