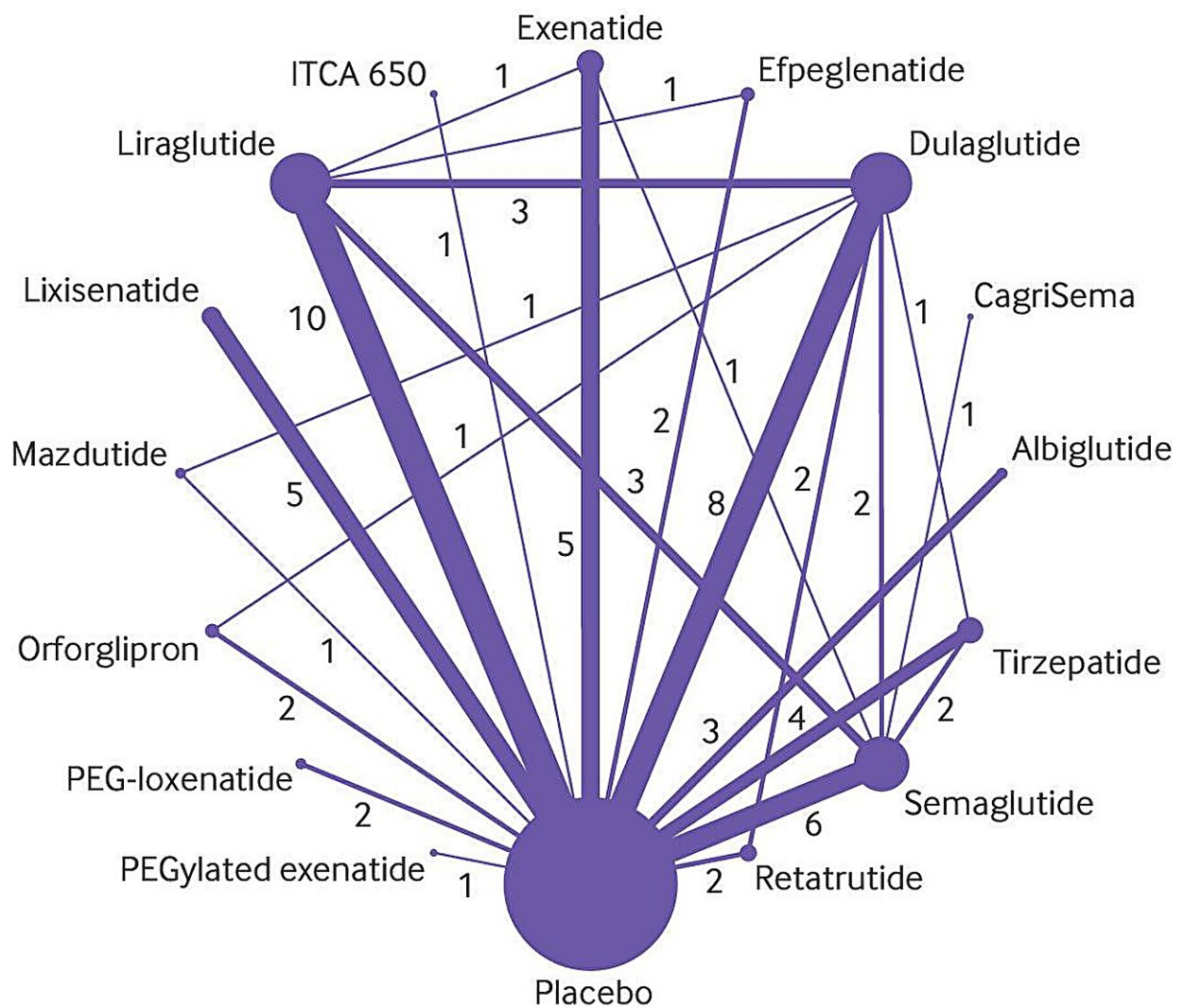


Research shows GLP-1 receptor agonist drugs are effective but come with complex concerns

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Network of available comparisons between GLP-1RAs and placebo for weight

loss. The size of the nodes is proportional to the number of trial participants, and the thickness of the line connecting the nodes is proportional to the randomized number of trial participants directly comparing the two treatments. Numbers represent the number of trials contributing to each treatment comparison. Credit: *BMJ* (2024). DOI: 10.1136/bmj-2023-076410

Drugs like Ozempic, Wegovy and Mounjaro have been around for years, but they've recently been making headlines due to a rise in popularity as weight loss agents. They all belong to a class of drugs known as glucagon-like peptide-1 receptor agonists (GLP-1RAs), which mimic a hormone (GLP-1) in the body that helps control insulin and blood glucose levels and promotes feelings of satiety.

These drugs are extremely effective for blood glucose control and [weight management](#), which, combined with their relatively limited side effect profile, makes them very appealing for diabetes treatment—the purpose for which they originally received FDA approval.

