Obesity Care

Focus on Pharmacotherapy

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"Seek simplicity, and mistrust it."
Alfred North Whitehead

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ABBREVIATIONS

AE	Adverse event
AKI	Acute kidney injury
ARR	Absolute risk reduction
ARD	Absolute risk difference
BMI	Body mass index (kg/m^2)
CADTH	Canadian Agency for Drugs and Technologies in Health
CDA-AMC	Canada's Drug Agency
CI	Confidence interval
CLE	Cutaneous lupus erythematosus
CNODES	Canadian Network for Observational Drug Effect Studies
CPAP	Continuous positive airway pressure
CV	Cardiovascular
DM	Diabetes mellitus
DPP-4	Dipeptidyl peptidase-4 inhibitor
eGFR	Estimated glomerular filtration rate
EOSS	Edmonton obesity staging system
EMA	European Medicines Agency
GI	Gastrointestinal
GLP-1	Glucagon like peptide-1 (receptor agonist)
HbA1C	Glycated hemoglobin A1C
HFpEF	Heart failure with preserved ejection fraction
HR	Hazard Ratio
IBT	Intensive behavioural therapy
IOC	International Obesity Collaborative
IWQOL-Lite	Impact of Weight on Quality of Life - Lite
KCCQ-CSS	Kansas cardiomyopathy questionnaire clinical summary score
MEN2	Multiple Endocrine Neoplasia syndrome type 2
MTC	Medullary thyroid cancer
NAION	Nonarteritic Anterior Ischemic Optic Neuropathy
NNT	Number needed to treat
NMA	Network meta-analysis
OR	Odds ratio
OSA	Obstructive sleep apnea
PAD	Peripheral arterial disease
PCS	Physical component summary
MA	Meta-analysis
MACE	Major adverse cardiovascular event
MCS	Mental component summary
MD	Mean difference
MHO	Metabolically healthy obesity
MI	Myocardial infarction
MID	Minimally important difference
NICE	National Institute for Health Care and Excellence
NYHA	New York Heart Association
RCT	Randomized controlled trial
RR	Relative risk
SF-36	Short-form health survey
SGLT2	Sodium-glucose cotransporter-2 (inhibitor)
SLE	Systemic lupus erythematosus
SMBG	Self measured blood glucose
SR	Systematic review
SU	Sulfonylurea
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TZD	Thiazolidinedione
WC	Waist circumference
6MWT	Six-minute Walk test

INTRODUCTION

Obesity

Obesity is a complex relapsing chronic disease in which abnormal or excess body fat (adiposity) impairs health, increases the risk of long-term medical complications, and reduces lifespan.[1,2] Many factors can contribute to the development of obesity. Factors include genetics, sex, ethnicity, access to health care, medication use, chronic stress, socioeconomic status, regional food, and built environments (how we live and work).[3]

People living with obesity have an increased risk of developing serious medical conditions including heart disease, cancer, stroke, diabetes, liver disease, osteoarthritis, depression, and anxiety, among others. Obesity is also associated with impaired quality of life and function, and increased risk of mortality.[3]

What is the Prevalence of Obesity?

The prevalence of obesity in Canada is increasing.[3] In 2018, Statistics Canada published that about 1 in 4 Canadian adults reported height and weight classified as obese, and 1 in 3 as overweight. Across Canada, the Atlantic provinces have some of the highest reported proportions of adults classified as obese.[4]

What is Obesity Care?

According to the International Obesity Collaborative (IOC), "obesity care delivered by qualified clinicians consists of evidence-based options that address comorbidities of obesity (diabetes, hypertension, hyperlipidemia, etc.) and improve well-being. Obesity care is about health, not weight. Weight loss is just one outcome of obesity care."[2]

Interventions in Obesity Care

Interventions for obesity care include medical nutrition therapy, physical activity, psychological and behavioural interventions, pharmacotherapy, and surgery.[2,5]

This evidence review focuses on medications that are Health Canada approved for weight management:

- Semaglutide injection (Wegovy)[6]
- Liraglutide injection (Saxenda)[7]
- Naltrexone/bupropion (Contrave)[8]
- Orlistat (Xenical)[9]

[*Note: setmelanotide injection (Imcivree) is Health Canada approved for weight management in adult and pediatric patients 6 years of age and older, but only for specific types of obesity due to very rare genetic conditions. Therefore, setmelanotide is considered outside of the scope of this review.*[10]*]*

Person-First Language

This document will use person-first language to address individuals with chronic diseases (e.g., "people living with obesity"). Person-first language is recommended by Obesity Canada and other international obesity associations to avoid the perpetuation of weight stigma in research and health care.[11]

Health care providers are encouraged to reflect on their own attitudes and beliefs related to obesity, and to use language that respects individual patient preferences.

Scope of the Evidence Review

This evidence review will focus on pharmacotherapy for adults living with obesity.

The following are considered outside of the scope of this review:

- Obesity care in people living with type 1 diabetes mellitus (T1DM), children, adolescents, pre-conception planning, pregnancy, and postpartum
- Antipsychotic-associated weight gain
- Use of setmelanotide injection (*see note on page 5*)
- Management of binge eating disorder
- Surgical interventions and pharmacotherapy after surgical interventions for obesity care

In preparing this document, we reviewed:

- Original publications of randomized controlled trials (RCTs) and meta-analysis (MA)
- Observational studies for safety outcomes
- Reports from Canadian and international health technology assessment agencies, including Canada's Drug Agency (CDA-AMC) [previously known as the Canadian Agency for Drugs and Technologies in Health (CADTH)], and the National Institute for Health and Care Excellence (NICE)
- Canadian and American clinical practice guidelines
- Health Canada approved drug product monographs
- Review articles

KEY MESSAGES

- Obesity care consists of evidence-based options that address comorbidities of obesity (diabetes, hypertension, hyperlipidemia, etc.) and improve well-being. Obesity care is about health, not weight. Weight loss is just one outcome of obesity care.[2]
- Obesity is a chronic disease in which abnormal or excess body fat (adiposity) impairs health, increases the risk of long-term medical complications and reduces lifespan. Although BMI is a common and simple metric, it is not part of the definition of obesity as a chronic disease.[1]
- A universal classification system is lacking, however Canadian guidelines endorse the use of the Edmonton Obesity Staging System (EOSS) which provides a framework to assess the spectrum of health implications related to obesity.[1,12]
- Body mass index (BMI) and waist circumference (WC) may be used in clinical practice as screening tools and can help identify individuals in whom more detailed assessments may be warranted, however, both have limitations.[1]
- Semaglutide injection (Wegovy), liraglutide injection (Saxenda), naltrexone/bupropion (Contrave), and orlistat (Xenical) have Health Canada approved indications for weight management.[6–9]
    - In general, these medications are indicated as adjuncts to lifestyle modification (physical activity and/or reduced calorie diet) in adults with a BMI ≥ 30 kg/m^2, or BMI ≥ 27 kg/m^2 in the presence of at least one weight-related comorbidity or risk factor.[6–9] (see Appendix 1 for full Health Canada approved adult indications).
    - The products and doses of semaglutide and liraglutide that are approved in Canada for weight management are different than those approved for the management of T2DM.[6,7]
- Semaglutide injection, liraglutide injection, and naltrexone/bupropion have been evaluated in patients living with obesity in multiple RCTs.[19-31] These RCTs have informed us that:
    - The amount of weight loss (see page 17) from these medications (in combination with lifestyle modification counseling) is variable amongst individuals.[19,20,27-31]
        - Most RCTs evaluated weight loss, a surrogate measure, as the primary outcome.
    - There is an observed trend that less weight loss may occur in patients living with obesity and T2DM compared to those living with obesity without T2DM, although this is based on indirect comparisons (see page 25).[19,20,27-31]
    - A single study directly compared semaglutide to liraglutide for weight loss outcomes. The study found a greater reduction in body weight with semaglutide compared to liraglutide, however, there are limitations to the study to consider (see page 22).[23]
    - Most of the weight loss associated with these medications occurs in the first 8-12 months of therapy, and then body weight appears to plateau (see page 25).[19,27,30]
    - A notable proportion of patients discontinued pharmacotherapy before the end of the trials, suggesting that some patients do not continue therapy long-term. [19,20,27–31]
    - For liraglutide and semaglutide, the most common adverse events (AEs) leading to discontinuation of therapy were gastrointestinal (GI) related (see page 38).[19,27]

