Predictive Biomarker Discovery in Schizophrenia Using Advanced Machine Learning to Decode Heterogeneity: Analysis of the CATIE Schizophrenia Trial

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INTRODUCTION

CHALLENGE OF HETEROGENEITY IN SCHIZOPHRENIA CLINICAL TRIALS

Schizophrenia is a complex psychiatric disorder with diverse etiologies and manifestations, making treatment response highly variable among patients, and complicating the identification of predictive biomarkers for effective treatments. Traditional machine learning (ML) approaches struggle with the complexity of capturing nuanced non-linear interactions within heterogeneous and small datasets typical of psychiatric research.

AIM

Leverage a novel AI algorithm to identify subsets of patients characterized by specific variables influencing treatment response in the CATIE schizophrenia trial.

METHODOLOGICAL ISSUE BEING ADDRESSED

Deconstructing the heterogeneous patient population in CATIE schizophrenia trial to uncover biomarkers that predict treatment response to guide precision medicine in schizophrenia.

METHODS

DATASET

CATIE schizophrenia trial (n=1600) testing several antipsychotics with respect to tolerability and efficacy. We utilized the perphenazine and olanzapine arms to build response models.

Primary Outcome: Time to all-cause treatment failure, indicated by discontinuation and medication change.

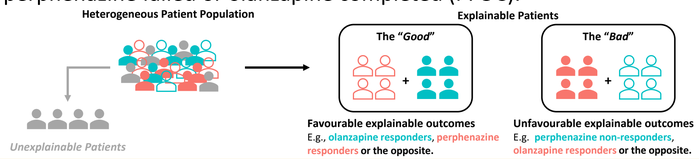
Data Types: Symptom Severity (PANSS, CGI, CDRS), Functional Outcome Measures (SF-12, QLS), Side Effects & AEs (AIMS, SAEPS, BAS, metabolic effects), Neurocognitive Assessments, Labs

MACHINE LEARNING APPROACH

A novel ML algorithm was used to analyze the clinical and functional assessment data. This approach uses **Sub-Insight Learning**, which deconstructs patient populations into explainable and unexplainable subpopulations.

- Analysis uses early variables (screening or baseline) to predict treatment response.
- By focusing on the explainable subpopulations, it identifies subpopulations characterized by 2-4 variables and their ranges, that can explain treatment response.

This approach is effective for heterogeneous and complex psychiatric data, as it discovers high-dimensional similarities among patients concerning specific clinical questions without overfitting. Patients were categorized as perphenazine completed or olanzapine failed (PCOF) and perphenazine failed or olanzapine completed (PFOC).



Goal: Identify variables that **simultaneously** characterize the "Good" patients that would result in favourable outcomes regardless of randomization.

RESULTS

Characterizing Subpopulations of Preferential Response to Olanzapine and Perphenazine

Olanzapine Preferential Response Subpopulation: n=220 (100 Perphenazine, 120 Olanzapine) characterized by 3 variables (Cohen's D=0.577, p=0.0031):

- PANSS Total Score between 69-132 (Range: 32-132)
- Clinical Global Impressions - Severity between 4-7 (Range 1-7)
- PANSS Mannerisms and Posturing between 1-2 (Range 1-7)

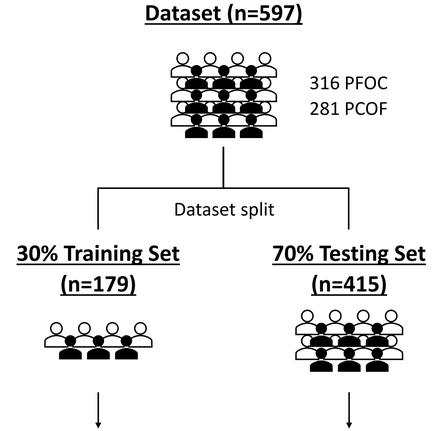
These variables suggest that patients with moderate to severe overall symptom burden with mild behavioral disturbances despite their illness severity have a higher likelihood of responding to olanzapine.

