# Obesity Care: Focus on Pharmacotherapy

DALHOUSIE UNIVERSITY — FACULTY OF MEDICINE Academic Detailing Service | nova scotia health Drug Evaluation Unit

## Weight Loss Outcomes: Summary of Randomized Controlled Trials

| Clinical Trial Program RCTs | STEP-1 (N=1961, 68 weeks) | SCALE Obesity & Prediabetes (N=3731, 56 weeks) | COR-1 (N=1742, 56 weeks) | STEP-8 (N=338, 68 weeks) | | STEP-2 (N=1210, 68 weeks) | SCALE Diabetes (N=846, 56 weeks) | COR-DM (N=505, 56 weeks) |
|---|---|---|---|---|---|---|---|---|
| **Treatment** | **Semaglutide 2.4 mg SC once weekly** | **Liraglutide 3.0 mg SC once daily** | **Naltrexone/Bupropion 16 mg/180 mg orally twice daily** | **Semaglutide 2.4 mg SC once weekly** | **Liraglutide 3.0 mg SC once daily** | **Semaglutide 2.4 mg SC once weekly** | **Liraglutide 3.0 mg SC once daily** | **Naltrexone/Bupropion 16 mg/180 mg orally twice daily** |
| | | | | Direct comparison | | | | |
| **Patient population** | Adults with a BMI ≥ 30 kg/m² or a BMI ≥ 27 kg/m² with weight-related co-morbidities, and who did ***not have diabetes*** | | | | | Adults living with a BMI ≥ 27 kg/m² ***and T2DM*** | | |
| **Mean % change in body weight** co-primary outcome | ↓15%<br>↓2% placebo | ↓8%<br>↓3% placebo | ↓6%<br>↓1% placebo | ↓15.8% | ↓6.4% | ↓10%<br>↓3% placebo | ↓6%<br>↓2% placebo | ↓5%<br>↓2% placebo |
| **Loss of ≥ 5 % body weight*** co-primary outcome | 86%<br>32% placebo<br>NNT = 2 (2-3¥) | 63%<br>27% placebo<br>NNT = 3 (3-4¥) | 48%<br>16% placebo<br>NNT = 4 (3-4¥) | Not reported | Not reported | 69%<br>29% placebo<br>NNT = 3 (3-4¥) | 54%<br>21% placebo<br>NNT = 4 (3-4¥) | 45%<br>19% placebo<br>NNT = 4 (3-6¥) |

*T2DM=Type 2 Diabetes Mellitus, SC=subcutaneously, BMI=body mass index, NNT=numbers needed to treat, ¥95 % Confidence Interval; *% = proportion of participants who experienced this outcome & -5% change in body weight generally represents a clinically meaningful weight loss. All co-primary outcome results were statistically significant. Only Health Canada approved dosing results included in this table.*

Baseline characteristics of participants enrolled in weight loss trials:

- Age ~ 45 years (~ 55 years diabetes trials)
- BMI ~ 36-38 kg/m²
- Body weight ~ 100 – 105 kg
- HbA1C ~ 8% (diabetes trials)

Participants were randomized to receive medication or placebo. In addition to medication, *all* participants received *lifestyle modification counseling* which generally included:

- ↓ calorie diet (e.g., 500 kcal deficit per day)
- ↑ physical activity (e.g., 150 minutes per week)

## Cardiovascular Outcomes: Summary of the SELECT Trial (n=17,604)

| | |
|---|---|
| **Patient Population** | Adults ≥ 45 years of age with BMI ≥ 27 kg/m² and *established CV disease without diabetes*. |
| **Intervention** | Semaglutide 2.4 mg SC once weekly (+ standard of care & lifestyle modification counseling) |
| **Comparison** | Placebo (+ standard of care & lifestyle modification counseling) |
| **Primary Outcome** | Major adverse cardiovascular events (MACE) = CV death, non-fatal MI, non-fatal stroke |
| **Results** | Semaglutide 2.4 mg once weekly reduced the absolute risk of experiencing a MACE over 40 months by 1.5% compared to placebo (+ standard of care); NNT 67 (95% CI; 44 to 136).<br>• HR 0.80 (95% CI; 0.72 to 0.90, P < 0.001)) |

**This document is not intended to be all-inclusive. Please refer to the Academic Detailing document "Obesity Care: Focus on Pharmacotherapy 2024": https://medicine.dal.ca/departments/core-units/cpd/programs/academic-detailing-service/AC-Service-Resources.html for more information and references.**

