Drug repurposing for opioid use disorders: integration of computational prediction, clinical corroboration, and mechanism of action analyses

M.S. Zhou, Q.Q. Wang, C.L. Zheng, J.A. Rush, N.D. Volkow, R. Xu

Substance use disorders (SUD) are estimated to affect 10.8% of the adult population in the US and account for 1.5% of global disease burden. Morbidity and mortality from opioid use disorders (OUD) and other SUD is a major public health crisis. There are few medications for SUD and while effective they are limited by limited utilization and high relapse rates. There is an urgency to accelerate SUD medication development. The traditional drug discovery process for medication development is lengthy and costly. In addition, the very modest investment from the pharmaceutical sector in SUDs has limited the discovery of new medications to a greater extent than for other neuro-psychiatric disorders. Thus, novel strategies to evaluate the potential for repurposing existing drugs to treat SUD could accelerate access to additional medications.

Methods We present an integrated drug repurposing strategy that combines computational prediction, clinical corroboration and mechanisms of action analysis. First, a phenome-driven network-based drug discovery system was developed to prioritize repurposed anti-SUD candidate drugs. Second, retrospective case-control studies were performed to evaluate the clinical efficacy of promising repurposed candidate drugs using EHRs of 72.9 million patients (20% of the U.S. population). Finally, potential mechanisms of action of promising repurposed candidate drugs in targeting SUD were identified by developing data-driven informatics approaches.

Results Among top ranked repurposed candidate drugs, tramadol, olanzapine, mirtazapine, bupropion and atomoxetine were associated with increased odds of OUD remission (adjusted odds ratio: 1.51[1.38-1.66], 1.90[1.66-2.18], 1.38 [1.31-1.46] 1.37[1.29-1.46], 1.48[1.25-1.76], p-value <0.001, respectively). Genetic and functional analyses showed these five candidate drugs directly target multiple OUD-associated genes including BDNF, CYP2D6, OPRD1, OPRK1, OPRM1, HTR1B, POMC,SLC6A4 and OUD-associated pathways, including opioid signaling, G-protein activation, serotonin receptors, and GPCR signaling.

Discussion The knowledge and data generated by this study (i.e., promising candidate drugs with both supporting clinical evidence and potential mechanism of actions) can set the foundation of experimental testing in animal models for SUD or for pilot testing in clinical trials. The drug discovery pipeline can be retargeted for drug repurposing for other SUD, including cocaine, marihuana, methamphetamine, benzodiazepine or inhalant use disorders.