

Gastrointestinal Safety Profile of Oral and Subcutaneous Semaglutide in Type 2 Diabetes: A Bayesian Network Meta-Analysis Based on PIONEER and SUSTAIN Series Trials

Jingfei Wang

Institute of Clinical Medicine, University of Tartu, Tartu, Estonia

Alastair Forbes

Institute of Clinical Medicine, University of Tartu, Tartu, Estonia

Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have become first-line therapeutic agents for type 2 diabetes (T2D), with gastrointestinal adverse events being their most common adverse effects. Oral semaglutide, the world's first approved oral GLP-1 agent, achieves transepithelial absorption in the stomach. Whether its direct contact with the gastrointestinal mucosa induces additional local irritation or a distinct adverse reaction profile remains insufficiently evaluated. This study employed a dual framework network meta-analysis to systematically assess gastrointestinal safety differences across oral and subcutaneous formulations of semaglutide, as well as other antidiabetic agents. We systematically included 22 randomized controlled trials (RCTs), strictly restricting interventions to approved standard doses. Outcome measures comprised six gastrointestinal endpoints, and interventions were classified into seven groups. All 22 included RCTs were judged to be at low-to-moderate risk of bias. Across all six gastrointestinal endpoints, both PO and SC semaglutide consistently ranked in the intermediate-to-high risk range. Direct pairwise comparisons showed no statistically significant differences between PO and SC across any of the six outcomes. Numerically, both formulations exceeded other GLP-1RAs in risk, though most comparisons did not achieve statistical significance. The gastrointestinal adverse event profile of oral semaglutide is highly consistent with that of subcutaneous semaglutide, with no statistically significant differences detected across all six endpoints. Both formulations are associated with significantly higher gastrointestinal risk compared with placebo, DPP-4 inhibitors, SGLT2 inhibitors, and insulin, and show numerically higher risk relative to other GLP-1 RAs. These findings support oral semaglutide as a well characterized, tolerable, non-injectable alternative for patients with T2D.

Keywords

Type 2 diabetes, Semaglutide, Glucagon-like peptide-1 receptor agonist, Gastrointestinal adverse events, Network meta-analysis.