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Electronic health record-based clinical trial emulation to evaluate candidates in real-world populations and prioritize prospective testing.

Summary: This talk presents an electronic health record (EHR)-based clinical trial emulation framework to prioritize repurposed medications for substance use disorders. Prior studies identified spironolactone and GLP-1 receptor agonists as associated with reduced alcohol use. We extend this validated approach to methamphetamine and other stimulant use disorders.

Abstract: This talk describes an electronic health record (EHR)-based trial emulation framework designed to prioritize repurposed medications for substance use disorders prior to prospective testing. As proof of concept, we applied EHR-based target trial emulation to alcohol use disorder (AUD) using the Veterans Aging Cohort Study-National, comprising >14.1 million patients receiving care in the largest integrated health system in the US. Initiation of spironolactone was associated with reductions in Alcohol Use Disorder Identification Test-Consumption (AUDIT-C) scores compared with propensity-score matched comparators (difference-in-difference [DiD] 0.17 points, 95% CI 0.09 to 0.25), with larger effects observed at doses ≥ 50 mg per day (DiD 0.69, 95% CI 0.50, 0.89; $p < 0.0001$), findings that motivated prospective clinical trials.

We subsequently evaluated glucagon-like peptide-1 receptor agonists (GLP-1RAs) using an active-comparator new-user design contrasting initiators with dipeptidyl peptidase 4 inhibitor users to minimize confounding by indication. GLP-1RA initiation was associated with significant reductions in alcohol use, particularly among individuals with AUD (DiD 0.65, 95% CI: 0.43, 0.88; $p < 0.0001$) and who report baseline hazardous drinking (DiD 1.00, 95% CI: 0.68, 1.33; $p < 0.0001$). Building on this framework, we extend EHR-based trial emulation to methamphetamine and other stimulant use. Multisignal phenotypes integrating diagnostic codes, toxicology results, prescription data, and natural language processing identify stimulant use trajectories. High-throughput machine learning prioritizes candidate medications, followed by full trial emulation. EHR-based trial emulation functions as a translational filter linking mechanistic discovery to randomized trials, advancing drug candidates supported by convergent real-world and biological evidence into prospective testing for substance use disorders.

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