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Repurposing ketamine to treat cocaine use disorder: integration of artificial intelligence-based prediction, expert evaluation, clinical corroboration and mechanism of action analyses

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Cocaine use disorder (CUD) is a significant public health issue for which there is approved medication. This study presents an integrated strategy to identify repurposed FDA-approved drugs for CUD treatment by combining artificial intelligence (AI)-based drug prediction, expert panel review, clinical corroboration, and mechanisms of action analysis, implemented in the National Drug Abuse Treatment Clinical Trials Network (CTN).

Based on AI-based prediction and expert knowledge, ketamine was ranked as the top candidate. Clinical corroboration utilized TriNetX to access EHRs from more than 90 million patients worldwide. A total of 7742 CUD patients who received anesthesia (3871 ketamine-exposed and 3871 anesthetic-controlled) and 7910 CUD patients with depression (3955 ketamine-exposed and 3955 antidepressant-controlled) were identified after propensity score-matching. EHR analysis outcome was a CUD remission diagnosis within 1 year of drug prescription. Patients with CUD prescribed ketamine for anesthesia displayed a significantly higher rate of CUD remission compared with matched individuals prescribed other anesthetics [hazard ratio (HR) = 1.98, 95% confidence interval (CI) = 1.42–2.78]. Similarly, CUD patients prescribed ketamine for depression evidenced a significantly higher CUD remission ratio compared with matched patients prescribed antidepressants or midazolam (HR = 4.39, 95% CI = 2.89–6.68). The mechanism of action analysis revealed that ketamine directly targets multiple CUD-associated genes (BDNF, CNR1, DRD2, GABRA2, GABRB3, GAD1, OPRK1, OPRM1, SLC6A3, SLC6A4) and pathways implicated in neuroactive ligand-receptor interaction, cAMP signaling, and cocaine abuse/dependence.

In summary, this study demonstrates the potential of AI in drug discovery for substance use disorders and supports ketamine as a potential treatment for CUD.