- Longer follow up studies designed to evaluate the durability of weight loss are required to confirm if weight loss with pharmacotherapy is sustained > 2-3 years (see page 25).
- Generally, it is believed that discontinuation of pharmacotherapy for obesity care results in weight regain (see page 27).[15,33,34]
    - Several studies have observed that when semaglutide or liraglutide are discontinued, mean body weight increases.[21,32,35]
    - The effect of stopping naltrexone/bupropion on body weight has not been reported.

➢ MA of RCTs found that orlistat statistically significantly reduced body weight compared to placebo or lifestyle modification alone, but the difference was not clinically significant.[16,17]

➢ Semaglutide is the only Health Canada approved medication for obesity care that has been evaluated in a CV outcome trial for effects on major adverse cardiovascular events (MACE).[26]

- Use of semaglutide 2.4 mg subcutaneously once weekly lead to a statistically significant improvement in MACE compared to placebo [absolute risk reduction (ARR) semaglutide vs. placebo = **1.5%**] in *some* people with obesity (see Table 18, page 32).
    - Individuals ≥ 45 years of age with a BMI ≥ 27 kg/m^2 and a *history of established cardiovascular (CV) disease,* without diabetes were included in the CV outcome trial.
- These results would not be generalizable to individuals living with obesity who <u>do not have established CV disease.</u>

➢ Commonly reported adverse events (AE) with GLP-1 receptor agonists in people living with obesity are GI-related (nausea, diarrhea, vomiting, and constipation). Most GI AEs are mild-to-moderate in severity, transient, and did not result in discontinuation of therapy.[19,27]

➢ Long-term safety data on GLP-1 receptor agonist use specific to the obesity care population and dosing is limited.

- Table 23 (page 55) provides a list of select potential adverse events and whether the risk is confirmed, probably associated, or if the association is uncertain or unknown.

➢ Naltrexone/bupropion has many drug interactions and precautions to consider (see Appendix 1).

➢ Pharmacotherapy recommendations from the Canadian Adult Obesity Clinical Practice Guidelines and Health Canada approved indications for semaglutide, liraglutide, and naltrexone/bupropion are reflective of the inclusion criteria of the pivotal trials for each of these medications (see page 60).[6–8,15,19,27,30]

- In general, RCTs included adults with a BMI ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 with weight-related co-morbidities.[19,27,30]
- Guideline recommendations for initiating pharmacotherapy using a BMI cutoff alone (i.e., BMI ≥ 30 kg/m^2) could potentially include some individuals who do not have abnormal or excess body fat (adiposity) impairing health.[15]
- This is important to consider in practice, as the current understanding of obesity as a chronic disease requires more than the recognition of abnormal or excessive body fat, but whether abnormal or excessive body fat is impairing health.[1]

SCREENING AND ASSESSING OBESITY

Obesity as a Chronic Disease

- A universal classification system of obesity is lacking.[12]
- Obesity Canada defines the condition as a "chronic disease in which abnormal or excess body fat (adiposity) impairs health, increases the risk of long-term medical complications and reduces lifespan."[1]
    - This definition reflects the current understanding that the disease requires more than the recognition of **excessive** body fat or **abnormal** fat, but whether abnormal or excessive body fat is impairing health.[1] It also reflects the complexity of both the disease and the assessment of people living with obesity.[13]
- Although BMI is a common and simple metric, it is not part of the definition of obesity as a chronic disease. It is known that individuals with the same body weight or the same BMI may have markedly different comorbidities and levels of health risk. The concept of adiposopathy or "sick fat" may provide some explanation for the variability of clinical manifestations of obesity for individuals with similar BMIs.[14]
    - Principles of adiposopathy [14]
        - Deposition of fat stores in body locations where fat is not physiologically stored such as liver, pancreas, heart, and skeletal muscle, and a shift to visceral adipose distribution (fat storage in the intra- and retroperitoneal space)
        - Inflammatory and adipokine dysregulation
        - Insulin resistance
    - It has been hypothesized that "the presence or absence of adiposopathy may therefore help explain the heterogeneity of obesity and its manifestations because the pathogenic potential of excess body fat is conditioned on adipose tissue dysfunction/ectopic fat deposition rather than simply on increased fat mass alone." [14]

Screening

- Before initiating screening or assessment for obesity, it is important to ask for the patient's permission to discuss the topic.[1]
- Calculated BMI (in kg/m^2) and measured WC (in centimeters) are the most common anthropometric parameters.[1]
- BMI and WC may be used in clinical practice as screening tools and can help identify individuals in whom more detailed assessments may be warranted, however, both have limitations.[1]
- Limitations of BMI [1]
    - Not a direct measure of body fat, cardiovascular (CV) risk, or health
    - Does not differentiate between central and peripheral fat deposits
    - Does not account for muscle mass and can over or underestimate body fat
    - Does not account for the effect of cardiorespiratory fitness

- Does not distinguish between men and women
- Less accurate in certain populations such as elderly, people with severe obesity, people with physical disability, and in patients with severe edema
- Over and underestimates body fat in certain ethnic groups such as Indigenous Peoples, South Asians, Chinese, and other populations

➢ Limitations of WC [1]

- WC is not a direct measure of visceral fat and is a less sensitive measure of visceral fat with increasing BMI
- There can be inter- and intra-reader variability in the measurement of WC
- WC is sensitive to abdominal distention due to food or fluid intake
- Varying cut-offs for ethnic populations
- Can be perceived as an intrusive measurement by some

➢ Utilization of BMI and WC together may identify the higher risk phenotype of obesity better than either indicator alone, especially in those with lower BMI.[1]

➢ Epidemiologic studies have shown that Asian populations have increased adiposity and cardiometabolic risk at lower BMI, and as such, alternate BMI ranges have been proposed for this patient population.[1]

Table 1. Classification of BMI [1]

Caucasian, Europid, and North American ethnicity		**South-, Southeast, or East Asian ethnicity**	
Category	BMI (kg/m^2)	Category	BMI (kg/m^2)
Underweight	< 18.5	Underweight	< 18.5
Normal	18.5-24.9	Normal	18.5-22.9
Overweight	25-29.9	Overweight – At risk	23-24.9
Obesity Class 1	30-34.9	Overweight – Moderate risk	25-29.9
Obesity Class 2	35-39.9	Overweight – Severe risk	> 30
Obesity Class 3	40-49.9		
Obesity Class 4	50-59.9		
Obesity Class 5	> 60		

BMI = body mass index

➢ There are variable WC ranges to define increased abdominal adiposity based on gender and ethnicity.[1] Obesity Canada provides the following proposed ranges: https://obesitycanada.ca/wp-content/uploads/2021/05/6-Obesity-Assessment-v6-with-links.pdf

Assessing excess or abnormal adiposity on health

➢ For most populations, the presence of overweight (BMI > 25 kg/m^2 for Caucasian, Europid and North American ethnicity, or BMI > 23 kg/m^2 for South-, Southwest-, or East Asian ethnicity) warrants further evaluation to identify cardiometabolic and other obesity-related complications.[1]

