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

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Introduction

- The placebo response is a significant contributor to failures in Phase II and III clinical trials[1]
- Factors including the therapeutic setting, interactions with staff, and discussing symptoms can contribute to the placebo response[2]
- Prospective lead-ins may reduce the likelihood of heightened placebo response by providing exposure to the clinical setting, regular appointments with staff, and experience discussing symptoms
- A meta-analysis of adjunctive ADT trials found that inclusion of a study-sponsored prospective lead-in did not significantly improve drug placebo separation[3]
- We tested associations between participation in a site-sponsored prospective lead-in (TRAIT) and change in blinded MADRS scores and response and remission rates across several phase II and III trials

Hypotheses

- Non-TRAIT participants would demonstrate greater change in blinded MADRS scores between baseline and the first assessment
- EOT blinded MARDS scores would not significantly differ between TRAIT and non-TRAIT participants
- Non-TRAIT participants would exhibit significantly greater variance in change in blinded MADRS scores

Methods

Sample

- 223 adults who self-identified interest in depression research participation through social media and other online advertising

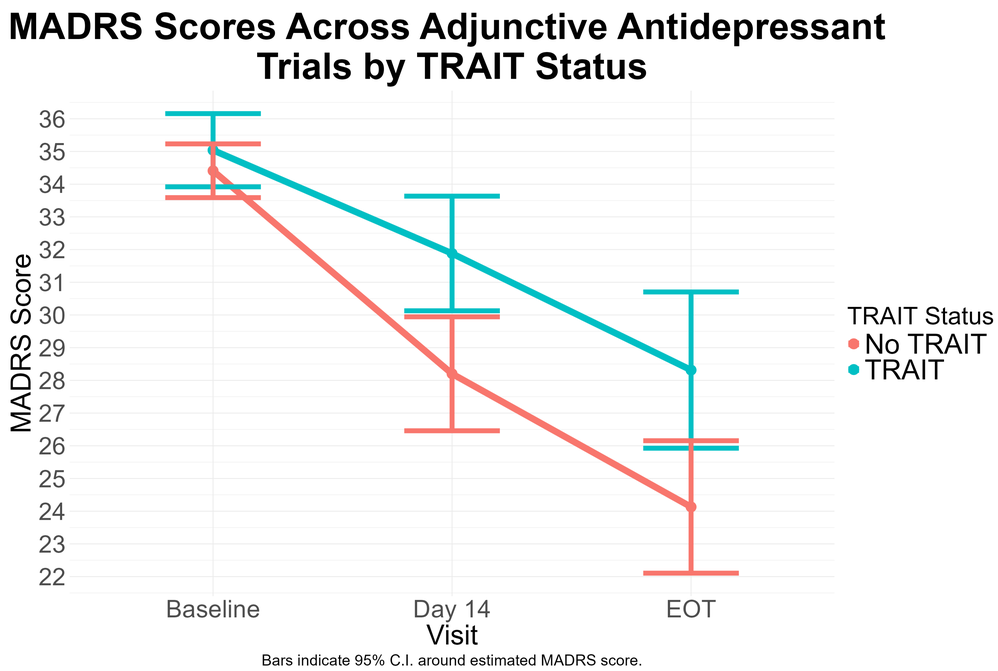
Measures

- **Dependent variable:** blinded MADRS scores collected in industry trials at day 14 and end of treatment
  - Response: Reduction in MADRS by >= 50%
  - Remission: MADRS score <= 10
- **Independent variables:** TRAIT participation status
- **Covariates:** Gender, age, change in rater, and length in time between baseline and end of treatment

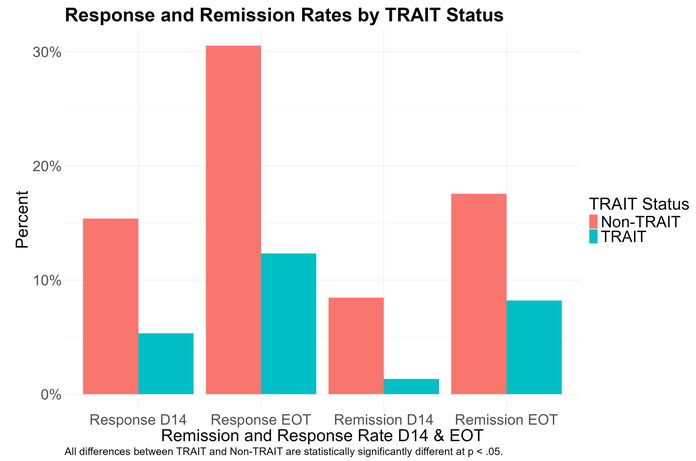
Analyses

- Multivariate latent change score models were fit to estimate change in blinded MADRS scores by TRAIT status
- Models were fit in a multigroup framework by TRAIT status to test differences in variance in change
- Logistic regression models adjusted for age and gender were fit to test associations between TRAIT status and response and remission rates

