Data Patterns Predict MADRS-CGI Discrepancies in Depression Trials: Implications for Rater Training and Data Monitoring

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SUBMISSION DETAILS

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Methodological Issue Being Addressed 1) Are MADRS item-level scores predictors of interscale discrepancies between the MADRS and CGI-S?
2) Are certain study visits more likely to have MADRS to CGI-S discrepancies?
3) Is there utility to taking a MADRS item-level approach for Risk-Based Data Monitoring (RBDM) for interscale discrepancies?

Introduction Two widely used Clinical Outcome Assessments (COAs) in antidepression trials are the Montgomery–Åsberg Depression Rating Scale (MADRS) and Clinical Global Impression - Severity (CGI-S). They are highly correlated and sensitive to symptom change during trials (Khan et al., 2022). Thus, discrepancies between MADRS and CGI-S scores can indicate rating error or excess variability which can compromise trial data, or possibly in some global trials cultural differences in depression experience (Engler, 2025). Published research suggests MADRS score ranges that should align with various CGI-S scores (Leucht et al., 2017), yet item-level variation as predictors of interscale discrepancies has not been explored and may have implications for trial monitoring, oversight, and rater training. This study examines whether specific participant presentations are more likely to be associated with discrepancies between MADRS to CGI-S scores.

Methods We examined MADRS individual items, interactions between items, and Study Visit (Baseline versus End of Treatment) as predictors of CGI-S scoring discrepancies using data from 5 global Major Depressive Disorder (MDD) clinical trials (N = 1722). Scoring discrepancy definitions were based on equipercentile linking literature for expected MADRS total to CGI-S scores (Leucht et al., 2017). Utilizing Baseline visit data and 81.2% of participants at available End of Treatment visit data (81.2% of participants)resulted in a total of 3120 MADRS to CGI-S scoring comparisons. These cases were randomly split into two subsamples (n = 1560) to allow a dataset for model testing and a second dataset for cross-validation.

Results We developed a logistic regression model to predict MADRS to CGI-S discrepancies, using individual MADRS items as predictors, as well as Visit as a predictor and potential moderator. To identify meaningful interactions and reduce overfitting, we applied LASSO regularization (main effects, item x item interactions, and Visit x item interactions). Although MADRS items tend to correlate, diagnostics indicated that multicollinearity was not a concern, and the initial model showed good discrimination (AUC = 0.76) between cases with and without discrepancies. We then entered variables identified in this process into logistic regression in the second subsample using

logistic regression. The final model was significant, LR $\chi^2(15) = 137.4$, $p<0.001$; Pseudo $R^2=0.10$; AUC=0.72. In this model, no individual items predicted scoring discrepancies, though two symptom clusters emerged as predictors (Reduced Sleep x Reduced Appetite interaction; Concentration x Pessimism interaction). Although not statistically significant, visits at End of Treatment trended toward having more scoring discrepancies ($p = .062$).

Conclusion MADRS to CGI-S scoring discrepancies are more likely when participants present with higher scores on both Reduced Appetite and Reduced Sleep, or with higher scores on both Concentration and Pessimism. As these symptoms reflect impairment in secondary MDD symptoms, these findings have important implications for rater training (considering all available information on impact of symptoms) and data monitoring during trials.

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Guidelines I have read and understand the Poster Guidelines

Disclosures The authors report no conflicts of interest of this work; all are current employees of Cronos Clinical Consulting, Inc., an IQVIA Business, provider of RBDM services for clinical trials.