➢ A clinical tool which may help guide the assessment of contributors to and complications of obesity is the 4M framework. The **4M** mnemonic encourages clinicians to consider **mental health**, **mechanical factors, metabolic risk** and **monetary health**/environmental factors in the assessment of individuals with obesity.[1]

- Some examples of health factors to consider in each category: [1]
    - Mental health: mood, anxiety, addiction, sleep, self-image
    - Mechanical: osteoarthritis, gout, obstructive sleep apnea (OSA), gastroesophageal reflux disease, urinary incontinence, intertrigo
    - Metabolic: type 2 diabetes mellitus (T2DM), hyperlipidemia, nutritional deficiencies, gout, hypertension, polycystic ovarian syndrome/hypogonadism, infertility, fatty liver, gallstones, CV disease, higher risk of certain cancers
    - Monetary/"milieu": socioeconomic status, access to food, occupation, disability, clothing, access to pharmacotherapy

- Elements of the 4M framework are incorporated into the Edmonton Obesity Staging System (EOSS). The EOSS is another clinical tool to assess the impact of obesity on health and to stratify the severity of the disease, and is endorsed by Canadian guidelines.[1] The EOSS also underscores the importance of examining the multiple domains in which abnormal or excess adiposity may impair health, as it is a measure of physical, mental, and functional health.[5] The EOSS is available here: https://www.cmaj.ca/content/cmaj/suppl/2020/07/27/192.31.E875.DC2/191707-guide-1-at.pdf
- A comprehensive review of obesity assessment and management is beyond the scope of this review. However, when considering interventions for obesity care, it may also be appropriate to evaluate concomitant medications which can be associated with weight gain. There are variabilities in reported weight gain attributed to certain pharmacologic agents. A reference guide can be found here: https://obesitycanada.ca/wp-content/uploads/2021/05/6-Obesity-Assessment-v6-with-links.pdf

PHARMACOTHERAPY

What medications have a Health Canada approved indication related to obesity care?

- Semaglutide injection (Wegovy), liraglutide injection (Saxenda), naltrexone/bupropion (Contrave), and orlistat (Xenical) have Health Canada approved indications for weight management.[6–9]
- In general, these medications are indicated as adjuncts to lifestyle modification (physical activity and/or reduced calorie diet) in adults with a BMI ≥ 30 kg/m^2, or BMI ≥ 27 kg/m^2 in the presence of at least one weight-related comorbidity or risk factor (e.g., hypertension, T2DM, or dyslipidemia). [6–9] (see Appendix 1 for full Health Canada approved adult indications).

Important Note*:* The products and doses of semaglutide and liraglutide that are approved in Canada for weight management **are different** than those approved for the management of T2DM.[6,7]

- Other medications are currently being evaluated for use in obesity care. For more information on some of these medications see the "Pharmacotherapy in the Pipeline" section on page 62.
- See note regarding setmelanotide injection (Imcivree) on page 5.

What are the proposed mechanisms of action of medications in obesity care?

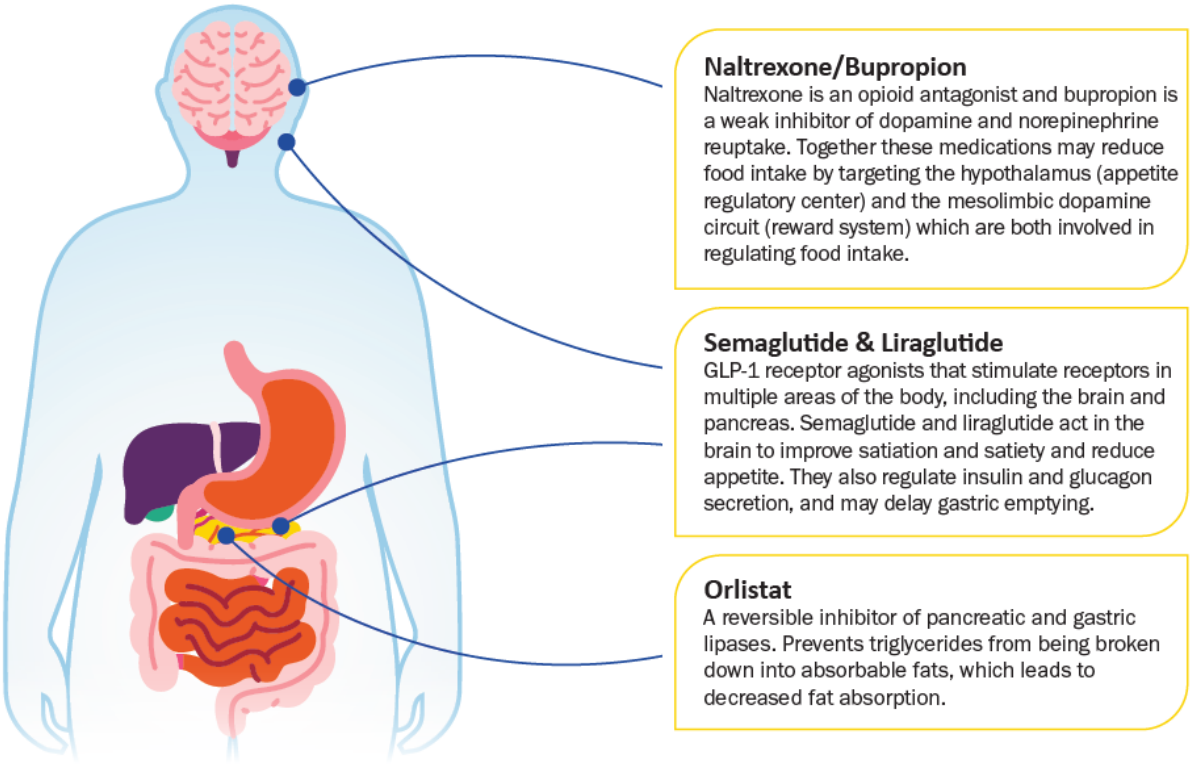

Figure 1: Proposed Mechanisms of Action of Medications in Obesity Care [6–9,15]
Graphic design credit to: Communications, Marketing & Creative Services, Dalhousie University at https://www.dal.ca/dept/cmc.html

How effective is pharmacotherapy for obesity care?

- Semaglutide injection, liraglutide injection, naltrexone/bupropion, and orlistat have all been studied in multiple RCTs in people living with obesity.[16,17]

> The primary outcomes of most obesity pharmacotherapy trials are weight loss outcomes. Weight loss is usually reported in trials as a percentage change in body weight. It is generally accepted that a change in weight of -5% represents a clinically meaningful weight loss.[17,18]

- **Orlistat will not be a focus of this section of the evidence review**.
    - Two recent network meta-analyses (NMA) of RCTs found that orlistat **statistically significantly** reduced body weight compared to placebo or lifestyle modification alone. However, the difference in weight loss between orlistat and placebo was **not clinically significant** [mean difference (MD) of weight loss < 5%].[16,17] Orlistat was considered "no better than lifestyle modification alone".[17]
        - Orlistat + lifestyle modification vs. placebo + lifestyle modification[16]
            - % body weight change at 12 months, MD = -2.34% [95% confidence interval (CI), -3.24 to -1.44][16]

Clinical Trial Programs

Semaglutide injection, liraglutide injection, and naltrexone/bupropion have been evaluated in patients living with obesity in manufacturer-sponsored, multi-study, clinical trial programs.

