

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

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SUBMISSION DETAILS

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Methodological Issue Being Addressed How can long range memory mechanisms enable machine learning to improve CNS clinical trials?

Introduction Recent advances in large language artificial intelligence models (LLMs) have been made possible due to the use of multi-head attention mechanisms through algorithms that are known as Transformers. These attention mechanisms allow for words that are far from each other in text to be associated with each other, despite their distance. An analogous but unique algorithm was developed to construct explainable models derived from psychiatric clinical trial data. Here we use this methodology to address the challenge of associating related clinical scale items to derive causal models for placebo and drug response using a variety of clinical scales. These collections of variables have been labeled as Causal Clusters.

Methods An algorithm using novel mathematics was used to integrate diverse data from demographic items, psychiatric scales, and safety measures collected from clinical trials. The mathematics used is not typical of most machine learning methods and is based on specialized dynamical systems that provides a way for the machine to sample combinations of variables with an improved efficiency. The methods used are related to those described here [1]. This empowers the machine learning algorithm to improve its ability to find causally connected collections of variables. When applied to existing machine learning methods this algorithm introduces a long-range memory mechanism reminiscent of attention mechanisms in LLMs. By utilizing these advanced AI methods, the system could navigate through the massive combinatorial space consisting of multiple variables to generate hypotheses about patient subpopulations. These hypotheses consisted of a list of variables from patients with anxiety and schizophrenia. Results for these analyses were then interpreted clinically.

Results Our approach uncovered subpopulations of placebo and drug responders using data from schizophrenia and anxiety trials. An additional adverse event hypothesis was generated from the schizophrenia data set.

In our recent Phase II Schizophrenia study involving 120 patients and over 100 variables derived from several clinical scales, we utilized our approach to accurately identify 55% of the placebo responders, with significant p-values persisting post-Bonferroni corrections. Notably, our model showcased an impressive 86% accuracy in discerning between a subtype of placebo responders and non-responders. We also describe the results of an analysis from a Phase III Anxiety study,

where we use a psychological scale with a cohort of 332 patients, revealed a "Causal Cluster" from clinical scales that accounted for 25% of the placebo responders at a 74% accuracy rate. However, the drug response in the active treatment group was less pronounced, explaining only 17% of responses, suggesting the drug's challenge in meeting its primary endpoint.

Our findings in the anxiety trial further indicated a specific subtype of patients who might exhibit unpredictable drug responses. This revelation offers a pivotal direction for future research, pointing towards the potential exclusion or intense examination of this patient subtype to enhance therapeutic efficacy. Additionally, we have extrapolated the nuanced individual scale items driving patient variability between the active and placebo arm. This establishes an important aspect of how enrichment can greatly improve clinical trial success rates, but also highlights how this needs to be executed carefully as improvement in the placebo response can damage drug response if the wrong psychological factors are utilized.

Our research underscores the potential of predictive modeling in psychiatric research and the importance of understanding patient subtypes. These insights pave the way for more precise and patient-centric therapeutic interventions in the fields of schizophrenia and anxiety.

Data Summary

Schizophrenia Data (Phase II)

- Clinical Scales (>100 variables)
- 120 patients randomized into placebo and treatment arms

Anxiety Data (Phase III)

- Clinical Scales (>100 variables)
- 161 placebo and 171 active patients
- 8 clinical scale items formed a Causal Cluster explaining 25% of the placebo responders with an accuracy of 74%

Conclusion This presentation illustrates the potential of this 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.

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Keywords

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Guidelines I have read and understand the Poster Guidelines

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