However, off-label use fueled by celebrities and social media is a growing concern. And even when physicians are prescribing GLP-1RAs for their intended uses, it's not a magic formula—there are complex considerations such as dosages, costs, side effects and comparisons between specific drugs.

"The current fervor for GLP-1RAs in the capital markets as well as in the general public, especially in terms of weight reduction, is probably going to result in overuse," said Chun-Su Yuan, MD, Ph.D., the Cyrus Tang Professor of Anesthesia and Critical Care at the University of Chicago. "This should raise a red flag."

Living up to the hype

While experts caution against overusing GLP-1RAs or viewing them as a universal cure-all for obesity, physicians and researchers agree that the drugs are highly effective for weight management and Type 2 diabetes treatment.

"Some other treatments for Type 2 diabetes can actually cause weight gain, whereas GLP-1RA drugs effectively control [blood glucose levels](#) while also reducing body weight," Yuan said.

Yuan and a group of other researchers recently published a [paper](#) in *BMJ* comparing the effectiveness of different GLP-1RAs. Different drugs performed better in different areas, but all 15 GLP-1RAs they analyzed were very successful in lowering blood glucose and achieving weight loss. They also identified some secondary benefits, such as lowering cholesterol.

Similarly, Eric Polley, Ph.D., a UChicago data science and public health expert, recently led a [study](#) published in *Nature Cardiovascular Research* that used statistical modeling to simulate a clinical trial comparing the effects of four different classes of diabetes medication in patients with moderate cardiovascular risk. GLP-1RA drugs came out on top, not only controlling blood glucose and weight but also reducing the risk of major heart-related events and the risk of death overall.

Not a silver bullet: Making nuanced decisions for each patient

However, GLP-1RAs are not universally effective for all patients, and Yuan said that even after deciding to prescribe this drug class, physicians should consider multiple factors when selecting a specific drug and dosage. For example, co-morbid conditions like hyperlipidemia could tip the scale and make one drug more suitable for a specific patient.

Polley pointed out that even patients with similar clinical profiles might prioritize different aspects of their health or quality of life.

"If cardiovascular health is what you think is important for deciding between these drug classes, I think our most recent study provides some strong evidence. But if there are other outcomes that your patient is concerned about, then you have to consider the effect size for those other outcomes," Polley said.

He and other experts are working on subsequent research examining the effects of different diabetes treatments on other health outcomes and concerns, including a patient's risk of cancer, blindness or amputation.

Another key consideration is side effects, which can vary significantly from patient to patient. While Yuan's recent study confirmed the efficacy of GLP-1RAs, the researchers also found that some patients did experience adverse side effects, especially related to gastrointestinal issues like nausea and vomiting. They highlighted the need to consider potential tradeoffs between efficacy and side effects, finding that higher doses can have stronger efficacy but also induce more severe side effects.

"It's also important to note that the long-term side effects of these drugs are not yet well-studied," Yuan said. "If large swathes of the general public start taking them off-label for weight loss and then we find out years later that there are bad [side effects](#), it could be a real issue."

Rethinking long-term weight management strategies to overcome cost barriers

Yet another dimension affecting the use of GLP-1RAs is cost. The drugs are expensive, and experts say the recent spike in popularity has already

led to shortages and increased hesitancy among insurance providers to cover these drugs.

"We know these drugs represent a massive breakthrough in our long fight against obesity-related clinical conditions, but their high cost has been the subject of substantial debate," said David Kim, Ph.D., a UChicago health economist and lead author of a [study](#) published in *Health Affairs Scholar*. "It presents a key barrier to equitable access to this great innovation."

In pursuit of more equitable and cost-effective approaches to leveraging GLP-1RAs, Kim and a group of other researchers analyzed the potential impact of alternative weight loss programs. Specifically, they proposed an approach in which GLP-1RAs could be prescribed for an initial period of weight loss before patients transitioned to cheaper alternative interventions for weight maintenance such as lower-cost medications, behavioral health programs and support from nutritionists.

"We wanted to challenge the assumption that once you're on a GLP-1RA drug, you have to keep taking it forever," Kim said. "That's where some of the affordability concerns are coming from: large populations are potentially eligible to take these drugs, and we can't pay for a lifetime supply for everyone."

The researchers' model suggested that even though the alternative weight-maintenance programs might be slightly less effective than long-term, full-dosage GLP-1RA use, the clinical benefits would only decrease slightly, while lifetime health care spending would decrease substantially.

"We argue that this alternative framework is a viable solution that provides greater flexibility for managing a limited [drug](#) supply and giving health care payers financial headroom to support more patients

accessing effective weight management treatment," Kim said.

More information: Haiqiang Yao et al, Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis, *BMJ* (2024). [DOI: 10.1136/bmj-2023-076410](https://doi.org/10.1136/bmj-2023-076410)

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