Introducing the Treatment Attitude Profile (TAP) Scale for Placebo Response Persona Discovery Using Attractor AI Technologies: Applications in Clinical Trial Patient Enrichment

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INTRODUCTION

BACKGROUND:

Placebo response in psychiatric clinical trials complicates the assessment of treatment efficacy by significantly hindering the success of tested interventions. Effective management and understanding of the placebo response is crucial in clinical trials to ensure the reliability of treatment efficacy results, particularly in psychiatric disorders, which vary widely in symptoms, severity, and placebo response, adding another layer of complexity to clinical research in this field. Addressing this issue is crucial for the development of effective psychiatric interventions.

CHALLENGE:

Placebo response significantly hinders the success of psychiatric clinical trials, often obscuring the true effectiveness of tested interventions. Although there are a multitude of clinical scales in use that try to identify problems associated with placebo response, this issue remains a major obstacle for successful clinical trials.

OPPORTUNITY:

Advancements in artificial intelligence (AI) have increased our understanding of the effects of the placebo response phenomenon by identifying key variables derived from clinical scales that can characterize placebo response well. This information can be used as selection criteria to exclude patients with certain characteristics to increase the probability of demonstrating a treatment-specific contribution to clinical effectiveness.

OBJECTIVES

We aim to develop a new clinical scale, the Treatment Attitude Profile (TAP) that incorporates a wide variety of factors leveraging insights from analyzing clinical scale data with a novel machine learning (ML) approach, NetraAI, to identify variables that characterize placebo response.

- NetraAI was designed to discover enrichment criteria from clinical trial data, making it highly explainable.
- Insights extracted via this system as they pertain to placebo response were used to inform the creation of the TAP.

METHODOLOGY

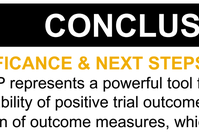
MACHINE LEARNING APPROACH:

NetraAI is powered by its **unique Attractor AI** capability to deconstruct patient populations into explainable and unexplainable subpopulations. This is a necessary step for small datasets (fewer than 500 samples) that is typical in psychiatric clinical trials, as these data do not represent the overall distribution of the disease, necessitating a more nuanced analysis approach.

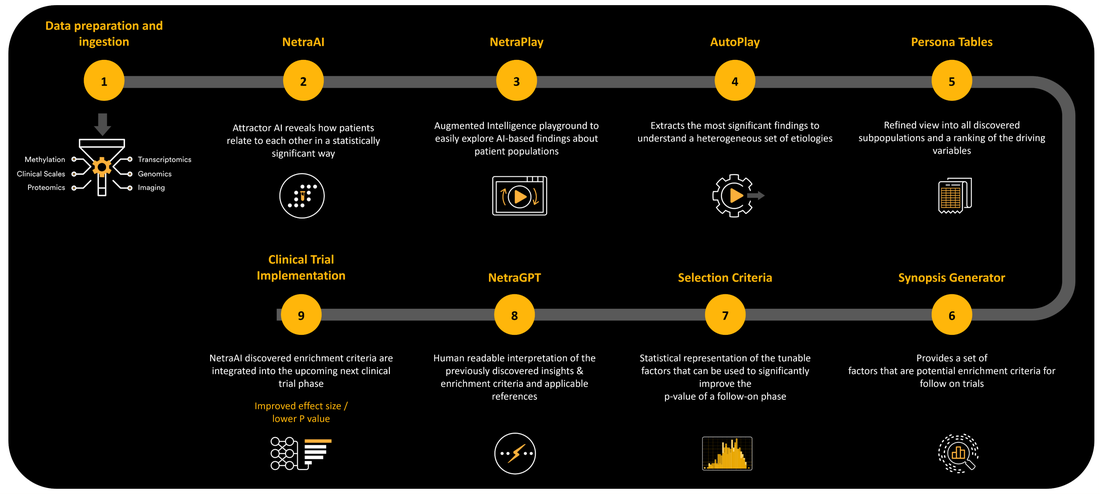
NetraAI identifies explainable patient populations that capture different aspects of complex diseases like psychiatric disorders. This unbiased vantage of patient populations allows us to better understand:

- **Heterogeneity of disease:** Understanding the diverse manifestations and progressions within psychiatric disorders.
- **Placebo response:** Identifying patterns and predictors of placebo effects among different patient groups.

This comprehensive understanding is reflected in the TAP, which resulted from millions of simulations through the NetraAI. These simulations help to characterize the most favourable patients for clinical trials, specificly a subset of Placebo Non-Responders/Treatment Responders (PNRTR). The variables in the TAP can help with providing a more refined characterization of these ideal subpopulations.