# Obesity Care: Focus on Pharmacotherapy

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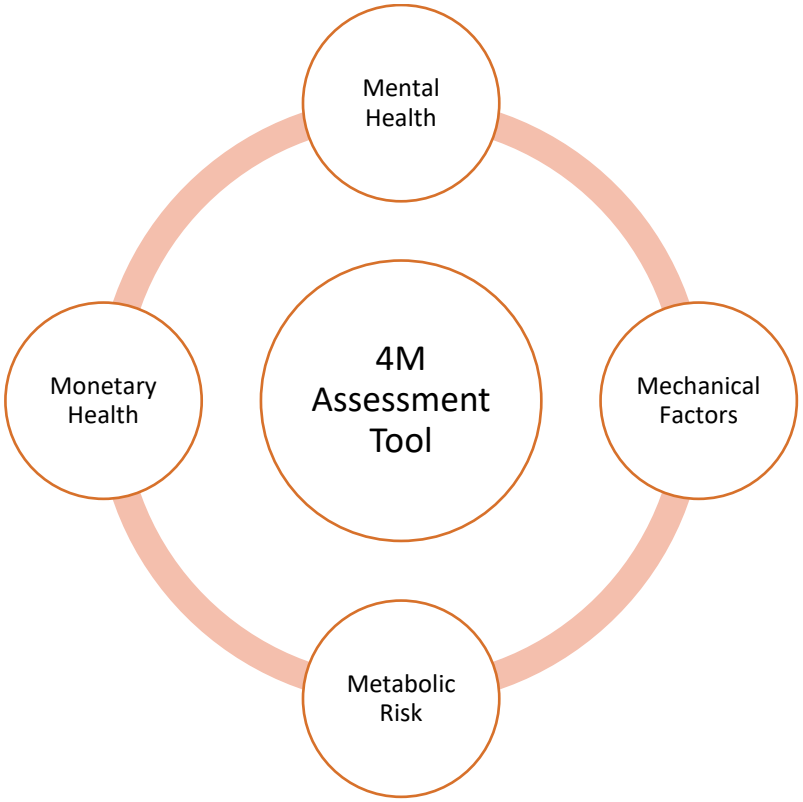
## Clinical Considerations

- Obesity Canada defines obesity as a chronic disease in which abnormal or excess body fat **impairs health**, increases the risk of long-term medical complications and reduces lifespan.
- Obesity care is about improving overall health and well-being.
- The 4M Framework helps explore the contributors to and complications of obesity. This tool encourages clinicians to consider mental, metabolic, and physical factors associated with obesity and impact on overall health.




**Semaglutide** injection[Wegovy], **liraglutide** injection[Saxenda], & **naltrexone/bupropion**[Contrave] have been evaluated in people living with obesity in multiple RCTs.

Most RCTs were designed to evaluate weight loss, a surrogate measure, as the primary outcome. <u>These RCTs have informed us that:</u>

- The amount of weight loss from these medications (in addition to lifestyle modification counseling) is variable amongst individuals.
- Most of the weight loss associated with these medications occurs in the first 8-12 months of therapy (onset ~ 4 weeks), and then body weight appears to plateau.
- Patients may not continue therapy long-term as a notable proportion of participants discontinued pharmacotherapy before the end of the trials.
- In general, discontinuation of pharmacotherapy appears to result in weight regain.
- Further studies are required to confirm the long-term impact of pharmacotherapy in the management of people living with obesity (i.e., > 2-3 years).

<u>Potential Safety Considerations:</u>

- *Naltrexone/bupropion:* Use is associated with many drug interactions (e.g., opioids) and precautions (e.g., seizure risk). GI-related adverse effects are common.
- *GLP-1 receptor agonists (semaglutide & liraglutide):* Long term safety data specific to obesity care is limited.

| Confirmed | Probably Associated | Uncertain or Unknown Association |
|---|---|---|
| • Nausea<br>• Vomiting<br>• Diarrhea<br>• Constipation<br>• Gallbladder-related disorders | • AKI *(volume depletion from GI AEs may ↑ risk of AKI)*<br>• Hypoglycemia *(concomitant SU or insulin therapy may ↑ risk of hypoglycemia; consider dose adjustments)* | • Acute pancreatitis<br>• Alopecia<br>• Aspiration risk during anesthesia<br>• Breast cancer<br>• Diabetic retinopathy<br>• Gastroparesis<br>• Intestinal obstruction<br>• Nonarteritic anterior ischemic optic neuropathy<br>• Pancreatic cancer<br>• Suicidality and self-harm<br>• Thyroid cancer* |

AE = adverse event, AKI = acute kidney injury, GI = gastrointestinal, SU = sulfonylurea, T2DM = type 2 diabetes mellitus. *GLP-1 receptor agonist use is contraindicated in people with a personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2.

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