Clinical Trial Program Names:

Semaglutide injection = STEP **Liraglutide injection = SCALE** **Naltrexone/bupropion = COR**

These programs have multiple RCTs that evaluate different clinical questions. The RCTs described in Table 2 evaluated adults living with obesity or overweight and will be the focus of this section of the evidence review.

Table 2. Brief Description of Select Clinical Trial Program RCTs[#]

Study (N)	Comparator^	Patient Population Enrolled *(see pages 14-23 and 32-37 for more details)*	Type of Primary Outcomes	Treatment Duration
Clinical Trial Program: STEP	**Intervention: semaglutide^, target maintenance dose 2.4 mg subcutaneously once weekly**			
STEP 1[19] (N = 1961)	Placebo	Adults (≥ 18 years) with BMI ≥ 30 or BMI ≥ 27 with weight-related comorbidities*, but not DM.	Weight loss	68 weeks
STEP 2[20] (N = 1210)		Adults (≥ 18 years) with BMI ≥ 27 and T2DM, for which they could be receiving oral antihyperglycemic agents.		68 weeks
STEP 4[21] (N = 803)		Adults (≥ 18 years) with BMI ≥ 30 or BMI ≥ 27 with weight-related comorbidities*, but not DM. *Note: Evaluated the effect of continuing versus stopping therapy on weight loss maintenance.*		48 weeks
STEP 5[22] (N = 304)		Adults (≥ 18 years) with BMI ≥ 30 or BMI ≥ 27 with weight-related comorbidities*, but not DM. *Note: Evaluated two-year therapy effects.*		2 years
STEP 8[23] (N = 338)	Liraglutide	Adults (≥ 18 years) with BMI ≥ 30 or BMI ≥ 27 with weight-related comorbidities*, but not DM.		68 weeks
STEP-HFpEF[24] (N = 529)	Placebo	Adults (≥ 18 years) with BMI ≥ 30 and HFpEF, without DM.	KCCQ-CSS & weight loss	52 weeks
STEP-HFpEF DM[25] (N = 616)		Adults (≥ 18 years) with BMI ≥ 30, HFpEF, and T2DM.		52 weeks
SELECT[26] (N = 17,604)		Older adults (≥ 45 years) with BMI ≥ 27 and established CV disease, without DM.	MACE	~34 months
Clinical Trial Program: SCALE	**Intervention: liraglutide^, target maintenance dose 3.0 mg subcutaneously once daily**			
SCALE Obesity & Prediabetes[27] (N = 3731)	Placebo	Adults (≥ 18 years) with BMI ≥ 30 or BMI ≥ 27 with dyslipidemia or hypertension, but not DM.	Weight loss	56 weeks
SCALE Diabetes[28] (N = 846)		Adults (≥ 18 years) with BMI ≥ 27 and T2DM, for which they could be receiving oral antihyperglycemic agents.		56 weeks
SCALE Insulin (N = 396)[29]		Adults (≥ 18 years) with BMI ≥ 27 and T2DM managed with basal insulin.		56 weeks
Clinical Trial Program: COR	**Intervention: naltrexone/bupropion^, target maintenance dose 16 mg/180 mg orally BID**			
COR-I[30] (N = 1742)	Placebo	Adults (18 - 65 years) with BMI 30 - 45 or BMI 27 - 45 and controlled hypertension and/or dyslipidemia, but not DM.	Weight loss	56 weeks
COR-DM[31] (N = 505)		Adults (18 - 70 years) with BMI 27 to 45 and T2DM, for which they could be receiving oral antihyperglycemic agents.		56 weeks

BID = twice daily, BMI = body mass index (units are kg/m^2), CV = cardiovascular, DM = diabetes mellitus, HFpEF = heart failure with preserved ejection fraction, KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire clinical summary score, MACE = major adverse cardiovascular events, N = number of participants enrolled, RCT = randomized controlled trial, T2DM = type 2 DM.
[#] There are other RCTs in the STEP, SCALE, and COR clinical trial programs, but they are outside of the scope of this review.
*Hypertension, dyslipidemia, obstructive sleep apnea, or CV disease. ^In addition to lifestyle modification counseling.

How much weight loss would be expected with pharmacotherapy in people living with obesity, but without diabetes?

- **STEP-1**, **SCALE Obesity and Prediabetes**, and **COR-I** were multicenter, double-blinded, placebo-controlled RCTs designed to evaluate weight loss outcomes in adults with a BMI ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 with weight-related co-morbidities, and who did not have diabetes.[19,27,30]
- The **STEP-1** trial enrolled 1,961 adults with a BMI ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 with weight-related co-morbidities (i.e., hypertension, dyslipidemia, obstructive sleep apnea (OSA), or CV disease), who did not have diabetes, and who had at least one unsuccessful dietary effort to lose weight.[19]
    - Participants were randomized to receive either semaglutide 2.4 mg (dose titrated over 16 weeks) or placebo subcutaneously once a week for 68 weeks.[19]
- The **SCALE Obesity and Prediabetes** trial enrolled 3,731 adults with a BMI ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 with dyslipidemia or hypertension, and who did not have diabetes.[27]
    - Participants were randomized to receive either liraglutide 3.0 mg (dose titrated over 4 weeks) or placebo subcutaneously once daily for 56 weeks.[27]
- The **COR-1** trial enrolled 1,742 adults aged 18 to 65 years with a BMI of 30 to 45 kg/m^2 and uncomplicated obesity or a BMI of 27 to 45 kg/m^2 and controlled hypertension and/or dyslipidemia, who did not have diabetes.[30]
    - Participants were randomized to one of three groups for 56 weeks of treatment (doses titrated over 3 weeks):[30]
        - oral sustained-release naltrexone/bupropion 16 mg/180 mg BID, or
        - oral sustained-release naltrexone/bupropion 8 mg/180 mg BID, or
        - oral placebo
    - This review will focus on the results of the sustained-release naltrexone/bupropion 16 mg/180 mg BID vs. placebo results, as this is the Health Canada approved dosing for Contrave.[8,30]
- Overall *design* of the **STEP-1**, **SCALE Obesity and Prediabetes**, and **COR-1** RCTs were similar.[19,27,30]
    - All participants of these three trials had *lifestyle modification counseling* to support a reduced-calorie diet (500 kcal deficit per day) and physical activity (150 minutes per week specified in the **STEP-1** and **SCALE Obesity and Prediabetes** trials).[19,27,30]
    - The primary outcomes evaluated weight loss.[19,27,30]
    - Many participants were excluded from **STEP-1** and **SCALE Obesity and Prediabetes**. Some of the key exclusion criteria included:[19,27]
        - Diabetes (T1DM or T2DM)
        - Use of medications that cause clinically significant weight gain/loss *(SCALE only)*
        - Uncontrolled thyroid disease

- Obesity induced by other endocrinologic disorders (e.g., Cushing's syndrome) *(SCALE only)*
- History of pancreatitis *(SCALE)* or history of acute pancreatitis within 180 days or history of chronic pancreatitis *(STEP)*
- History of major depressive disorder within 2 years or history of other severe psychiatric disorder or history of suicide attempt
- A personal or family history of multiple endocrine neoplasia type 2 (MEN2) or medullary thyroid carcinoma (MTC)
- Uncontrolled hypertension *(SCALE only)*
- New York Heart Association Class IV *(STEP only)*
- Individuals of child-bearing potential who are pregnant, breastfeeding or intend to become pregnant or are not using adequate contraceptive methods.