PNRTR: Placebo Non-Responder/Treatment Responder
PRTNR: Placebo Responder/Treatment Non-Responder



RESULTS

Placebo Response Modeling in a Takeda Bipolar Trial

DATASET:

Takeda Bipolar Trial (NCT01467700) which assessed the therapeutic efficacy of a treatment for acute depressive disorder using clinical scales.

- n = 378 patients.
- **Clinical Scale Data:** MADRS, HAM-A, YMRS, CTSS-M
- **Primary Endpoint:** 50% improvement in MADRS from baseline
- *Note: Trial failed as the study drug did not show significant separation from placebo.*

RESULTS:

Training Data: n=115 patient training set allowed for the identification of an explainable subpopulation of 71 patients who exhibited placebo response. This subgroup was characterized by:

- 6 CTSS clinical scale items, and
- 2 YMRS items

Testing Data: n=239 independent drug participants with baseline CTSS-M due to no significant differences from placebo. The NetraAI model:

- Correctly predicted placebo responders (PRs) 87% of the time.
- Accurately identified 39/44 (88% accuracy) drug non-responders (DNRs) and incorrectly identified 5/44 drug responders (DRs).

This high level of predictive accuracy is essential for refining clinical trial designs and enhancing patient selection strategies.

NetraAI Selection Criteria

Placebo Non-Responder (PNR) Characteristics
Less desire to get better
Think less of medication
Struggled for less time
Forget more often
Feel worse about signing up
More faith in talk therapy
Total Score high
Slept slightly better

IMPACT ON TAP DEVELOPMENT:

The key variables identified by NetraAI were used to develop the TAP. These include:

- Treatment attitude
- Impact of symptoms
- Sleep quality

These factors are integrated into the TAP to refine patient selection and outcome measurement in clinical trials to reduce placebo response and more accurately reflect treatment effects.

Placebo Response Modeling in a Failed Phase III Anxiety Trial

DATASET:

- 171 active patients and 161 controls with ~100 independent variables per subject.

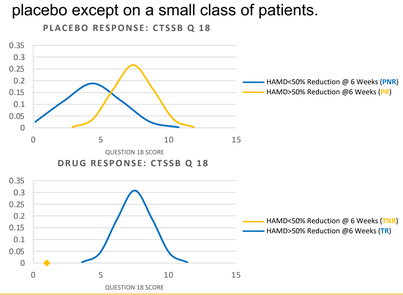
RESULTS:

Placebo Response: 8 variables (CTSS-Q16, Q18, Q20, Q21, Q25, Q26, Total CTSS, and HAMD1) captured:

- 55/73 PRs and 50/88 PNRs (mixed class)
- 42% of PNRs were highly explainable with an accuracy of 74%.

Drug Response: 6 variables (CTSS-Q6, Q7, Q9, Q18, Q21, and HAMD – Work and Activities) explained 10 DNR perfectly .

- Drug response was very poor and acted much like a placebo except on a small class of patients.



NetraAI Selection Criteria

Inclusion Criteria	Expected Effect on Study Population
CTSS Q18 ≥ 4 (Signing up for this study has made me feel better)	**Removes most DNR but keeps many PR, eliminating PNR**
CTSS Q25 ≥ 2 (Compared to how you feel now, how do you expect to feel a year from now?	Removes many PR and keeps many PNR Removes most DR and DNR with high screen fail rate
CTSS Q26 ≥2 How do you expect to feel at the end of treatment?	Removes many PR and keeps most PNR; more DNR
CTSS Q9 ≥4 I think I will improve during the study even if I get a placebo	Removes many DNR and keeps most DR; more PR remain
CTSS Q7 ≥7 So far, I like this study	Removes many DNR and keeps most DR No cut off score significantly reduces relative number of PR
Total Score CTSS ≥40	Any cut off seems to remove PR, PNR, DR, and DNR similarly

IMPACT ON TAP DEVELOPMENT:

The NetraAI analysis identified key attitudinal variables including:

- Patients' attitudes towards treatment
- Expectations about the clinical trial program they are in

These insights are integrated into the TAP to better assess and predict which patients would demonstrate placebo responses in a clinical trial.

