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GLP-1 Receptor Agonists vs Lifestyle Therapy Alone for Weight Loss in Adults With Obesity Without Diabetes

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Clinic Scenario

- In clinic, we frequently see adults with obesity who have not achieved meaningful weight loss despite sustained lifestyle modification.
- It is often unclear whether starting a GLP-1 receptor agonist provides significant additional benefit compared with continuing lifestyle therapy alone.
- Providers and patients question:
- Is medication truly more effective?
- Is ≥5% weight loss achievable?
- Are side effects and cost justified?
- Many patients asked whether medication can realistically help them achieve weight loss when lifestyle efforts have failed.

Background & Significance

Obesity affects ~40% of U.S. adults[1] and is associated with:
- Type 2 diabetes [2]
- Cardiovascular disease [2]
- Reduced quality of life [2]

First-line therapy = lifestyle modification; Many patients fail to achieve ≥5% weight loss with lifestyle alone

GLP-1 receptor agonists [3-6]:
- Increase satiety, delay gastric emptying, promote sustained weight loss
- Clinical trials report 10–20% weight loss over 1 year

Clinical question: Are GLP-1s superior to continued lifestyle therapy alone in non-diabetic adults?

PICO Question: In adults ≥40 with obesity without diabetes who failed lifestyle therapy, does GLP-1 treatment lead to greater weight loss than lifestyle therapy alone?

Search Strategy

Database: PubMed Clinical Queries (Therapy, Narrow)
Search Terms:
("obesity" OR "overweight") AND
("GLP-1 receptor agonist" OR semaglutide OR liraglutide) AND
("randomized controlled trial")

Filters Applied:
Humans, Adults (≥18 years)
Randomized Controlled Trials
Publication date: 2015–2024
Titles and abstracts screened (143 total)
Selected 3 high-quality RCTs most aligned with PICO

Search Results

Study	Design	Patients	Comparison(s)	Outcome(s)	Results
doi:10.1056/NEJMoa2032183	RCT, randomized, placebo-controlled	1961 adults with BMI ≥30 (or ≥27 with ≥1 weight-related comorbidity), without diabetes. Mean age ~46 yrs. International multicenter. 2:1 randomization	Once-weekly subcutaneous semaglutide and lifestyle intervention vs placebo and lifestyle intervention for 68 weeks	Primary: % change in body weight; ≥5% weight loss. Secondary: ≥10% and ≥15% weight loss, physical functioning, adverse effects	Semaglutide produced significantly greater weight loss than placebo (−14.9% vs −2.4%).
doi:10.1001/jama.2021.1831	RCT, randomized, double-blind, parallel-group, phase 3a RCT	611 adults w/o diabetes with BMI ≥30 or ≥27 with ≥1 comorbidity; mean age 46 yrs; 81% women	Weekly subcutaneous semaglutide 2.4 mg and intensive behavioral therapy and initial low-calorie diet vs placebo and same behavioral therapy/diet for 68 weeks	Co-primary: % change in body weight; ≥5% weight loss. Secondary: ≥10% and ≥15% weight loss; adverse events	Semaglutide led to greater weight loss than placebo (−16.0% vs −5.7%; P<.001), with more patients achieving ≥5%, ≥10%, and ≥15% loss. GI side effects were more common, with 3.4% discontinuing due to GI events.
doi:10.1056/NEJMoa1411892	RCT, randomized, double-blind	Adults with BMI ≥30 kg/m² or ≥27 kg/m² with ≥1 comorbidity (e.g., prediabetes, hypertension, dyslipidemia); ~3,731 participants randomized in SCALE Obesity and Prediabetes trial	Once-daily subcutaneous liraglutide 3.0 mg + diet and exercise vs placebo + diet and exercise for ~56 weeks	% change in body weight; proportions achieving ≥5% and >10% weight loss; adverse events	Liraglutide produced significantly greater weight loss than placebo (mean 8.4 kg > 2.8 kg; difference ~−5.6 kg; P < 0.001). More liraglutide participants lost ≥5% (63.2% vs 27.1%) of baseline weight. Mild–moderate nausea/diarrhea were common adverse events.

Conclusion

GLP-1 receptor agonists produce significantly greater clinically meaningful weight loss compared with lifestyle therapy alone. ≥5% weight loss was consistently achieved at higher rates with GLP-1 therapy. The few side effects were primarily gastrointestinal. [3-5]

Limitations:
Cost and insurance barriers because one thing patients encounter is insurance approval of these drugs.
Medication shortages is another one because of the increase of demand for these weight loss drugs.

GLP-1 therapy appears appropriate for adults with obesity who fail lifestyle therapy, but access, affordability, and long-term sustainability remain important considerations. Future studies should evaluate longitudinal outcomes, effects, and strategies to improve equitable access to treatment.

References

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