Effects of Participation in a Prospective Lead-in Antidepressant Study on Blinded MADRS Scores in Adjunctive Antidepressant Trials

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Methodological Issue Being Addressed A meta-analysis of adjunctive treatment clinical trials for depression found that inclusion of a study-sponsored prospective adjunctive antidepressant (ADT) lead-in study did not significantly improve drug versus placebo separation in rates of response and remission. Here we assess the impact of a site-sponsored ADT prospective lead-in (PLI) on change in blinded Montgomery-Asberg Depression Rating Scale (MADRS) in adjunctive antidepressant trials compared to participants who did not participate in a PLI. Using longitudinal structural equation modeling, we explore differences in patterns of mean change and variance in change in MADRS scores between participants who did and did not participate in a site-sponsored PLI prior to enrolling in an adjunctive ADT trial.

Introduction The placebo response, characterized by comparable score changes between drug and placebo conditions, is a significant contributor to failures in phase II and III clinical trials. Factors including the therapeutic setting, interactions with staff, practice discussing symptoms, and expectancy effects have been shown to increase the likelihood of a placebo response.3 These factors may be mitigated by PLIs where participants gain exposure to the clinic setting and staff. PLIs that feed adjunctive medication trials may also serve to reduce expectancy effects if participants in the lead-in study are prescribed a new medication or a new dose of a current medication. We tested the association between participation in such a site-sponsored six-week antidepressant PLI (TRAIT) and change in blinded MADRS scores across several phase II and III adjunctive antidepressant trials.

Methods Participants were 211 individuals (61% female; 36% TRAIT participants) who enrolled in an industry-sponsored adjunctive antidepressant clinical trial. MADRS scores blinded to drug/placebo randomization collected at baseline, day 14, and end of treatment (ranging from day 28 to day 56) were aggregated across several Phase II and Phase III antidepressant trials. A latent change score model was fit to test associations between participation in TRAIT and change in MADRS scores between baseline and day 14 and between baseline and end of treatment. The latent change score approach permitted us to include all covariates and test all associations in a single model. Baseline MADRS scores and the latent change scores were regressed on TRAIT status. Participant age at baseline and sex were included as covariates in the model. Additionally, changes in MADRS scores were adjusted for rater changes. We also tested associations between TRAIT

status and “super responders”, defined as participants demonstrating a greater than 50% reduction in MADRS scores between baseline and day 14.

Results Mean baseline MADRS scores did not differ significantly between TRAIT and non-TRAIT participants. Non-TRAIT participants demonstrated a greater decline in MADRS scores between baseline and day 14 (-6.0 points) relative to TRAIT participants (-3.3 points). Likewise, non-TRAIT participants demonstrated a greater decline in MADRS scores between baseline and end of treatment (-9.8 points) relative to TRAIT participants (-6.6 points). Non-TRAIT participants had significantly greater variance in change in MADRS scores between baseline and day 14 ($X2 = 5.3$, $df = 1$, $p = .021$). Variance in change between baseline and end of treatment did not significantly differ between TRAIT and non-TRAIT participants ($X2 = 2.0$, $df = 1$, $p = .161$). Non-TRAIT participants were 2.8 times more likely than TRAIT participants to be “super responders” at day 14.

Conclusion Findings suggest that participation in a site-sponsored lead-in antidepressant study prior to participation in an adjective antidepressant trial reduced the likelihood for potentially problematic patterns of response that could impair drug versus placebo separation. On average, participants in the lead-in antidepressant study demonstrated a 19% decline in blinded MADRS scores between baseline and end of treatment but were 3 times less likely to show an abnormally large early response. Among participants in the lead-in study, 51% of the total change in blinded MADRS scores occurred between baseline and day 14. Comparatively, in participants who did not participate in the lead in study, 62% of the total change in MADRS scores occurred between baseline and day 14. Thus, participants in the lead-in antidepressant study demonstrated a steadier, more consistent pattern of change in blinded MADRS scores across the duration of an adjunctive clinical trial. Participation in a lead-in antidepressant study provides participants experience interacting with site staff, receiving new medication from the site, and discussing their symptoms with a clinician, potentially reducing the likelihood that these factors may contribute to change in symptoms during a clinical trial.

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