- Some of the key exclusion criteria for the **COR-1** trial were:[30]
  - Diabetes (T1DM or T2DM)
  - Obesity of known endocrine origin (e.g., untreated hypothyroidism, Cushing's syndrome, established Polycystic Ovary Syndrome[31])
  - Cerebrovascular, CV, hepatic, or renal disease
  - History of seizures
  - History of serious psychiatric illness
  - History of drug or alcohol misuse in the previous 12 months
  - Pregnant or breastfeeding individuals

➢ *Participants* enrolled in **STEP-1**, **SCALE Obesity and Prediabetes**, and **COR-1** were similar.[19,27,30]

- Mean age ~45 years [19,27,30]
- Predominately white and female [19,27,30]
- Baseline mean body weight ~100-105 kg [19,27,30]
- Baseline mean BMI 36-38 kg/m^2 [19,27,30]
  - **STEP-1** and **SCALE Obesity and Prediabetes:** Most had a BMI ≥ 30 kg/m^2. Only 3-6% of participants had BMIs between 27 and < 30 kg/m^2. [19,27]
- About a third of participants of **STEP-1** and **SCALE Obesity and Prediabetes** reported a history of dyslipidemia and/or hypertension at baseline.[19,27] Only 2.5% of participants in **STEP-1** had a history of coronary artery disease.[19]

- *Results: Weight loss*

Table 3. Weight loss results of STEP-1[19]

Outcomes	Semaglutide 2.4 mg weekly (n = 1306)	Placebo (n = 655)	Absolute Difference or Odds Ratios (OR) Semaglutide vs. Placebo (95% CI)	P value	NNT* (95% CI)
	68 weeks				
Coprimary outcomes					
Mean % change in body weight	-14.85%	-2.41%	-12.44% (-13.37 to -11.51)	<0.001	
Loss of ≥ 5% body weight (% of participants)	86.4%	31.5%	OR = 11.2 (8.9 to 14.2)	<0.001	2 (2-3)
Select secondary outcomes					
Loss of ≥ 10% body weight (% of participants)	69.1%	12.0%	OR = 14.7 (11.1 to 19.4)	<0.001	
Loss of ≥ 15% body weight (% of participants)	50.5%	4.9%	OR = 19.3 (12.9 to 28.8)	<0.001	
Mean change in waist circumference	-13.54 cm	-4.13 cm	-9.42 cm (-10.30 to -8.53)	<0.001	
Mean kg change in body weight#	-15.3 kg	-2.6 kg	-12.7 kg (-13.7 to -11.7)	NA	

CI = confidence interval, n = sample size, NA = not available, NNT = number needed to treat, OR = odds ratio. # p values were not reported for this outcome as results were not adjusted for multiplicity, therefore, interpret the results of this outcome with caution. *NNTs were calculated for primary outcomes using ORs at https://www.nntonline.net/visualrx/.

Table 4. Weight loss results of SCALE Obesity and Prediabetes[27]

Outcomes	Liraglutide 3.0 mg daily (n = 2437)	Placebo (n = 1225)	Absolute Difference or Odds Ratios (OR) Liraglutide vs. Placebo (95% CI)	P value	NNT* (95% CI)
	56 weeks				
Coprimary outcomes					
Mean change in body weight					
% of body weight	-8.0%	-2.6%	-5.4% (-5.8 to -5.0)	<0.001	
Kg of body weight	-8.4 kg	-2.8 kg	-5.6 kg (-6.0 to -5.1)	<0.001	
Loss of ≥ 5% body weight (% of participants)	63.2%	27.1%	OR = 4.8 (4.1 to 5.6)	<0.001	3 (3-4)
Loss of ≥ 10% body weight (% of participants)	33.1%	10.6%	OR = 4.3 (3.5 to 5.3)	<0.001	5 (4-6)
Select secondary outcomes					
Loss of ≥ 15% body weight# (% of participants)	14.4%	3.5%	OR = 4.9 (3.5 to 6.7)	<0.001	
Mean change in waist circumference	-8.2 cm	-3.9 cm	−4.2 cm (-4.7 to -3.7)	<0.001	
Mean change in BMI	-3.0 kg/m^2	-1.0 kg/m^2	−2.0 kg/m^2 (-2.2 to -1.9)	<0.001	

BMI = body mass index, CI = confidence interval, n = sample size, NNT = number needed to treat, OR = odds ratio. # This outcome was evaluated post hoc, therefore interpret the results of this outcome with caution. *NNTs were calculated for primary outcomes using ORs at https://www.nntonline.net/visualrx/.

Table 5. Weight loss results of COR-1[30]

Outcomes	Naltrexone/ bupropion 16 mg/180 mg BID (n = 471)	Placebo (n = 511)	Absolute Difference Naltrexone/Bupropion vs. Placebo	P value	NNT* (95% CI)
	56 weeks				
Coprimary outcomes					
Mean % change in body weight	-6.1%	-1.3%	-4.8%	<0.0001	
Loss of ≥ 5% body weight (% of participants)	48%	16%	32%	<0.0001	4 (3-4)
Select secondary outcomes					
Loss of ≥ 10% body weight (% of participants)	25%	7%	18%	<0.0001	
Loss of ≥ 15% body weight (% of participants)	12%	2%	10%	<0.0001	
Mean kg change in body weight	-6.1 kg	-1.4 kg	-4.7 kg	<0.0001	
Mean change in waist circumference	-6.2 cm	-2.5 cm	-3.7 cm	<0.0001	

BID = twice daily, CI = confidence interval, n = sample size, NNT = number needed to treat. *NNTs were calculated for primary outcomes at https://www.graphpad.com/quickcalcs/NNT1/.

Academic Detailing Comment: Individual response to pharmacotherapy is heterogeneous.

- The mean % change in body weight represents the average weight loss across the study population.
- Within the study populations, individual participant body weight loss was variable.[19,27,30]
    - Not all participants experienced the coprimary outcome of ≥ 5% body weight loss.[19,27,30]
    - There was a trend across the **STEP-1**, **SCALE Obesity and Prediabetes**, and **COR-1** trials that fewer participants experienced the higher % body weight loss outcomes compared to the lower % body weight loss outcomes.[19,27,30]
        - For example, in **STEP-1**, 86% of participants in the semaglutide group experienced ≥ 5% body weight loss after 68 weeks of treatment (coprimary outcome), whereas 50% of participants experienced ≥ 15% body weight loss (secondary outcome).[19]

- In each of these three trials, a notable proportion of patients discontinued therapy before the end of the trial. Discontinuation rates were similar across medication and placebo groups.[19,27,30]
    - **STEP-1**: ~20% of participants stopped therapy early.[19]
    - **SCALE Obesity and Prediabetes**: ~30% of participants stopped therapy early.[27]
    - **COR-1**: ~50% of participants stopped therapy early.[30]
        - In COR-1, discontinuation occurred early, generally in the first 4 months.[30]
    - For information regarding discontinuation due to adverse effects see page 38.

How much weight loss would be expected with pharmacotherapy in people living with obesity and type 2 diabetes mellitus (T2DM)?

- **STEP-2**, **SCALE Diabetes**, **SCALE Insulin** and **COR-DM** were multicenter, double-blinded, placebo-controlled RCTs designed to evaluate weight loss outcomes in adults living with T2DM and a BMI ≥ 27 kg/m^2.[20,28,29,31]
- The **STEP-HFpEF DM** trial also included patients with T2DM and is described in the CV outcomes section further along (see page 34).[25]
- The **STEP-2** trial enrolled 1,210 adults living with T2DM, a BMI ≥ 27 kg/m^2, and a history of at least one unsuccessful dietary effort to lose weight.[20]
    - Participants were randomized to receive semaglutide 2.4 mg (dose titrated over 16 weeks) or semaglutide 1 mg (titrated over 8 weeks) or placebo subcutaneously once a week for 68 weeks.[20]
    - This review will focus on the results of the semaglutide 2.4 mg vs. placebo results, as this was the primary analysis the study was designed to assess.
- The **SCALE Diabetes** trial enrolled 846 adults living with T2DM and a BMI ≥ 27 kg/m^2.[28]

- Participants were randomized to receive either liraglutide 3.0 mg (dose titrated over 4 weeks) or liraglutide 1.8 mg (dose titrated over 2 weeks) or placebo subcutaneously once daily for 56 weeks.[28]
- This review will focus on the results of the liraglutide 3.0 mg vs. placebo results.

