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Computational Drug Discovery for Cocaine and Opioid Use Disorders

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Among U.S. residents ages 12 or older, 21.6 million required treatment for alcohol and illicit substance problems in 2019, but only 4.2 million who reported receiving treatment in the past year. Substance use disorders (SUDs) can be treated with behavioral counseling, medical devices, and a handful of FDA-approved medications that usually target brain functioning. Given the neuromolecular contributions to SUDs, the current study used transcriptome-wide brain data and *in vitro* neuronal signatures of FDA approved compounds to identify and validate potential repurposable medications for cocaine and opioid use disorder. We identified potential therapeutics using all publicly available transcriptome-wide *post mortem* brain data from human addiction neurocircuitry for cocaine (n=71) and opioid users (n=98) and their matched controls, as well as TWAS associations in 13 brain regions for opioid use disorder (n=82,707). Our *in silico* drug discovery approach used multi-level meta-regression that compared all cocaine and opioid expression profiles to the neuronal signatures of 829 repurposable compounds from the L1000 Library of Integrated Network-Based Cellular Signatures. We benchmarked findings against current SUD therapeutics and used a computational follow-up of pre-clinical models of cocaine (n=33) and opioid use (n=50) to prioritize treatments for experimental validation. Our analyses identified two repurposable medications that counteracted expression profiles for human cocaine use disorder and opioid use disorder, as well as pre-clinical models of opioid and cocaine use (all $p_{adj} < 0.05$). Ibrutinib, the potential medication for cocaine use disorder, was experimentally validated using the *Drosophila melanogaster* model, where it reduced incidence of cocaine-dependent startle-induced seizures.