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Brief Report

Balancing the Risks and Benefits of GLP-1 Agonists for Weight Loss

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ABSTRACT

The emergence of GLP-1 agonists has revolutionized the management of type 2 diabetes and obesity. Their efficacy in inducing weight loss and improving glycaemic control is undeniable. However, the rapid expansion of their use necessitates a cautious approach, given the potential for adverse effects. GLP-1 agonists mimic the actions of the incretin hormone, glucagon-like peptide-1. While their therapeutic benefits are substantial, concerns have arisen regarding the long-term safety profile of GLP-1 agonists. Gastrointestinal adverse effects, such as nausea, vomiting, and diarrhoea, are common but often resolve with continued use. However, more severe gastrointestinal complications, including pancreatitis and gallbladder disease, have been reported. Despite these potential adverse effects, GLP-1 agonists remain valuable tools in the management of type 2 diabetes and obesity. However, their use should be carefully considered on an individual basis, with regular monitoring for any adverse reactions. Healthcare providers must maintain vigilance and engage in open communication with patients to optimize treatment outcomes while minimizing risks. As our understanding of GLP-1 agonists evolves, continued research is imperative to elucidate their long-term safety profile and identify patient populations at increased risk of adverse events.

Keywords: GLP-1 agonists, Obesity, Incretin, Weight loss, Gastrointestinal.

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INTRODUCTION

Obesity is a chronic condition characterized by excessive body fat accumulation, leading to various health problems. It is a global epidemic with significant implications for individuals and healthcare systems.[1,2] There are several challenges in the clinical management of obesity.[2,3] Obesity is influenced by genetic, environmental, behavioural, and physiological factors, this complex aetiology makes it difficult to manage the condition with a single approach. While lifestyle modifications (diet, exercise) are foundational, long-term weight loss is challenging due to limited availability of effective treatments. Currently available medications and surgical options have limitations and are not suitable for everyone.[4,5] The concurrence of comorbidities like diabetes, heart disease, and sleep apnoea further complicates the treatment and increases risks. In addition to these the episodes of relapse adds further complexities in clinical management as weight loss is frequently followed by regain, highlighting the need for sustained support and behavioural changes. Hence addressing obesity requires a multidisciplinary approach involving healthcare providers, policymakers, and the community to create supportive environments and effective interventions. Recently GLP-1 agonists have gained increasing use for the management of weight loss.

GLP-1 agonists are a class of medications used to treat type 2 diabetes.[6,7] They work by mimicking the effects of Glucagon-Like Peptide-1 (GLP-1), a hormone produced in the intestines. Currently five GLP-1 receptor agonists are approved by US FDA (Figure 1). There is also a class of medications called dual Glucose-dependent Insulinotropic Polypeptide (GIP)/GLP-1 receptor agonists. While not solely GLP-1 agonists, they share pharmacological similarities. Currently, the only FDA-approved drug in this class is tirzepatide (Mounjaro) (Figure 1). The mechanism of action of GLP-1 agonists (Figure 2) involve binding to and activating GLP-1 receptors in the pancreas, leading to 1) Increased insulin secretion (GLP-1 agonists stimulate the release of insulin from the beta cells in the pancreas, which helps to lower blood sugar levels), 2) Decreased glucagon secretion (GLP-1 agonists also suppress the release of glucagon, a hormone that raises blood sugar levels), 3) Slowed gastric emptying (GLP-1 agonists slow down the rate at which food leaves the stomach, which can help to reduce postprandial blood sugar spikes) and 4) Increased satiety (GLP-1 agonists can also help to reduce appetite and food intake, leading to weight loss).[6,8-10]

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GLP-1 agonists are administered by injection (either subcutaneously or intravenously) or orally.[6,9] The half-life of GLP-1 agonists varies depending on the specific drug, but it is generally in the range of 1-2 hr. GLP-1 agonists are metabolized by the liver and kidneys. GLP-1 agonists are effective in lowering blood sugar levels in patients with type 2 diabetes. They can also help to reduce HbA1C levels, which is a measure of sustained long-term blood sugar control. In addition, GLP-1 agonists can help to reduce the risk of cardiovascular events, such as heart attack and stroke. The most common adverse effects of GLP-1 agonists are nausea and vomiting, while other possible side effects can include diarrhoea, headache, and fatigue.[11-13]

