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In Silico Genetic & Neuromolecular Drug Repurposing for Opioid Use Disorder

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We developed a drug discovery tool that matches human disease signatures to in vitro transcriptional responses of therapeutics in human cell lines. When applying this method to various neuropsychiatric traits, our method correctly identified associations with FDA approved medications for these disorders ~70% of the time, but these were only associated with height ~15% of the time (padj < 0.05). Additionally, we applied this method to cocaine use disorder data and experimentally validated a top medication in a few animal models of cocaine use in independent labs and species. To discover treatments for opioid used disorder (OUD), we applied our method to genome-wide association (GWAS; n=~70,000) and RNA-sequencing data from post-mortem human brain samples (n=~250). Our study focused on 829 repurposable compounds (e.g., Prozac) and leveraged thousands of in vitro therapeutic signatures from the L1000 database. Using multi-level meta-regression, we matched OUD disease signatures with FDA approved treatments in the L1000 database. The one FDA approved medication for OUD in the L1000 database (naltrexone) was significantly associated with OUD as well as various other novel compounds (padj < 0.05). To prioritize findings for follow-up investigation, we screened compounds for blood-brain-barrier permeability and also tested whether compounds were associated with RNA-sequencing data on pre-clinical models of opioid use. Several of these compounds readily cross the blood-brain-barrier and correlate with rodent opioid self-administration data. In sum, we identified promising new therapeutics that were associated with opioid use across a multitude of datasets.