



# Mission Slimpossible Part 2: Oral GLP-1 agonists for weight loss

## CLINICAL QUESTION

**Are oral GLP-1 agonists effective for weight loss?**

## BOTTOM LINE

**In adults with obesity, oral semaglutide in a new high-dose formulation (50mg daily; not available in Canada) can result in ~15% body weight loss at 68 weeks (versus 2% placebo), with 69% of people losing at least 10% of their body weight (versus 12% placebo). Mean weight loss with the currently available 14mg formulation is ~5%.**

## EVIDENCE

- Results statistically different unless indicated.
- One industry-funded randomized, controlled trial (RCT)<sup>1</sup> on weight loss:
  - 667 adults with obesity and no diabetes (105 kg, BMI=38), given semaglutide 50mg (modified formulation) orally or placebo for 68 weeks, plus lifestyle intervention. At 68 weeks:
    - Mean weight loss: 15% (16kg) versus 2% (2.5kg) placebo.
    - Proportion of patients with >10% weight loss: 69% versus 12% placebo.
    - Withdrawals due to adverse events: 6% versus 4% placebo (statistics not provided):
      - Mainly gastrointestinal.

- Gallbladder disorders (mainly cholelithiasis) 4% versus 1% placebo (no statistics).
  - “Altered skin sensation” (examples: paresthesia, sensitive skin): 13% versus 1% placebo (no statistics).
- Systematic reviews (3-11 RCTs, 1300-9890 patients) where weight loss was secondary outcome (up to 14mg semaglutide):
  - ~3kg more weight lost than placebo at 26-82 weeks.<sup>2-5</sup>
  - Gastrointestinal side effects 4-9% versus 1-2% placebo.<sup>3</sup>
- Industry-sponsored RCT (weight loss as secondary outcome) not in above reviews.<sup>6</sup> 1606 patients with diabetes (96kg, BMI=34), given semaglutide 14mg, 25mg, or 50mg. At 52 weeks:
  - Mean weight loss: 5.4% [4.4kg (14mg)], 6.6% [6.7kg (25mg)], 7.3% [8kg (50mg)]. No statistics 25 versus 50mg doses.
  - >10% weight loss: 14% (14mg), 29% (25mg), 37% (50mg), no statistics 25 versus 50mg.
  - Withdrawals due to adverse events: 10% (14mg), 12% (25mg), 13% (50mg). No statistics.

## CONTEXT

- Weight loss is dose dependent, with efficacy similar between semaglutide 50mg oral daily and 2.4mg subcutaneous weekly.<sup>6,7</sup>
- Oral semaglutide used in RCTs (i.e., 50 mg) is a different formulation than the one currently available (i.e., 3-14mg) (altered to improve bioavailability).<sup>1</sup>
  - Low-dose oral semaglutide (14mg) daily costs~\$250/month; not covered by most insurance plans. Cost of higher dose not yet known.
- Other oral GLP-1 agonists in development; may have similar benefits.<sup>8</sup>

## REFERENCES

1. Knop FK, Aroda VR, doVale RD, *et al.* Lancet. 2023; 402:705-19.
2. Li A, Su X, Hu S, Wang Y. Diabetes Res Clin Pract. 2023 Apr; 198:110605.
3. Li J, He K, Ge J, *et al.* Diabetes Res Clin Prac. 2021 Feb; 172:108656.
4. Avgerinos I, Michailidis T, Liakos A, *et al.* Diabetes Obes Metab. 2020 Mar; 22(3):335-45.
5. Vosoughi K, Atieh J, Khanna L, *et al.* EClinicalMedicine. 2021; 42:101213.
6. Aroda VR, Aberle J, Bardtrum L, *et al.* Lancet. 2023; 402:693-704.
7. Ojeniran M, Dube B, Paige A, *et al.* Can Fam Physician. 2021; 67(11):842.
8. Wharton S, Blevins T, Connery L, *et al.* New Engl J Med. 2023; 389(10):877-88.

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*Authors do not have any conflicts of interest to declare.*

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