➢ The smaller **SCALE Insulin** trial enrolled 396 adults living with T2DM and a BMI ≥ 27 kg/m^2.[29]

- Participants were randomized to receive liraglutide 3.0 mg (dose titrated over 4 weeks) or placebo subcutaneously once daily for 56 weeks.[29]

➢ The **COR-DM** trial enrolled 505 adults living with T2DM and a BMI ≥ 27 and ≤ 45 kg/m^2.[31]

- Participants were randomized to receive either sustained-release naltrexone/bupropion 16 mg/180 mg BID (titrated over 3 weeks) or placebo orally for 56 weeks.[31]

➢ At baseline, participants of the **STEP-2**, **SCALE Diabetes**, and **COR-DM** trials had to have an HbA1c of 7-10% and could be receiving oral antihyperglycemic agents *(no insulin)*.[20,28,31]

- **STEP-2** and **SCALE Diabetes** specified that eligible patients could be on up to 3 oral antihyperglycemic agents [metformin, thiazolidinedione (TZD), sulfonylurea (SU), or Sodium-Glucose Transport Protein 2 (SGLT2) inhibitors (*SGLT2 inhibitors were allowed in STEP-2 only*)]. [20,28]
- For participants of **STEP-2** and **SCALE Diabetes** on a SU at baseline, the SU dose was recommended to be reduced by 50% to mitigate risk of hypoglycemia.[20,28]

➢ Participants of **SCALE Insulin** had to have a baseline HbA1c of 6-10% and be receiving stable treatment with a *basal insulin*. Participants could also be taking up to 2 oral antihyperglycemic agents.[29]

- For individuals with an HbA1c ≤ 8% at baseline, it was recommended to reduce the dose of basal insulin by 15–20%. Insulin doses were then adjusted based on self-measured blood glucose (SMBG). Initiation of *bolus insulin was permitted after the first 5 weeks*, but only after optimization of the basal insulin dose.[29]
- For participants on a SU at baseline, the SU dose was recommended to be reduced by 50% to mitigate risk of hypoglycemia.[29]

➢ The overall *design* of **STEP-2**, **SCALE Diabetes**, **SCALE Insulin**, and **COR-DM** were similar.[20,28,29,31]

- Participants in all of these trials had *lifestyle modification counseling* to support a reduced-calorie diet (e.g., 500 kcal deficit per day) and physical activity (150 minutes per week specified in the **STEP-2** and **SCALE Diabetes** trials).[20,28,29,31]
    - In **SCALE Insulin**, an intensive behavioral therapy (IBT) program was provided to participants. IBT consisted of physical activity (moderate intensity activity for 250 min/week), a reduced calorie diet (1200 to 1800 kcal/day depending on body weight), and behavioral counseling (23 x 15-minute sessions over 56 weeks).[29]
- The primary outcomes assessed weight loss.[20,28,29,31]

- The exclusion criteria were similar to the **STEP-1, SCALE Obesity and Prediabetes,** and **COR-1** trials (see page 14-15), except that in **STEP-2**, **SCALE Diabetes**, **SCALE Insulin**, and **COR-DM,** patients with T2DM were included.[19,20,27–31] Some additional key exclusion criteria were:[20,28–30]
    - Insulin use (*except in SCALE Insulin*)
    - Uncontrolled and potentially unstable diabetic retinopathy or maculopathy *(STEP-2)* or known proliferative retinopathy or maculopathy requiring acute treatment *(SCALE Diabetes)*
    - Recurrent major hypoglycemia or hypoglycemic unawareness *(SCALE Diabetes and SCALE Insulin)*
    - Use of any medication (except the specified allowed antihyperglycemic agents) which could interfere with glucose levels (e.g. systemic corticosteroids) (*SCALE Diabetes*)
    - Severe microvascular or macrovascular complications of diabetes *(COR-DM)*

➢ *Participants* enrolled in **STEP-2**, **SCALE Diabetes**, **SCALE Insulin**, and **COR-DM** were similar.[20,28,29,31]

- Mean age ~55 years (~10 years older than those enrolled in the **STEP-1, SCALE Obesity and Prediabetes**, and **COR-1** trials). [19,20,27–31]
- Baseline mean HbA1c was 8% across the trials.[20,28,29,31]
- Predominately white; ~50% female. [20,28,29,31]
- Baseline mean body weight ~100-105 kg. [20,28,29,31]
- Baseline mean BMI 36-37 kg/m^2.[20,28,29,31]
    - **STEP-2** and **SCALE Diabetes:** Most had a BMI ≥ 30 kg/m^2. 12-17% of participants had BMIs < 30 kg/m^2.[20,28]
- Mean duration of T2DM:
    - **STEP-2** and **SCALE Diabetes:** 7-8 years [20,28]
    - **SCALE Insulin**: ~12 years.[29]
- ~70% of participants enrolled in **STEP-2** and **SCALE Diabetes** reported a history of dyslipidemia and/or hypertension at baseline.[20,28] In **STEP-2** 8% of participants had a history of coronary artery disease.[20]
- Baseline renal function:
    - **STEP-2:** Excluded participants with an eGFR < 30 mL/min/1.73m^2 or eGFR < 60 mL/min/1.73m^2 if on a SGLT2 inhibitor. Only 5% of participants had an eGFR of 30 to < 60 mL/min/1.73m^2 .[20]
    - **SCALE Diabetes, SCALE Insulin,** and **COR-DM:** Not reported. [28,29,31]
- Baseline antihyperglycemic agent use:[20,28,29,31]

- Use of different classes of antihyperglycemic agents was balanced across treatment groups in the trials.[20,28,29,31]
- Across the studies, most participants (~80-90%) were on metformin or another biguanide.[20,28,29,31] Use of other antihyperglycemics agents varied across studies:
  - **STEP-2** and **SCALE Diabetes**: ~25% of patients were on a SU, <10% were on a TZD, and in **STEP-2** ~25% of patients were on a SGLT2 inhibitor.[20,28]
  - **SCALE Insulin**: 100% of patients were on basal insulin, 35% were on a SU, ~20% were on an SGLT2 inhibitor, and only ~2% were on a TZD.[29]
  - **COR-DM**: ~50% of patients were on a SU, and ~30% were on a TZD.[31]

➢ *Results: Weight loss*

Table 6. Weight loss results of STEP-2[20]

Outcomes	Semaglutide 2.4 mg weekly (n = 404)	Placebo (n = 403)	Absolute Difference or Odds Ratios (OR) Semaglutide vs. Placebo (95% CI)	P value	NNT* (95% CI)
	68 weeks				
Coprimary outcomes					
Mean % change in body weight	-9.64%	-3.42%	-6.21% (-7.28 to -5.15)	<0.0001	
Loss of ≥ 5% body weight (% of participants)	68.8%	28.5%	OR = 4.88 (3.58 to 6.64)	<0.0001	3 (3-4)
Select secondary outcomes					
Loss of ≥ 10% body weight (% of participants)	45.6%	8.2%	OR = 7.41 (4.89 to 11.24)	<0.0001	
Loss of ≥ 15% body weight (% of participants)	25.8%	3.2%	OR = 7.65 (4.11 to 14.22)	<0.0001	
Mean change in waist circumference	-9.4 cm	-4.5 cm	-4.9 cm (-6.0 to -3.8)	<0.0001	
Mean kg change in body weight#	-9.7 kg	-3.5 kg	-6.1 kg (-7.2 to -5.0)	NA	

CI = confidence interval, n = sample size, NA = not available, NNT = number needed to treat, OR = odds ratio. # p values were not reported for this outcome as results were not adjusted for multiple comparisons, therefore, interpret the results of this outcome with caution. *NNTs were calculated for primary outcomes using ORs at https://www.nntonline.net/visualrx/.

