Abstract

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Title: Machine Learning Applied To Predicting Placebo Response For Clinical Trials in Bipolar Disorder: Recent Results And Advances including Quantum Machine Learning

Question Being Asked: Can Machine Learning be used to predict placebo response in a consistent way for CNS clinical trials?

Introduction

Placebo response for CNS clinical trials especially with mood disorders, namely Major Depression and Bipolar Disorder, is a cause for concern. Placebo responders can easily obfuscate potentially positive results and a method to correct this effect is a desirable technology that is currently missing. Here we utilized modern machine learning methods to create a model for *Placebo Non-Response* that can be used to demonstrate efficacy, even when the existence of placebo responders could reduce signal without the use of this methodology.

Methods

We obtained data from a failed trial meant to evaluate depression in Bipolar Disorder from a large pharmaceutical company where all patient identification has been removed. The data was reshaped into a structure suitable for our machine learning platform. The data contained 64 placebo patients and approximately 150 variables consisting of clinical data in addition to clinical scale data including the HAMA and MADRS. Despite this being a small sample size, our unique technology is capable of learning from data of this size. Validation for this has been provided by hundreds of tests but also with a validation we performed on a failed drug arm where the response rate was very poor. Three methods were employed:

1) This placebo cohort data was passed through a proprietary expansion software program that created thousands of artificial “placebo arm patients” based on the distribution and values of the actual patients given placebo. This large set was used to train thousands of Random Forest + XGBoost + Deep Neural Network models, out of which a “best model” was tested on a data set it has never seen before.
2) A proprietary machine learning method called NetraAI was used to learn from this data set because of its ability to learn from small data sets. This method created 12 models out of which a “best model” was used to test on a data set it has never seen before.
3) We ran our data through the DWave Quantum Computer and utilized the Quantum Boltzmann Machine approach.

The model in number 2 was queried and asked to explain what variables were driving the resulting clustering of patients.

We validated the model by testing it on a test set of 218 bipolar I patients that were given a drug for depressive episodes. The drug was deemed ineffective and thus we asked the machine to predict non-responders.

Results

We discovered a model that is excellent at predicting placebo non-responders. In fact, if the machine claims that someone is a non-responder it will be correct 94% of the time. The fascinating thing about this result however are the variables chosen and they corroborate common sense regarding placebo response. In brief, there are a set of psychological attitudes which come together in a non-linear way to characterize a type of patient that will not respond to placebo, e.g., the desire to be part of the trial. No one variable alone is capable of having this efficacy.

As mentioned above, the model was tested on a failed cohort of 219 patients where the mechanism of action was deemed ineffective who happened to have the correct variables captured. The machine selected 55 people for whom it was very confidant should not respond and indeed 87% of those individuals were in fact non-responders. Less impressively, the machine was correct at predicting responders to this drug 71% of the time.

Conclusion

We have preliminary results that suggest it is possible to predict placebo response in mood disorder cohorts (bipolar disorder and depression), specifically placebo non-response, with a set of simple attitudinal based measures that we have identified as working together in a non-linear way. We will also present other placebo response models that we have discovered by working with other groups but the particular non-response model seems to be very well suited for CNS clinical trials. We will also discuss

some work we have done with a new computational paradigm which will have an impact in the clinical trial space – Quantum machine learning.

Disclosures

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The authors report no conflicts of interest for this work