Variable	Total Sample (*n* = 223)	TRAIT (*n* = 81, 36%)	Non-TRAIT (*n* = 142, 64%)
Age	38.7 (14.4)	40.0 (15.2)	38.0 (14.0)
MADRS (BSL)	34.7 (4.8)	34.6 (4.9)	34.9 (4.7)
MADRS (D14)	29.4 (9.6)	31.7 (7.3)	28.1 (10.5)
MADRS (EOT)	25.7 (11.6)	28.2 (10.3)	24.3 (12.1)
Gender			
Male	90 (40.5%)	41 (50.6%)	49 (34.8%)
Female	132 (59.5%)	40 (49.4%)	92 (65.2%)



Bars indicate 95% C.I. around estimated MADRS score.



Results

Mean Change in Blinded MADRS Scores

- Non-TRAIT participants demonstrated significantly greater decline in MADRS scores between baseline and day 14 [B = 3.12, p = .007] and between baseline and EOT [B = 3.56, p = .013]

Mean Change in Blinded MADRS by TRAIT Status	Non-TRAIT x̄ [95% C.I.]	TRAIT x̄ [95% C.I.]
Mean Change BSL to Day 14	-6.2 [-7.8, -4.6]	-3.2 [-4.7, -1.7]
Mean Change BSL to EOT	-10.3 [-12.1, -8.4]	-6.7 [-8.8, -4.6]

- At baseline, mean MADRS scores were not significantly different between non-TRAIT participants [34.4, 95% C.I. 33.6, 35.2] and TRAIT participants [35.0, 95% C.I. 33.9, 36.2]
- At day 14, mean MADRS scores were significantly lower for non-TRAIT participants [28.2, 95% C.I. 26.5, 29.9] than TRAIT participants [31.9, 95% C.I., 30.1, 33.6]
- At EOT, mean MADRS scores were not significantly different between non-TRAIT participants [24.1, 95% C.I. 26.2, 33.4] and TRAIT participants [28.3, 95% C.I. 25.9, 30.7]

Variance in Change in Blinded MADRS Scores

- Non-TRAIT participants demonstrated significantly greater variance in the change score parameters between BSL and Day 14 relative to TRAIT participants [X^2 = 13.8, df = 1, p < .001]
- Non-TRAIT participants demonstrated significantly greater variance in the change score parameters between BSL and EOT relative to TRAIT participants [X^2 = 3.9, df = 1, p = .049]

Conclusions

- Consistent with previous research[3], participants completing a site-sponsored prospective lead-in (TRAIT) showed smaller overall improvements in blinded MADRS scores compared with non-TRAIT participants in subsequent placebo-controlled trials.
- Greater variance around mean patterns of change for non-TRAIT participants suggests a greater risk for extreme deviations from the mean pattern of change.
- Significantly lower estimated Day 14 MADRS scores — and higher response and remission rates — among non-TRAIT participants further support the possibility of early extreme symptom change after trial initiation.
- TRAIT participation did not prevent detection of clinical improvement: blinded MADRS scores decreased by an average of 24% from baseline to end of treatment.
- By screening out participants likely to respond to nonspecific trial effects (e.g., visit attendance, clinician interaction), site-sponsored prospective lead-in programs may improve detection of true drug-related symptom change.

Limitations

- The use of blinded MADRS scores prohibited us from directly testing placebo response differences.
- Different drugs have different expected response times. There were not significant differences in the proportion of TRAIT participants across studies included in this analysis. It is unlikely that drug differences were responsible for the divergence in scores at day 14.

References

1. Furukawa TA, Cipriani A, Atkinson LZ, Leucht S, Ogawa Y, Takeshima N, Hayasaka Y, Chaimani A, Salanti G. Placebo response rates in antidepressant trials: a systematic review of published and unpublished double-blind randomised controlled studies. *The Lancet Psychiatry*, 2016; 1059-1066.
2. Rutherford BR, Roose SP. A model of placebo response in antidepressant clinical trials. *Am J Psychiatry*, 2013;723-733.
3. Iovieno N, Papakostas GI. Does the presence of an open-label antidepressant treatment period influence study outcome in clinical trials examining augmentation/combination strategies in treatment partial responders/nonresponders with major depressive disorder?. *The Journal of Clinical Psychiatry*. 2012; 676-683.

Disclosures

The authors report no conflicts of interest for this work; all are current employees of Adams Clinical, an independent CNS research site that conducts self-sponsored and industry-sponsored pharmaceutical trials.

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