Evolution to the Treatment Attitude Profile (TAP) Scale

The newly developed Treatment Attitude Profile (TAP) incorporates a wide variety of factors that can be used to characterize placebo response, impacting clinical trial outcomes, that can be categorized into the following themes:

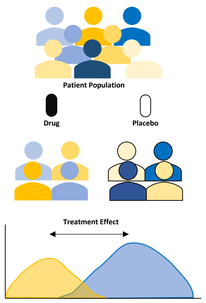
- **Symptom Impact and Severity**
- **Treatment Perception and Efficacy**
- **Treatment Management and Behavior**
- **Patient-Doctor Relationship and Clinical Interaction**
- **Psychological and Emotional Well-Being**
- **General Health and Lifestyle**
- **Trial Participation History**

FUNCTIONALITY AND IMPACT OF THE TAP:

The TAP not only characterizes placebo response but also differentiates drug response and the distinctiveness of the drug from placebo. Through the refined perspectives provided by NetraAI, the TAP provides:

- A detailed view of what elements drive drug and placebo responses
- Which items are directly related to mechanism of action
- Which items are related to disease symptomology versus attitudinal factors

This high-resolution understanding, in conjunction with simulations that attempt to identify PNRTR subpopulations, can be utilized by clinical trialists to optimize future trials for success by better understanding the underlying factors influencing outcomes, with a relatively low burden.



The insights gained from NetraAI are used to identify the variables that can be used to maximize the difference between placebo and drug effect.

APPLICATIONS OF THE TAP:

The TAP's comprehensive overview allows trialists to more accurately predict which patients are likely to exhibit placebo response. The TAP can be used to:

- Enhance patient selection and trial design
- Have more efficient trials
- Have a higher likelihood of detecting treatment effects with smaller sample sizes, greater speed, and lower costs

CONCLUSIONS & SIGNIFICANCE

SUMMARY OF KEY FINDINGS:

1) **Evolution of the Treatment Attitude Profile (TAP):** The TAP consists of a concise set of questions developed using insights from NetraAI that provides a comprehensive overview of patient attitudes. It has been designed to be used by trialists to refine patient selection and trial design, enhancing the efficiency of clinical trials. The creation of the TAP benefited from having a unique machine intelligence, the NetraAI, learn from several psychiatric clinical trials and reveal factors that were driving placebo and drug response.

2) **NetraAI fractures data into explainable and unexplainable subpopulations to extract powerful insights about the patient population while avoiding overfitting:** NetraAI, equipped with its Attractor AI technologies is capable of analyzing and learning from datasets with lower numbers of patients, which is typical for clinical trials (n<500) to identify variables predictive of placebo response. Analyzing a bipolar trial and anxiety trial, the variables of interest were predominantly attitudinal factors that could be used to predict placebo responders.

The variables identified by NetraAI as significant predictors of placebo responders were used to formulate the TAP.

SIGNIFICANCE & NEXT STEPS:

The TAP represents a powerful tool for researchers and clinicians to mitigate the impact of placebo response and increase the reliability of positive trial outcomes. By integrating patient attitude data into trial protocols, trialists can enhance the precision of outcome measures, which is particularly important in psychiatric research, where placebo effects can heavily skew data, obscuring the true efficacy of treatment.

Impact of Artificial Intelligence in Clinical Trials: This work underscores the potential of AI for transforming how clinical trials can be conducted. The ability of AI to analyze complex datasets to identify predictive variables transforms the trial design process, making it more adaptive and targeted. This shift is paving the way for more effective and efficient psychiatric treatment discovery.

Efficiency and Cost-Effectiveness: The variables used in the TAP allow for a more nuanced understanding of treatment effects even with smaller sample sizes, accelerate the trial process, and reducing costs. By enabling trials to operate with smaller sample sizes while not compromising on outcomes, the TAP contributes to a more scalable research environment.

DISCLOSURES

Joseph Geraci is the founder of NetraMark and is a significant shareholder of NetraMark Holdings, which is a publicly traded company. Bessi Qorri, Luca Pani, and Larry Alphs are employed by NetraMark
Luca Pani's disclosures (past 3 years): AbbVie, USA; Acadia, USA; Alexion, Italy; BCG, Switzerland; Boehringer Ingelheim International GmbH, Germany; Compass Pathways, UK; EDRA-LSWR Publishing Company, Italy; Ferrer, Spain; Gedeon-Richter, Hungary; GLG-Institute, USA; Immunogen, USA; Inpeco SA, Switzerland; Ipsen-Abireo, France; Johnson & Johnson USA; NeuroCog Trials, USA; Novartis-Gene Therapies, Switzerland; Sanofi-Aventis-Genzyme, France and USA; NetraMark, Canada*; Otsuka, USA; Pfizer Global, USA; PharmaMar, Spain; Relmada Therapeutics, USA*; Takeda, USA; Vifor, Switzerland; WCG-VeraSci/Clinical Endpoint Solutions, USA (*options/shares)

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