Using AI on Data from Anxiety and Schizophrenia Trials to Identify Causal Clusters of Variables for Drug & Placebo Response Via Long Range Memory to Improve Clinical Trial Outcomes

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BACKGROUND

Clinical scales are commonly used research tools in psychiatric and psychological research that use objective scales and/or qualitative, open-ended responses to collect objective data. These approaches allow researchers to gather a large quantity of data, relatively quickly.

CHALLENGES:

- Placebo response is a confounding factor in clinical trials, diminishing study power and impairing measurement of treatment efficacy.
- Associating related clinical scale items to derive causal models for placebo and drug response using a variety of clinical scales and other clinical trial data.

NEED:

- Efficient and effective way to minimize the placebo response and increase drug-placebo differences to improve subsequent trial design.

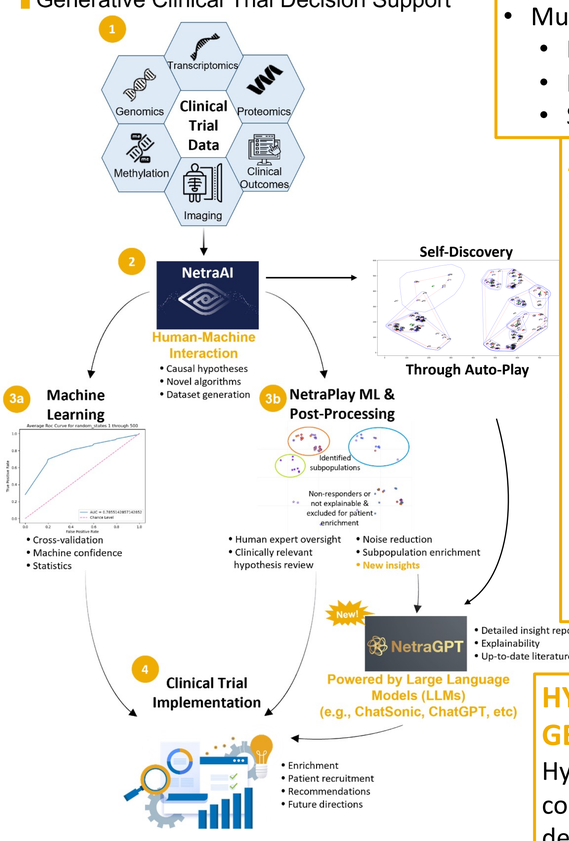
OBJECTIVES

Use artificial intelligence (AI) large language models (LLMs) in anxiety and schizophrenia trials to:

- Construct explainable models derived from psychiatric clinical trial data to derive variables that explain placebo and drug response (causal clusters).
- Identify variables from the generated hypotheses that can be used as inclusion and exclusion criteria to maximize endpoint effect size for subsequent larger clinical trials by reducing placebo response and increasing drug response.

METHODOLOGY & WORKFLOW

NetraMark Workflow
Generative Clinical Trial Decision Support



DATASETS:

- Multimodal data
  - Demographic items
  - Psychiatric scales
  - Safety measures

AI APPROACH:

- Long-range memory mechanism reminiscent of attention mechanisms in LLMs.
- Navigate through combinations of multiple variables to generate hypotheses about patient subpopulations.

HYPOTHESIS GENERATION:

Hypotheses consisting of a combination of variables describing drug or placebo response can be interpreted clinically.

RESULTS

NetraAI uncovered markers of placebo and drug responders using data from anxiety trial (phase III) to improve trial outcomes.

Anxiety Trial (Phase III) Details :

- Clinical Scales (>100 variables)
- Placebo Response Propensity Scale (PRPS)
- 161 placebo and 171 active patients

Markers of Placebo Response:

- 73 responders, 88 non-responders
- CTSSQ18 and Total CTSS explain 55/73 placebo responders
- CTSSQ26 and 27 explain 37 non-responders (42%) with an accuracy of 74%.

Markers of Drug Response:

- 69 responders, 102 non-responders
- A few hypotheses generated correlating a small group of non-responders.
- 10 drug non-responders came together according to a combination of variables.

