Identifying Efficacy Variables for the Use of Escitalopram in Mild Major Depression Disorder (MDD): Implications for Treatment-Resistant MDD Trials

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INTRODUCTION

CHALLENGES IN CLINICAL TRIALS FOR DEPRESSION

Major Depressive Disorder (MDD) clinical trials face the challenge of patient heterogeneity with respect to treatment response. This necessitates large sample sizes, prolonged time for recruitment, high study costs, and often failed studies. This heterogeneity leads to a trial-and-error approach to treatment, causing significant delays in finding effective treatments for individual patients.

AIM

Utilize clinical scale data from an MDD trial to identify biomarkers predictive of patient response to an SSRI and provide a feasible Inclusion/Exclusion strategy.

METHODOLOGICAL ISSUE BEING ADDRESSED

Can machine learning (ML) technology identify unique subpopulations in MDD clinical trials with varying responses to escitalopram treatment for depression?

METHODS

DATASET

- Exploratory escitalopram drug arm with 172 MDD patients
- 362 variables/subject including data from clinical scales: CGI, SEXFX, DARS, SHAPS, MINI, MADRS, BRIAN, YMRS, QIDS, QLESQ, PSQI, and SPAQ
- Primary Endpoint: 50% MADRS improvement from baseline over 8 weeks

MACHINE LEARNING APPROACH

A novel ML algorithm, powered by attractor AI algorithms deconstructs the patient population into explainable and unexplainable subpopulations.

Sub-insight analysis utilizes advanced attention mechanisms to identify a set of patients and variables that significantly correlate with response. The machine can train itself to recognize when there is high confidence vs low confidence for identifying responsive patients.

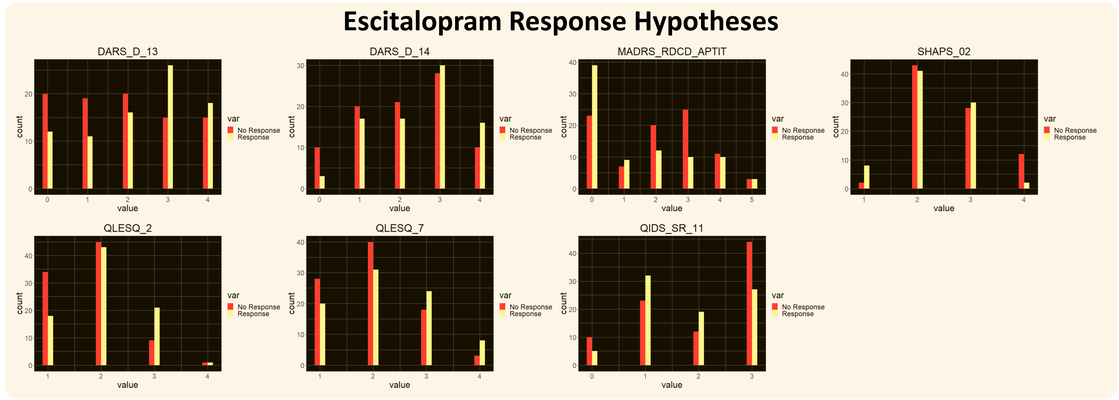
- Explainable subpopulations are used to generate hypotheses to explain what might impact patient outcomes.
- Key variables derived from the hypotheses generated are used as guidance to identify distinct patient populations corresponding to different responses to escitalopram and ultimately to improve subsequent trials with I/E criteria.

RESULTS

Identification of an Escitalopram Response Patient Subpopulation

We identified a subpopulation of 110/172 patients (~60% of patients) characterized by a set of 7 variables.

- 50 drug responders
- 60 drug non-responders



Variables Characterizing Escitalopram Response

- **DARS13**: I would eat as much of these foods as I could
- **DARS14**: I would make an effort to eat/drink these foods/drinks
- **MADRS**: Reduced Appetite
- **SHAPS2**: I have enjoyed being with my family or close friends
- **QLESQ2**: How satisfied are you with your mood?
- **QLESQ7**: How satisfied are you with leisure activities?
- **QIDS_SR_11**: View of myself

Model Generation and Cross-Validation Statistics

Cross-validation techniques were employed to test the efficacy of our model generation approach.

- Cross-validation with ~65% accuracy using state-of-the-art feature selection methods without our sub-insights.
- Cross-validation with 94% accuracy for predicting response, non-response, and a no-call class using insights from our methodology and the 7 variables that characterized the 110-patient subset.

Potential Selection Criteria Based on ML Analysis

The identified variables can be used to develop trial inclusion and exclusion criteria. These findings provide a robust approach for patient selection that includes individuals with mild to moderate depression and would require validation in follow-up clinical trials to confirm their clinical significance.

Inclusion Criteria for Subsequent Trials

Inclusion Criteria	Expected Effect on Study Population
DARS13 score > 2	• Increased likelihood of efficacy • Increase screen failure by ~50%
MADRS: Reduced Appetite $\leq$ 1	• Increased likelihood of efficacy • Increase screen failure by ~40%
QIDS_SR_11 $\leq$ 2	• Increased likelihood of efficacy • Increase screen failure by ~50%

Three of the provided significant variables form an Inclusion/Exclusion Persona that can be used to enhance the number of escitalopram responders, and decrease the escitalopram non-responders, while not losing a large proportion of patients. This AI-based process could be used to provides feasible I/E strategies for a variety of psychiatric conditions including major depression.

CONCLUSIONS AND SIGNIFICANCE

Proof-of-value of the power of ML to identify subpopulations with MDD that display a response to escitalopram.

- 7 item persona enrichment criteria for refining patient selection for future trials with escitalopram
- The partition capabilities of the Attractor AI technology can be used to identify responsive patient subpopulations for subsequent trials. These same methods can be used to mitigate placebo response.

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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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