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Off-Label Use of SGLT2 Inhibitors for Weight Loss— We Must Not Open That Pandora's Box!

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ABSTRACT

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are increasingly discussed for weight management, yet their off-label use raises significant concerns. Evidence shows only modest weight loss, below clinically meaningful thresholds and likely overestimated in trial settings. Efficacy and safety data from populations living with diabetes, chronic kidney disease, or heart failure cannot be extrapolated to individuals with obesity alone. Off-label use may expose patients to avoidable risks, including infections and rare severe complications, while undermining pharmacovigilance. Ethical, social, and system-level consequences—including misuse, inequitable access, and drug shortages—further challenge justification.

Key words: Obesity; Off-label use; Safety; Weight loss

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As bodyguards of drug safety (1), we are writing to share additional insights inspired by recent speculations on the use of SGLT2 inhibitors for anti-obesity treatment (2). Consequently, we wish to provide a timely and comprehensive overview of the safety considerations surrounding sodium–glucose cotransporter 2 (SGLT2) inhibitors in weight management. We are concerned that such discussions, if not framed with sufficient caution, risk legitimizing off-label use of these agents for obesity in individuals without diabetes, chronic kidney disease (CKD), or heart failure—settings where neither efficacy nor safety has been adequately established.

First issue is the effect size. The magnitude of weight loss achievable with SGLT2 inhibitors is modest at best. For instance, Cheong et al. in their meta-analysis of 116 randomized controlled trials (combined cohort of 98,497 patients) demonstrated a mean body weight reduction of only –1.79 kg (95% CI: –1.93 to –1.66; $p < 0.001$) compared with placebo (3). Although statistically significant, this weight loss result does not meet the standardized meaningful weight loss threshold of ≥5%. Moreover, most RCTs combined pharmacotherapy with lifestyle interventions—nutritional counseling and structured physical activity—which are seldom replicated in real-world settings. Consequently, one should anticipate even smaller effects outside the controlled environment of clinical trials.

Second, efficacy and safety observed in a specific population cannot be directly extrapolated to a different one. The enthusiasm to generalize findings from trials in diabetes, CKD, and heart failure populations to individuals with obesity alone is methodologically unsound. In these landmark studies—EMPA-REG OUTCOME, DECLARE-TIMI 58, CANVAS, DAPA-HF, DELIVER, EMPEROR-Reduced, EMPEROR-Preserved, DAPA-CKD, and EMPA-KIDNEY (4-13) — weight loss was a secondary outcome, and just exploratory. Such signals, while intriguing, cannot be extrapolated as robust evidence for efficacy in a distinct, metabolically heterogeneous, non-diabetic population. External validity matters: the safety and benefit profile established in individuals with diabetes, heart failure or CKD cannot be assumed to hold in the general population living with overweight or obesity.

Third issue is a different risk/benefit profile of the same drug if used for different indications. Broadening use without solid evidence risks eroding the favorable drug safety profile that SGLT2 inhibitors have earned within their approved indications. Off-label prescribing invites preventable adverse events— genital and urinary tract infections, volume depletion, and rare but devastating complications such as euglycemic ketoacidosis and Fournier's gangrene (13). In a context where expected benefit is marginal, these risks become unjustifiable. Furthermore, widespread off-label use may undermine the ability of pharmacovigilance systems to accurately monitor and identify true drug-related safety signals in approved indications. If adverse events begin emerging in low-benefit, off-label contexts, it could blur interpretation of safety data, confuse causality assessment, and ultimately erode public trust in both the medicine and its regulators.

Fourth, the social and ethical consequences also deserve careful attention. Patients living with obesity often encounter stigma, limited access to multidisciplinary care, and fragmented treatment pathways, which can make them more likely to turn to quick medical fixes in search of relief (14). Already, reports of unregulated or counterfeit "black-market" access to weight-loss drugs have surfaced globally (15). In this context, any scientific endorsement, even implicit, of SGLT2 inhibitors for obesity may unintentionally fuel unsafe self-medication practices, parallel markets, and misuse. We therefore have a

profound responsibility, as clinicians and scientists, to communicate carefully and avoid opening a Pandora's box of off-label and risky weight loss interventions.

Beyond the patient level, there are important system-wide implications. Expanding off-label demand could strain supply chains, leading to drug shortages for patients with diabetes, CKD, and heart failure—populations in which SGLT2 inhibitors confer proven cardiorenal and survival benefits. Increased treatment-related adverse events, including urinary tract infections and resultant antibiotic exposure, could further aggravate healthcare costs and contribute to antimicrobial resistance, adding to the already heavy burden on healthcare systems.

Ethically, prescribing a potent agent for an unproven indication raises questions of professional accountability. If even one patient develops euglycemic ketoacidosis or a necrotizing infection from an off-label attempt to achieve minimal weight loss, the prescriber bears the moral and potentially legal responsibility. When benefits are marginal and harms predictable, the principle of primum non nocere must prevail.

In summary, SGLT2 inhibitors remain transformative drugs for diabetes, CKD, and heart failure, but their repurposing for obesity lacks evidence, external validity, and ethical justification. The modest weight reduction does not offset the potential clinical, pharmacovigilance, and societal harms. We must exercise extreme care in how such ideas are communicated in scientific literature, particularly in prestigious journals whose readership can shape prescribing behavior worldwide. Rather than opening Pandora's box, let us close it firmly—preserving the integrity, safety, and public trust that these valuable medicines deserve (16).



Figure 1. Conceptual illustration of the risks and hazards linked to off-label SGLT2 inhibitor use for weight loss.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS
A.B., B.J., and S.J. contributed equally to all aspects of the preparation of this manuscript and meet the ICMJE criteria for authorship.

ETHICAL BACKGROUND

Informed consent statement: Not applicable. **Data availability statement:** Not applicable. **Ethical Approval:** Not applicable.

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