Placebo Response Prediction for Optimizing Treatment Effect Estimation in Major Depressive Disorder

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Methodological Issue Being Addressed Variability in the magnitude of clinical responses in the placebo arms of randomized clinical trials (RCTs) can result in effective drugs failing to reach the patient. Despite randomization efforts to control confounding factors, including placebo response, there remains a need for systematic approaches to reduce the effect variability that placebo response has on treatment effect estimation. Eliminating the baseline-predictable component of placebo response facilitates a more unbiased evaluation of treatments.

Introduction In this analysis, we developed a prognostic model to estimate placebo response in adjunctive MDD trials, utilizing data available at or prior to baseline. The prognostic model generates a prognostic score for all study participants. This score could then be used as an adjustment variable in a regression model of the trial outcome to estimate the treatment effect (1) We anticipate this will increase the statistical power to detect a more unbiased treatment effect.

Methods Using historical trial data, we developed a prognostic model to predict patient-level placebo response. The model was constructed using placebo arms (all trials had background SSRI/SNRI in placebo arms) from three MDD historical trials (NCT04080752, NCT00095134, NCT03227224). The 6-week Hamilton Depression Rating Scale (HDRS), a measure of depression symptom severity, was selected as the model outcome.

A robust pipeline was developed incorporating feature selection, imputation, and different machine learning models. The models considered included several model types, such as linear regression with and without elastic-net penalty, random forest, and others.

The final model was selected using a cross-validation step in which models built on 2 historical trials were tested on the 3rd trial. This was repeated for each of the 3 historical trials. The performance of the resulting model was evaluated in a separate independent test trial, which was not used in building the model, and therefore demonstrates performance in unseen clinical trials.

Results During cross-validation, the 6-week HDRS scores predicted using the developed model were correlated with the observed (Pearson correlation of 0.37-0.44). The mean absolute error (MAE) was 5.4-6.6. A correlation of 0.38 and MAE of 6.0 was achieved when the model was applied to the independent test trial suggesting our approach is generalizable.

Comparatively a model using baseline HDRS alone resulted in a correlation of 0.35 and an MAE of 6.5 on the independent test trial (and Pearson correlation of 0.22-0.42 in cross validation). This suggests our model's use of additional informative features (eg. duration of current MDD episode, patient demographics, medication history, etc) results in improved predictive performance.

Conclusion We demonstrate the potential of using historical relevant trials to predict placebo response for individuals participating in MDD trials. Our proposed modeling approach is unique in that it incorporates multiple clinical trials to develop a prognostic model, with performance tested on separate independent test trials. In future, we aim to incorporate additional historical clinical trials into the modeling effort to further confirm generalizability. The patient-level prognostic scores generated by the model will be used to mitigate the residual imbalance, reduce variance, and increase the likelihood of detecting a more unbiased treatment effect in future MDD trials.

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References

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