Statistical enrichment potential using the SIGH-D in an open-label lead-in trial

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Introduction

- Increasing sample homogeneity is a key strategy for improving statistical power and enhancing the likelihood of detecting treatment effects in psychiatric trials[1,2]
- Enrichment approaches must avoid reliance on clinical response or demographic features to preserve trial integrity and generalizability[3,4]
- Sum scores from depression rating scales provide limited insight into the multidimensional structure of depressive symptoms and obscure atypical symptom-relationship patterns[5,6]
- Work using the MADRS has shown that individual-level symptom-structure profiling can quantify anomalous symptom organization[7]
- We evaluate whether SIGH-D item scores collected during an open-label antidepressant lead-in can generate symptom-structure–based anomaly scores to support response-agnostic statistical enrichment for subsequent adjunctive trials

Hypotheses

- A site-sponsored, open-label lead in can be used to generate robust and stable anomaly scores, based on symptom structure
- Using an anomaly cut-off developed for the MADRS, open-label non-responders are more likely to be statistically enriched than open-label responders.

Methods

Sample

- 194 MDD trial participants recruited in 2022-2024 who were enrolled in the TRAIT-MDD-107 study (NCT04748276), a site sponsored prospective lead-in trial designed to increase efficiency of MDD trial recruitment into second and third-line MDD industry trials[8]

Measures

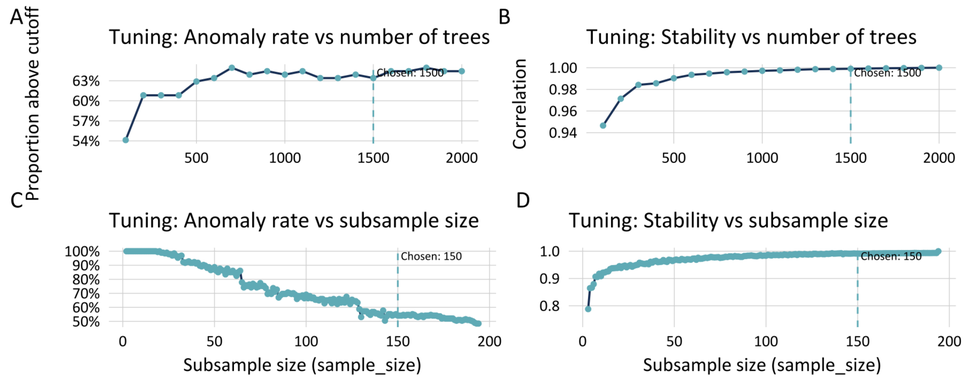
- Hamilton Depression Rating Scale scores obtained from clinician-administered Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D)

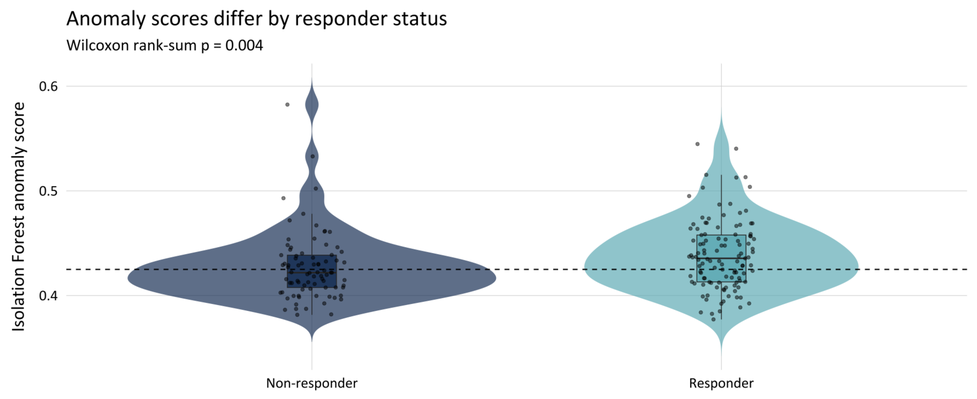
Protocol

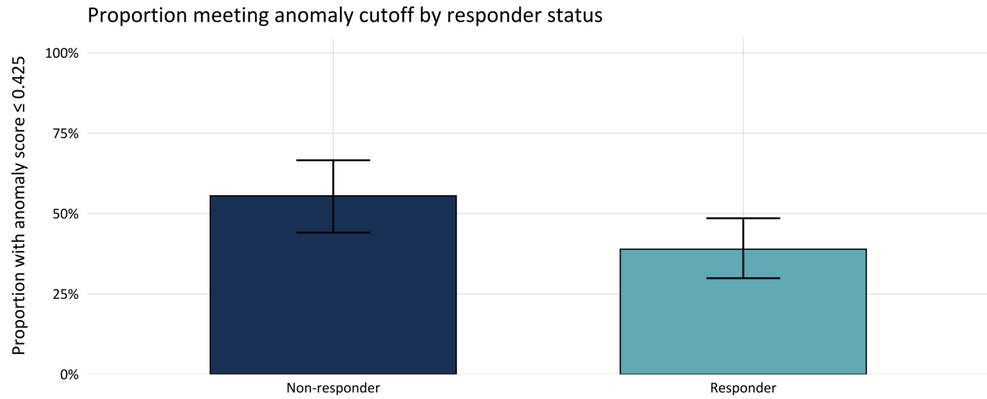
- Participants were given the SIGH-D at screening visit (Day-1), three weeks after starting an antidepressant (Day-21), and six weeks after starting an antidepressant (Day-42)

Analyses

- Individual structural changes in symptoms were quantified by computing variance-covariance difference (VCD) vectors using paired scores from Day-1 and Day-21 for all items
- VCD vectors served as features for an Isolation Forest model, producing anomaly scores reflecting participants' respective deviations from canonical depressive symptom structure
- Enrichment rate for the overall sample, antidepressant responders, and antidepressant non-responders were calculated using an anomaly score cutoff previously validated for the MADRS[7]







Results

Anamoly Score Stability

- The Isolation Forest Model using 1500 trees and a subsample size of 150 demonstrated similar stability to the MADRS-based model in the existing literature[7]

Group Differences

- Anomaly scores for the antidepressant non-responder(*N = 81)* group were significantly lower than those in the responder (*N = 113)* group
  - Wilcoxon with continuity correction: *W* = 3466, *p = 0.004*
- A significantly higher percentage of non-responders met the previously-established enrichment cutoff compared to responders
  - 55.6% vs 38.9%; Fisher's Exact odds ratio = 0.512, *p = 0.028*

Conclusions

- Anomaly scores derived from site-level SIGH-D scores can be used for an enrichment model, with a reasonable degree of stability which is agnostic to treatment response and demographics
- Antidepressant non-responders in an open-label prospective lead in were substantially enriched for canonical depression symptom structure when compared to antidepressant responders
- Enrichment rate of antidepressant non-responders in an open-label prospective lead in were comparable to those found prospectively in an industry screening process[7]
- Findings suggest that TRAIT non-response is associated with a more canonical depression symptom structure, which could indicate more appropriateness for their subsequent placebo-controlled industry trials, than individuals who did not participate in a prospective lead in

Limitations

- Sample size and the lack of high-quality factor information on the SIGH-D limited the ability to select a SIGH-D specific cutoff for the anomaly score
- VCD vectors were derived using one pre-treatment score and one score halfway into treatment

Future Directions

- We are conducting analyses to examine whether anomaly scores derived during open-label lead in predict blinded MADRS score vectors when participants enter an industry trial
- We are also conducting analyses to determine if anomaly scores from open-label lead in predict outcomes such as early termination and adverse events.

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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.