Development of the Treatment Attitude Profile (TAP) Scale: AI/ML-Driven Insights for Clinical Trial Enrichment to Minimize Placebo Response

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What is the Methodological Issue Being Addressed? How can placebo response be minimized using a novel patient-rated scale and machine learning technology?
Placebo response presents a significant challenge in psychiatric clinical trials, obscuring the true efficacy of investigational treatments. It is particularly problematic due to the heterogeneous nature of psychiatric disorders, which exhibit significant variability in symptoms, severity, and response. This complicates the interpretation of trial results, potentially causing promising treatments to appear ineffective. Addressing placebo response is crucial to improving the reliability of clinical trials, ensuring that true treatment effects are accurately measured and that efficacious interventions are successfully identified. Leveraging insights from AI/ML-based analyses of clinical trials can enhance our understanding of placebo response by identifying key variables and response patterns that predict placebo effects. This allows for better patient selection and trial designs that minimize these confounding factors. Key patient attitude variables previously correlated with placebo response were used to drive the development of the Treatment Attitude Profile (TAP) scale.

Introduction Effective management and understanding of placebo response are crucial to ensure the reliability of treatment efficacy results. By utilizing AI/ML to analyze patient attitude self-assessments to identify key variables predictive of placebo response and integrating these insights into selection criteria, the TAP scale can be used to enhance trial design, ultimately improving the interpretability of clinical trial outcomes.

Methods The TAP scale was developed using a novel ML approach designed to discover enrichment criteria from patient self-assessments. This approach deconstructs the patient population into explainable and unexplainable subpopulations, making it effective for small datasets characteristic of psychiatric clinical trials. By focusing on the explainable subpopulations, it is possible to identify variables that characterize subsets of placebo responders. Two failed clinical trials were analyzed using this approach:
•Takeda Bipolar Trial (NCT01467700): n=378 patients with clinical scale data (MADRS, HAM-A, YMRS, CTSS-M). Primary endpoint: 50% improvement in MADRS from baseline.
•Phase III Anxiety Trial: 171 active patients and 161 controls, with approximately 100 independent variables per subject including variables from the following scales: CTSS-B, HAM-A, SDS, CGI-S. HAMD-17, DSST, HVLT-R, PSWQ, MINI, DSL
By identifying variables that characterize subpopulations of placebo response, the TAP was

developed, which provides a comprehensive profile of patient attitudes and behaviours that influence clinical trial outcomes. The identified attitudinal variables include patients' attitude towards treatment and expectations about the clinical trial program. This scale can then be used for more precise patient selection and for enhancing the design of clinical trials to mitigate the impact of placebo response.

Results Using our novel ML analysis, we identified sets of variables that effectively characterized subpopulations of placebo responders:
•Bipolar Trial: An explainable subpopulation of 71/115 placebo responders in the training set was characterized by 6 CTSS and 2 YMRS clinical scale items related to treatment attitude, impact of symptoms, and sleep quality. This model correctly predicted placebo responders with 87% accuracy and replicated on an independent data set.
•Anxiety Trial: 8 variables were found to capture placebo response with 74% accuracy , while 6 CTSS variables and HAMD work and activities explained a subpopulation of 10 drug non-responders. Drug response was very poor and acted much like a placebo, except in a small class of patients. Insights gained from this work were amalgamated to develop the TAP.

Conclusion The TAP represents the culmination of years of research into placebo responder characterization through a variety of clinical scales, including those with attitudinal questions. The TAP has the potential to enhance the precision of outcome measures, which is crucial in psychiatric research where placebo effects can heavily skew data and negatively effect clinical trials. The integration of the TAP with AI methods will be explored in future work.

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Keywords

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Guidelines I have read and understand the Poster Guidelines

Disclosures Dr. Joseph Geraci is the founder of NetraMark and is a significant shareholder of

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