Perphenazine Preferential Response: n=60 (20 Perphenazine, 40 Olanzapine) characterized by 3 variables (Cohen's D=0.948, p=0.037):

- PANSS Hallucinatory Behavior between 1-3 (Range 1-7)
- PANSS Suspiciousness/Persecution between 3-4 (Range 1-6)
- PANSS Marder Factor Negative Symptoms between 16-21 (Range 7-40)

These variables suggest that patients with moderate negative symptoms with mild to moderate hallucinations and delusions are more likely to respond to perphenazine.

Using Hold-Out Validation to Identify Characteristics of Preferential Olanzapine Response



NetraAI is run on the 30% Testing Set to identify subpopulations that characterize preferential response to Olanzapine or Perphenazine.

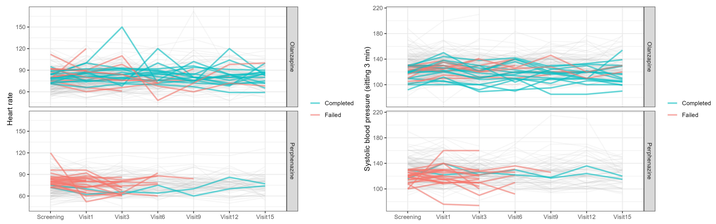
Surviving personas from the Training Set are validated in the Testing Set.

70% Testing Set was used to represent a pool of patients to replicate a clinical trial.

Distribution of variables in personas are checked for normality and tests are adjusted accordingly.

Olanzapine Preferential Response

- **Training Set (n=179):** Subpopulation n=57 (25 Perphenazine, 32 Olanzapine) characterized by 3 variables (Cohen's D=0.882, p=0.0401):
  - Vitals – Heart Rate (HR) between 71-120 (Range 55-120)
  - Vitals – Blood Pressure (Sitting 3 mins) mmHg (Systolic) between 92-131 (Range 92-190)
  - PANSS Total Score between 69-132 (Range 33-132)
- **Validated in Testing Set (n=415):** n=136 (93 Olanzapine, 43 Perphenazine); Cohen's D=0.514, p=0.0167.



This subpopulation, generally confined to a narrower HR/BP range, appeared more resilient and showed significantly better adherence to Olanzapine. No severe events were observed in this subpopulation.

Perphenazine Preferential Response

- **Training Set (n=179):** n=31 (16 Perphenazine, 15 Olanzapine) characterized by 3 variables (Cohen's D=0.073, p=0.0478):
  - Number of past medical history events ≥9 (fewer ongoing medical events) (Range 5-9)
  - PANSS Marder Factor: Cognitive Disorganized Thought between 5-12 (Range 5-26)
  - PANSS Unusual Thought Content Score between 1-2 (Range 1-7)

Identified and replicated in the Training Set, this subpopulation profile failed to replicate in the Testing Set.

CONCLUSIONS AND SIGNIFICANCE

Our advanced ML approach using Sub-Insight Learning effectively identified meaningful subpopulations within the CATIE schizophrenia trial. By focusing on subsets of variables that explain treatment response in explainable subpopulations, we overcome the limitations of traditional ML methods in handling heterogeneous psychiatric data. This class of methods are able to find high effect size subpopulations that lead to more robust models that replicate. This approach allows for the development of comprehensive patient profiles corresponding to schizophrenia clinical trials, offering a granular understanding of treatment effects. Using hold-out validation testing, we can replicate subpopulations characterized by 3 variables that correspond to preferential treatment response to olanzapine. This study underscores the potential of innovative ML techniques in advancing clinical trial enrichment strategies in psychiatry, paving the way for more successful trials with fewer failures, and a greater separation between arms.

DISCLOSURES

J.G is the founder of NetraMark and is a significant shareholder of NetraMark Holdings, which is a publicly traded company. B.Q., L.P., M.T, C.C.,P.L., and L.A. are employed by NetraMark. L.P.'s disclosures: 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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