Table 7. Weight loss results of SCALE Diabetes[28]

Outcomes	Liraglutide 3 mg daily (n = 412)	Placebo (n = 211)	Absolute Difference Liraglutide vs. Placebo (95% CI)	P value	NNT* (95% CI)
	56 weeks				
Coprimary outcomes					
Mean % change in body weight	-6.0%	-2.0%	-4.00% (-5.10 to -2.90)	<0.001	
Loss of ≥ 5% body weight (% of participants)	54.3%	21.4%	32.9% (24.6 to 41.2)	<0.001	4 (3-4)
Loss of ≥ 10% body weight (% of participants)	25.2%	6.7%	18.5% (12.7 to 24.4)	<0.001	6 (4-8)
Select secondary outcomes					
Mean change in waist circumference	-6.1 cm	-2.7 cm	-3.22 cm (-4.2 to -2.23)	<0.001	
Mean change in BMI	-2.2 kg/m^2	-0.8 kg/m^2	-1.50 kg/m^2 (-1.83 to -1.18)	<0.001	
Mean kg change in body weight#	-6.4 kg	-2.2 kg	N/A	N/A	

BMI = body mass index, CI = confidence interval, n = sample size, NA = not available, NNT = number needed to treat. # p values were not reported for this outcome, therefore, interpret the results of this outcome with caution. *NNTs were calculated for primary outcomes at https://www.graphpad.com/quickcalcs/NNT1/.

Table 8. Weight loss results of SCALE Insulin[29]

Outcomes	Liraglutide 3 mg daily (n = 198)	Placebo (n = 198)	Absolute Difference or Odds Ratios (OR) Liraglutide vs. Placebo (95% CI)	P value	NNT* (95% CI)
	56 weeks				
Coprimary outcomes					
Mean % change in body weight	-5.8%	-1.5%	-4.3% (-5.5 to -3.2)	<0.0001	
Loss of ≥ 5% body weight (% of participants)	51.8%	24.0%	OR = 3.4 (2.2 to 5.3)	<0.0001	4 (3-6)
Select secondary outcomes					
Loss of ≥ 10% body weight (% of participants)	22.8%	6.6%	OR = 4.2 (2.2 to 8.2)	<0.0001	
Mean change in waist circumference	-5.3 cm	-2.6 cm	-2.7 cm (-3.9 to -1.5)	<0.0001	

CI = confidence interval, n = sample size, NNT = number needed to treat, OR = odds ratio. *NNTs were calculated for primary outcomes using ORs at https://www.nntonline.net/visualrx/.

Table 9. Weight loss results of COR-DM[31]

Outcomes	Naltrexone/bupropion 16 mg/180 mg BID (n = 265)	Placebo (n = 159)	Absolute Difference	P value	NNT* (95% CI)
	56 weeks				
Coprimary outcomes					
Mean % change in body weight	-5.0%	-1.8%	-3.2%	<0.001	
Loss of ≥ 5% body weight (% of participants)	44.5%	18.9%	25.6%	<0.001	4 (3-6)
Select secondary outcomes					
Loss of ≥ 10% body weight (% of participants)	18.5%	5.7%	12.8%	<0.001	
Mean change in waist circumference	-5.0 cm	-2.9 cm	-2.1 cm	0.006	

BID = twice daily, CI = confidence interval, n = sample size, NNT = number needed to treat. *NNTs were calculated for primary outcomes at https://www.graphpad.com/quickcalcs/NNT1/.

- *Results: HbA1c*
  - Each of these trials evaluated change in HbA1c as a secondary outcome.

Table 10. Change in HbA1c in STEP-2, SCALE Diabetes, SCALE Insulin, and COR-DM [20,28,29,31]

Trial	Drug and Dose	Drug	Placebo	Absolute Difference (95% CI)	P value
		Change in HbA1c from baseline to 56 or 68 weeks			
STEP-2	Semaglutide 2.4 mg subcut once weekly	-1.6%	-0.4%	-1.2% (-1.4 to -1.0)	<0.0001
SCALE Diabetes	Liraglutide 3.0 mg subcut once daily	-1.3%	-0.3%	-0.93% (-1.08 to -0.78)	<0.001
SCALE Insulin		-1.1%	-0.6%	-0.5% (-0.8 to -0.3)	<0.0001
COR-DM	Naltrexone/bupropion 16 mg/180 mg po BID	-0.6%	-0.1%	-0.5%	<0.001

subcut = subcutaneously, po = orally, BID = twice daily, CI = confidence interval, HbA1c = hemoglobin A1c

- Across **STEP-2**, **SCALE Diabetes**, and **SCALE Insulin**, there was a *consistently observed trend* that some participants in the GLP-1 receptor agonist groups had a dose reduction or discontinuation of at least one concomitant antihyperglycemic agent over the duration of the trial. [20,28,29] For example:
  - The proportion of participants who had a dose reduction or discontinuation of at least one concomitant antihyperglycemic agent during the trial was:
    - **STEP-2**: semaglutide 2.4 mg group = 28.6% vs. placebo group = 7.1%[20]

- **SCALE Diabetes**: liraglutide 3.0 mg group = 13.1% vs. placebo group = 5.7%[28]

- **SCALE Insulin**: 24 participants who had completed the trial (21 in the liraglutide group and 3 in the placebo group) were no longer using insulin at the study end.[29]
- It is important to note that **STEP-2** and **SCALE Diabetes** participants had a baseline HbA1c between 7% and 10%, and in **SCALE Insulin** a baseline HbA1c between 6% and 10%.[20,28,29]
    - Therefore, the proportion of patients requiring discontinuation or dose adjustments of concomitant antihyperglycemic agents may be different in patients who have lower HbA1c at baseline.
- Based on these results, in patients living with diabetes and obesity who are initiating therapy with a GLP-1 receptor agonist as part of their obesity care, glycemic status should be monitored and antihyperglycemic agents adjusted as needed.

➢ In each of these trials, a notable proportion of patients discontinued therapy before the end of the trial.

- **STEP-2**: ~12% of participants stopped treatment early. Discontinuation rates were similar in the semaglutide and placebo groups.[20]
- **SCALE Diabetes**: ~25% of participants stopped liraglutide early (~35% stopped placebo early).[28]
- **SCALE Insulin**: ~20% of participants stopped treatment early. Discontinuation rates were similar in the liraglutide and placebo groups.[29]
- **COR-DM**: ~50% of participants stopped naltrexone/bupropion early (~40% stopped placebo early).[31]
- For information regarding discontinuation due to adverse effects see page 38.

Academic Detailing Comment: Saxenda (liraglutide) product monograph - Insulin warning

Although the SCALE Insulin trial was published in 2020, as of July 2024, the Health Canada approved Saxenda (liraglutide) product monograph states that "Saxenda and insulin should not be used together. Saxenda has not been studied in patients taking insulin".[7]

Is semaglutide more effective than liraglutide for weight loss outcomes?