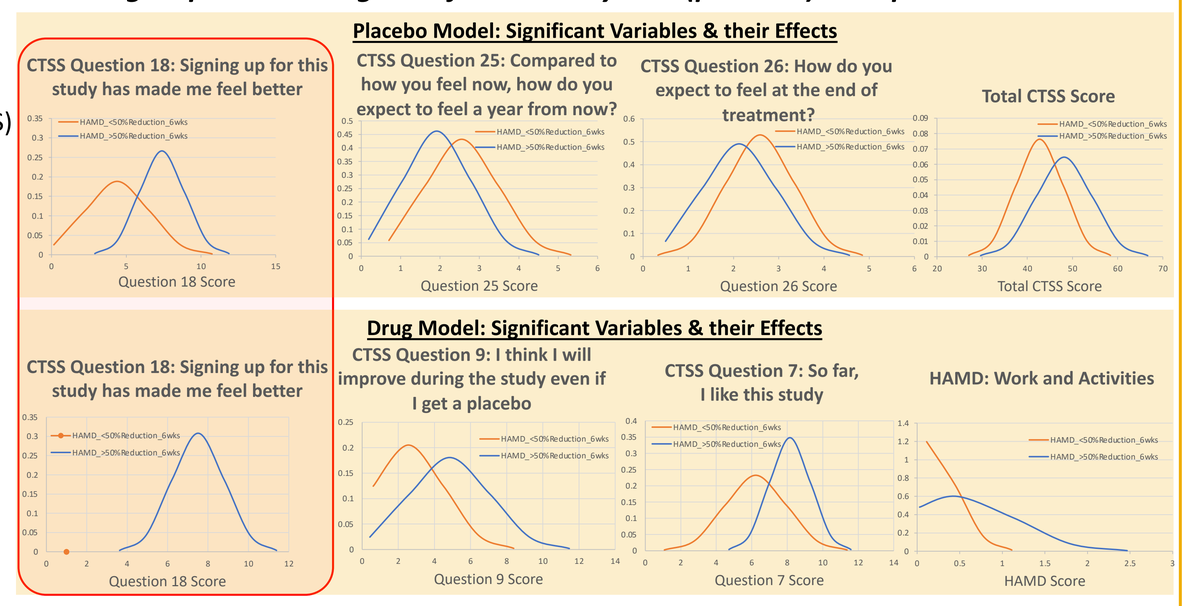


Figure 1. Significant variables extracted by NetraAI affecting placebo and drug response in a phase III anxiety trial. Top row represents significant variables in the placebo arm. Bottom row represents significant variables in the treatment arm. Note: CTSS Question 18 appears in both study arms.

This information provides trialists with information about how enriching for certain scale item responses may positively affect endpoint analytic results in future clinical trials with this compound.

- Results suggest that the anxiety drug failed to meet its endpoint but identified a subtype of patients that may not respond in a predictable way and should be excluded from subsequent trials.
- Question 18 presents a challenge as it characterizes both placebo and drug response and highlights the need to exercise caution when adding inclusion/exclusion criteria in clinical trials.

Shifting the effect size in a phase IIa schizophrenia trial using NetraAI by identifying markers of placebo and drug response.

Schizophrenia Data (Phase IIa)

- Clinical Scales (138 variables):
  - CGI-5
  - LOF
  - Strauss-Carpenter Level of Functioning
  - PANSS
  - Physiological measurements
- 87 patients randomized into placebo (n=39) and treatment arms (n=48)

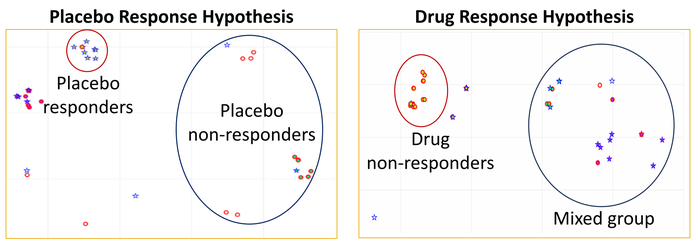


Figure 2. NetraMark hypotheses for phase IIa schizophrenia trial.

Explainable perspectives that can be used to enrich patient populations.

- 50% of placebo responders defined.
- 85% of drug responders can be explained.
- 37.5% of drug responders are strongly explainable with 16/18 being drug non-responders.