GLP-1 agonists were initially developed and approved for the management of type 2 diabetes.[6,9] They have since demonstrated significant efficacy in weight management and are increasingly being explored for therapeutic use in various other conditions including 1) Heart Failure, 2) Non-Alcoholic Steatohepatitis (NASH), 3) Polycystic Ovary Syndrome (PCOS) and 4) Alzheimer's Disease.[11,14,15] While GLP-1 agonists may be effective, there are limited data on safety and efficacy especially with their off-label use. In a recent study published in JAMA,[16] Sodhi and colleagues shed light on the risks associated with the off-label use of Glucagon-Like Peptide-1 (GLP-1) receptor agonists for weight loss. While GLP-1 agonists are well-established for the treatment of diabetes, their use for weight loss has grown in popularity. The study's findings raise important considerations regarding the potential gastrointestinal adverse events linked to these medications.[12,13] The study focused on two main GLP-1 agonists, liraglutide and semaglutide, and compared them to an active comparator, bupropion-naltrexone, which is unrelated to GLP-1 agonists but used for weight loss. The research involved a substantial cohort of patients over a 14-year period, and the results were striking.

The study[16] found a significant increase in the risk of certain gastrointestinal adverse events, including pancreatitis, gastroparesis, and bowel obstruction, among GLP-1 agonist users compared to those taking bupropion-naltrexone (Figure 2). However, in contrast to published reports,[17,18] it is essential to note that this study didn't observe increased risk of biliary disease. This finding indicates that patients considering GLP-1 agonists for weight loss must weigh these potential risks against the benefits. One of the strengths of this study is its large sample size, which provides robust statistical evidence. The authors also adjusted for several confounding factors, such as age, sex, and smoking, to ensure the reliability of their findings.[16] Sensitivity analyses were conducted to examine the results from different perspectives, further strengthening the conclusions of this study. Despite these strengths, this study does have limitations.[16] Notably, the researchers could not confirm whether all GLP-1 agonist users were taking these medications specifically for weight loss. Additionally, the absence of data on Body Mass Index (BMI) required the use of estimated analysis to gauge the potential impact of unmeasured confounding variables on the results.

The implications of this study are significant, especially given the increasing interest in using GLP-1 agonists for weight loss. While these drugs have shown promise in this regard, the heightened risk of specific gastrointestinal adverse events suggests a need for a careful risk-benefit evaluation. The decision to use GLP-1 agonists for weight loss should be a well-informed one, and patients should consult with their healthcare providers to thoroughly discuss the potential benefits and risks. Furthermore, the study highlights the importance of conducting more comprehensive research on

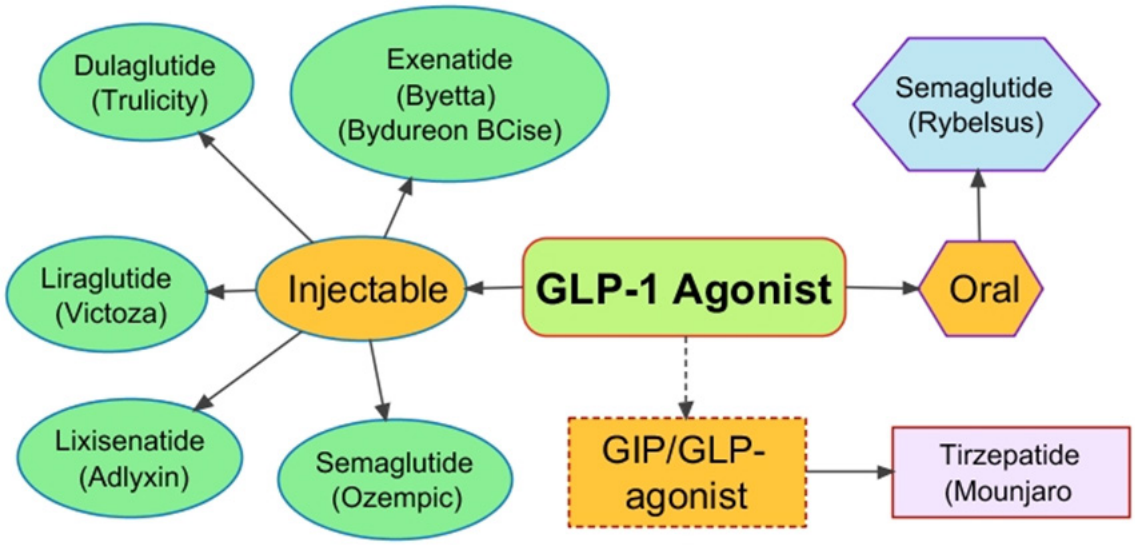

Figure 1: GLP-1 agonists approved for clinical use. GLP-1 agonists are available in three different versions i.e., 1) injectable, 2) oral and 3) dual GIP (glucose-dependent insulinotropic polypeptide)/GLP-1 receptor agonists.

