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Metabolic medicines and addiction: what GLP-1 receptor agonists might add to substance use care

Clinical trials and equitable care pathways are needed to build on early evidence of benefit

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Substance use disorders (SUDs) are common and burdensome for patients, families, and health systems,[1 2] yet effective albeit underused drugs exist for only some conditions.[2 3] Glucagon-like peptide-1 (GLP-1) receptor agonists, used to treat type 2 diabetes and obesity,[4] have been proposed as anti-craving agents because GLP-1 signalling interacts with brain reward and stress circuits.[5] In a linked paper, Cai and colleagues (doi:10.1136/bmj-2025-086886) tested this hypothesis using routinely collected healthcare data from US veterans with type 2 diabetes.[6]

Using Veterans Affairs data, the authors emulated eight parallel target trials[6 7] comparing initiation of a GLP-1 receptor agonist with initiation of a sodium-glucose cotransporter-2 (SGLT-2) inhibitor; an active comparator with similar cardiometabolic indications. In veterans without a baseline SUD, initiation of a GLP-1 receptor agonist was associated with lower hazards of incident alcohol (hazard ratio 0.82), cannabis (0.86), cocaine (0.80), nicotine (0.80), opioid (0.75), and other SUDs (0.87) over three years, with net three year risk differences of roughly 1-6 fewer cases per 1000 people.[6] More clinically consequential were the findings among veterans with a pre-existing SUD, shifting the question from prevention to harm reduction. In this group, initiation of a GLP-1 receptor agonist was associated with fewer SUD related emergency department visits (hazard ratio 0.69), hospital admissions (0.74), and mortality (0.50), overdose (0.61), and suicidal ideation or attempt (0.75), translating to about 1-10 fewer events per 1000 people over three years.[6] These results suggest that any potential benefit is not restricted to a single diagnosis or substance and may extend to acute and life threatening consequences of addiction.

Why might a drug for type 2 diabetes affect addiction outcomes? Preclinical and early clinical evidence suggests GLP-1 receptor activation can reduce reward-driven seeking behaviours.[5] A randomised trial of semaglutide in adults with alcohol use disorder reported reductions in alcohol craving and some drinking outcomes over short follow-up,[8] and systematic reviews suggest early trials show signals for alcohol and nicotine outcomes.[9] Observational analyses in other settings have also reported lower risks of alcohol and cannabis use disorders and opioid related outcomes among users of GLP-1 receptor agonists.[10 -13] Cai and colleagues' study design strengthens causal interpretation through a new user design, an active comparator, extensive confounding control, and negative control analyses.[6 7]

Caution is still warranted. Residual confounding is plausible in data (for example, differences in health seeking behaviour, access, or clinician choice). SUDs and overdoses can be underdiagnosed, and ascertainment may differ if groups have different contact with services. The cohort included predominantly older men, so generalisability to women, younger people, and non-US settings is uncertain.[6] Finally, the estimated "net" effect reflects the effect of starting a GLP-1 receptor agonist rather than an SGLT-2 inhibitor; it does not establish benefit versus no treatment or versus evidence based addiction pharmacotherapy.

What should patients and clinicians do now? For patients with type 2 diabetes who also live with (or are at risk of) an SUD, the key message is not to wait for a single "magic bullet." Evidence based treatments, opioid agonist treatment for opioid use disorder, and pharmacotherapies plus psychosocial support for alcohol use disorder remain the preferred treatments.[2 3] But these results suggest that when GLP-1 receptor agonists are clinically indicated for cardiometabolic reasons, potential benefits for substance related outcomes may be an added consideration in shared decision making.[4] Clinicians in diabetes and obesity services should screen for alcohol and drug use, offer stigma-free support options, and coordinate care with addiction and mental health teams. Families often carry the consequences of relapse and overdose; integrated care that addresses both metabolic disease and substance use can reduce avoidable crises.

The implications are pragmatic rather than revolutionary; policymakers should therefore avoid premature "Ozempic for addiction" narratives. If ongoing trials confirm meaningful benefits, affordability and supply will become ethical issues. GLP-1 receptor agonists remain costly, and access is unequal across and within countries; equity should be monitored throughout. A repurposed indication should not widen health inequities or divert supply away from established indications. Instead, it should prompt payers and regulators to invest in integrated models linking metabolic, mental health, and addiction services alongside safety surveillance.

The research agenda is clear. Randomised trials are needed in diverse populations, including people without diabetes and those receiving standard drugs for opioid and alcohol use disorders, to test whether GLP-1 receptor agonists add benefit to patient important outcomes (use reduction, overdose, quality of life, and functioning).[8 9] Trials should examine dose, duration, and whether effects differ across GLP-1 receptor agonist molecules. Mechanistic studies can clarify whether benefits are mediated by weight loss, improved glycaemic control, reduced

inflammation, or direct central nervous system effects. It is also hypothesised that incretin treatments may shift a dysregulated immunometabolic "set point"; an idea to test in studies ranging from basic mechanistic work to pragmatic trials and real world implementation research. Implementation research, codesigned with patients and families, should evaluate how to deliver combined cardiometabolic and addiction care without increasing burden or stigma.

For now, Cai and colleagues' target trial emulation strengthens the case that GLP-1 receptor agonists may influence substance related outcomes in real world practice.[6] The challenge is to translate this signal into trials and equitable care pathways while continuing to scale proven treatments for SUDs.

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