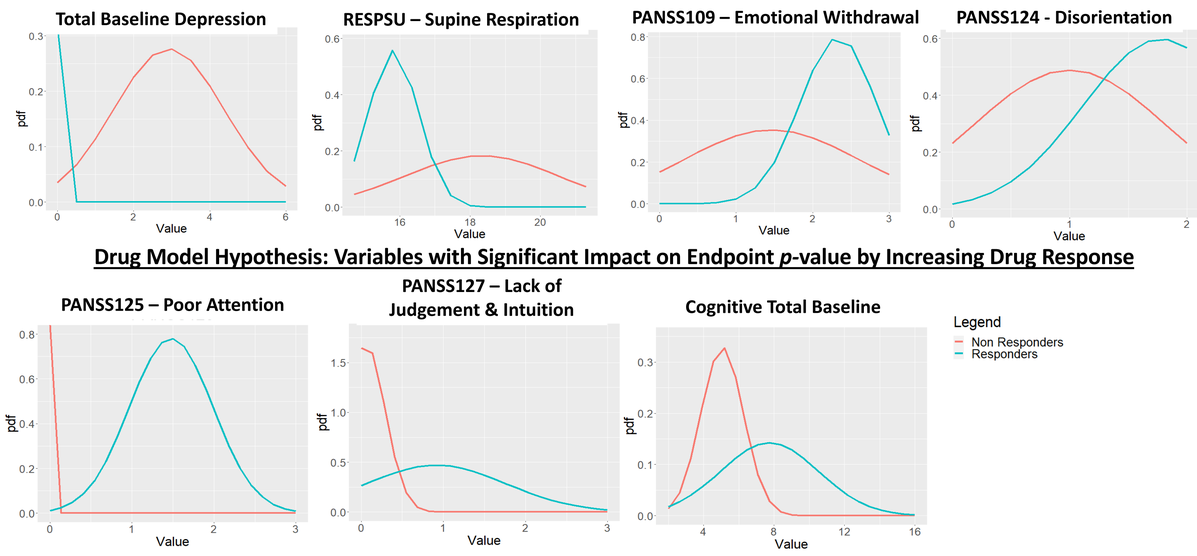


Figure 3. Significant variables extracted by NetraAI affecting placebo and drug response in a phase IIa schizophrenia trial. Top row represents significant variables in the placebo arm. Bottom row represents significant variables in the treatment arm. Red = non-responders; Blue = responders.

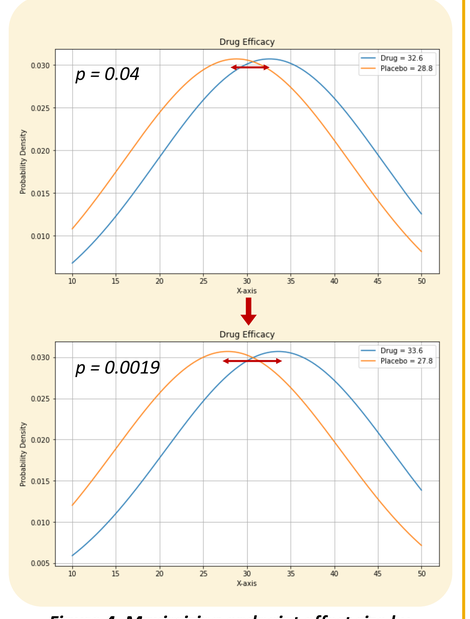


Figure 4. Maximizing endpoint effect size by combining both NetraAI hypotheses.

With our recommendations we are able to shift the *p*-value from 0.04 to 0.0019 by altering less than 20% of each arm with respect to improved efficacy in the drug arm and reduced response in the placebo arm. (**Figure 4**)

CONCLUSIONS & SIGNIFICANCE

SUMMARY OF KEY FINDINGS

1. **Identifying markers of placebo and drug response in a phase III anxiety trial.**
   - Identified 8 clinical scales explaining 25% of placebo responders and 5 clinical scales explaining a small group of drug non-responders.
   - Highlights the importance of identifying variables that affect placebo response and drug response since some variables (Question 18) play a role in both and can impact endpoint effect size (**Figure 1**).

2. **Shifting endpoint effect size in a phase IIa schizophrenia trial.**
   - Identifying hypotheses for placebo and drug response (**Figure 2**) with variables that have a significant impact on endpoint *p*-value by decreasing placebo response or increasing drug response (**Figure 3**).
   - Using the variables from the generated hypotheses and assuming a larger trial with 100 patients in both the placebo and active drug arm, we can shift the *p*-value from 0.04 to 0.0019 (**Figure 4**).

CLINICAL TRIAL SIGNIFICANCE OF METHODOLOGY AND FINDINGS

- This work illustrates the potential of a unique approach using long-range memory mechanisms to discover causal clusters – multi-item characterizations providing AI-generated hypotheses with causal implications, utilizing data from an anxiety and schizophrenia trial.
- This method offers critical scale item-level insights for pre-randomization enrichment decisions,, enhancing psychiatric clinical trials' success rates.
- These insights provide a mechanism where a drug can be tested on a subtype of patients through a Causal Cluster biomarker label or abandoned to conserve resources for another drug trial.

FUTRE USE AND APPLICATION

- Use variables identified through hypothesis generation to impact clinical trial endpoint outcomes by adding inclusion and exclusion criteria to improve efficacy in the active drug arm and reduce response in the placebo arm that can be applied to subsequent clinical trials.

NETRAMARK

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