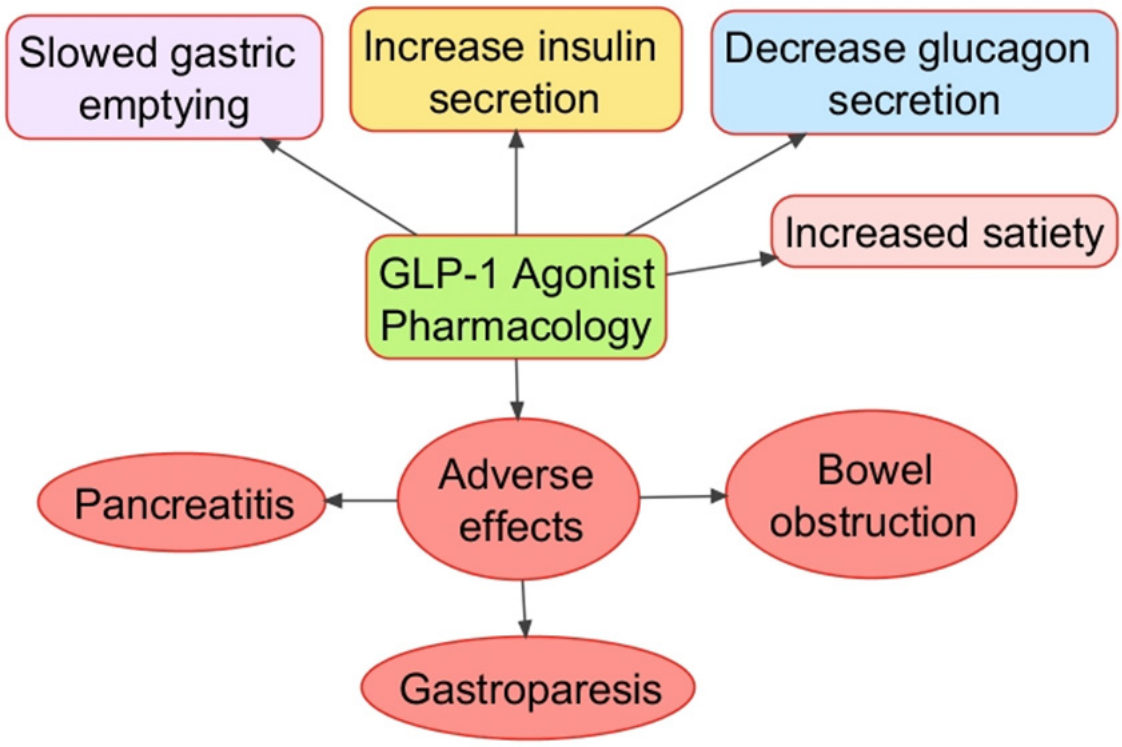

Figure 2: Pharmacology of GLP-1 agonists. The four major mechanism of action of GLP-1 agonists are shown in addition to the three major adverse effects associated with clinical use of GLP-1 agonists.

the use of GLP-1 agonists for weight loss. Larger, well-designed clinical trials with extended follow-up periods are necessary to provide a more complete understanding of the potential risks and benefits. In addition chrono pharmacological[19] data on GLP-1 agonists will be valuable in limiting the potential adverse effects observed. This would allow patients and physicians to make informed decisions about whether these medications are appropriate for their specific circumstances and optimally designing the therapeutic regimen.

CONCLUSION

In conclusion, Sodhi and colleagues' study underscores the need for a balanced approach to using GLP-1 agonists for weight loss. The benefits of weight loss should be carefully weighed against the potential risks, particularly regarding pancreatitis, gastroparesis, and bowel obstruction. Patients and healthcare providers must collaborate to make well-informed decisions that align with individual health goals and medical histories. As the medical community continues to explore the application of GLP-1 agonists for weight loss, it's prudent to remain vigilant in assessing their safety and efficacy on an ongoing basis.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ABBREVIATIONS

BMI: Body Mass Index; **GIP:** Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon like peptide 1; **HbA1C:** Hemoglobin A1C; **JAMA:** The Journal of the American Medical Association; **NASH:** Non-Alcoholic Steatohepatitis; **PCOS:** Polycystic Ovary Syndrome; **US FDA:** United states Food and Drug administration.

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