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Toward Precision Treatment of Substance Use Disorders with Machine Learning Models and Pharmacogenetics

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Background: Using machine learning (ML) combined with a pharmacogenomic approach we aimed to advance precision medicine by identifying a profile of ideal or likely responders (LRs) to both zonisamide and topiramate. Three AUD clinical trials with genetically defined European Americans (N=132 zonisamide, N=277 topiramate) were used.

Rationale/Significance: Pharmacogenetic studies of AUD to date have yielded conflicting results. Polygenic Risk Scores (PRS) derived from large samples can be used to generate PRS variables for smaller target samples like clinical trials, and PRS can be included as variables in ML models.

Hypothesis: ML models can identify ideal or likely responders with enough predictive capability to be useful clinically. The addition of genomic data via multiple PRS would be informative.

Results: The zonisamide Random Forest (RF) model was fairly accurate in identifying LRs among patients randomized to zonisamide (AUC = 0.837, accuracy = 0.743). Two PRS were identified as the most important features in predicting LR status with alcohol craving being the third most predictive. Without the PRS, AUC dropped to 0.767. Two PRS were important variables in the topiramate model (R2 = 0.36), but less so than in the zonisamide model.

Discussion: RF/ML models have good predictive capabilities and are potentially clinically useful in determining whether a prospective patient will respond to zonisamide or topiramate before treatment. PRS were important informative variables that generally improved the predictive capability of the models. Further development of predictive modeling including the use of improved PRS may increase the value of this precision medicine approach.