➢ The **STEP-1** and **SCALE Obesity and Prediabetes** trials compared semaglutide and liraglutide respectively to placebo.[19,27] Although the patient populations enrolled in these two trials were similar, there are limitations to indirectly comparing the results. To determine if one drug is more effective than another, the two drugs should be directly compared in the same trial. This is what **STEP-8** was designed to do.[23]

➢ The **STEP-8** trial, a multicenter, open-label, RCT with 338 participants, directly compared the efficacy of semaglutide versus liraglutide in adults with a BMI ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 with weight-related co-morbidities, and who did not have diabetes.[23]

- Inclusion criteria, exclusion criteria, baseline characteristics of participants, and lifestyle modification counseling were similar to those of the **STEP-1** trial (see page 14).[19,23]
- Participants were randomized to one of four groups for 68 weeks of treatment:[23]
    - Semaglutide 2.4 mg (dose titrated over 16 weeks) subcutaneously once a week
    - Matched placebo subcutaneously once a week
    - Liraglutide 3.0 mg (dose titrated over 4 weeks) subcutaneously once daily
    - Matched placebo subcutaneously once daily
- *Note: A semaglutide 1.7 mg maintenance dose was permitted if participants could not tolerate the 2.4 mg dose. If participants did not tolerate the liraglutide 3.0 mg maintenance dose, treatment was discontinued.*[23]
    - The rationale provided for this decision was that this "ensured the liraglutide regimen was consistent with the approved prescribing information…".[23]
    - Most participants in the semaglutide group (~85%) were receiving the 2.4 mg dose at the end of the trial.[23]
- The primary outcome was the % change in body weight from baseline at week 68.[23]
- *Results: Weight loss*
    - The semaglutide group had a statistically significantly greater mean reduction in body weight compared to liraglutide.[23]
        - Mean % change in body weight: Absolute difference = -9.4% (95% CI, -12.0 to -6.8) [23]

Table 11. Weight loss results of STEP-8 [23]

Outcomes	Semaglutide 2.4 mg weekly (n = 126)	Liraglutide 3.0 mg daily (n = 127)	Absolute Difference or Odds Ratios (OR) Semaglutide vs. Liraglutide (95% CI)	P value
	68 weeks			
Primary outcome				
Mean % change in body weight	-15.8%	-6.4%	-9.4% (-12.0 to -6.8)	<0.001
Select secondary outcomes				
Loss of ≥ 10% body weight (% of participants)	70.9%	25.6%	OR = 6.3 (3.5 to 11.2)	<0.001
Loss of ≥ 15% body weight (% of participants)	55.6%	12.0%	OR = 7.9 (4.1 to 15.4)	<0.001
Loss of ≥ 20% body weight (% of participants)	38.5%	6.0%	OR = 8.2 (3.5 to 19.1)	<0.001

CI = confidence interval, n = sample size, OR = odds ratio.

- Discontinuation rates were notably higher in the liraglutide group compared to the semaglutide group (liraglutide = 27.6% versus semaglutide = 13.5%).[23]
    - This was likely due in part to the dose reduction allowed for semaglutide, but not for liraglutide.
    - Given the small sample size of the trial, this may have impacted the results and should be considered as a potential limitation to the study.

SUMMARY: Weight Loss Outcomes

- The **STEP-1**, **SCALE Obesity and Prediabetes**, and **COR-1** RCTs evaluated semaglutide, liraglutide, and naltrexone/bupropion, respectively, in adults with a BMI ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 with weight-related co-morbidities, and who did not have diabetes.[19,27,30] Similarly, the smaller **STEP-2**, **SCALE Diabetes**, **SCALE Insulin**, and **COR-DM** RCTs evaluated the same medications in adults living with a BMI ≥ 27 kg/m^2 and T2DM.[20,28,29,31]
  - Participants were randomized to receive drug or placebo, in addition to lifestyle modification counseling for ~ 1 year.
    - Lifestyle modification counseling usually included a reduced-calorie diet (e.g., 500 kcal deficit/day) and increased physical exercise (e.g., 150 minutes/week). [19,20,27–31]
  - The primary outcomes evaluated were weight loss outcomes. [19,20,27–31]
  - Participants of **STEP-2**, **SCALE Diabetes**, and **COR-DM** had to have a baseline HbA1c of 7-10%, and could be receiving oral antihyperglycemic agents (no insulin).[20,28,31] Participants of **SCALE Insulin** had to have a baseline HbA1c of 6-10% and be receiving basal insulin, and could also be taking up to 2 oral antihyperglycemic agents.[29]
    - Participants of **STEP-2**, **SCALE Diabetes**, and **SCALE Insulin** on SU at baseline: SU dose was recommended to be ↓ by 50% to mitigate risk of hypoglycemia. [20,28,29]
    - Participants of **SCALE Insulin** with an HbA1c ≤ 8% at baseline: It was recommended to ↓ dose of basal insulin by 15 to 20%. Insulin doses were then adjusted based on SMBG.[29]
  - Many individuals were excluded from the trials (see pages 19). [19,20,27–31]
  - Baseline patient characteristics:
    - Mean age:
      - ~45 years (**STEP-1**, **SCALE Obesity and Prediabetes**, **COR-1**)[19,27,30]
      - ~55 years (**STEP-2**, **SCALE Diabetes**, **SCALE Insulin**, **COR-DM**)[20,28,29,31]
    - Mean body weight ~100-105 kg [19,20,27–31]
    - Mean BMI 36 to 38 kg/m^2 [19,20,27–31]
      - **STEP-1, STEP-2, SCALE Obesity and Prediabetes, and SCALE Diabetes:** most had a BMI ≥ 30 kg/m^2. [19,20,27,28]

Table 12. Summary of Weight Loss Outcome Results: STEP-1, SCALE Obesity and Prediabetes, and COR-1[19,27,30]

At 56 or 68 weeks	**Semaglutide 2.4 mg subcutaneously once weekly**[19]	**Liraglutide 3.0 mg subcutaneously once daily**[27]	**Naltrexone/bupropion 16 mg/180 mg orally twice daily** [30]
Coprimary Outcomes			
Mean % change in body weight	↓15% (placebo ↓2%)	↓8% (placebo ↓3%)	↓6% (placebo ↓1%)
Mean kg change in body weight	(see below)	↓8 kg (placebo ↓3 kg)	(see below)
Loss of ≥ 5% body weight (% of participants)	86% (placebo 32%) NNT = 2 (2-3)	63% (placebo 27%) NNT = 3 (3-4)	48% (placebo 16%) NNT = 4 (3-4)
Loss of ≥ 10% body weight (% of participants)	(see below)	33% (placebo 11%) NNT = 5 (4-6)	(see below)
Select Secondary Outcomes*			
Loss of ≥ 10% body weight (% of participants)	70% (placebo 12%)	(see above)	25% (placebo 7%)
Loss of ≥ 15% body weight (% of participants)	51% (placebo 5%)	14% (placebo 4%)	12% (placebo 2%)
Mean kg change in body weight	↓15 kg (placebo ↓3 kg)	(see above)	↓6 kg (placebo ↓1 kg)

NNT = number needed to treat [reported as NNT (95% CI)]. *Should be interpreted with caution and considered exploratory.

Table 13. Summary of Weight Loss Outcome Results: STEP-2, SCALE Diabetes, and COR-DM[20,28,31]

At 56 or 68 weeks	**Semaglutide 2.4 mg subcutaneously once weekly**[20]	**Liraglutide 3.0 mg subcutaneously once daily**[28]	**Naltrexone/bupropion 16 mg/180 mg orally twice daily**[31]
Coprimary Outcomes			
Mean % change in body weight	↓10% (placebo ↓ 3%)	↓6% (placebo ↓ 2%)	↓5% (placebo ↓ 2%)
Loss of ≥ 5% body weight (% of participants)	69% (placebo 29%) NNT = 3 (3-4)	54% (placebo 21%) NNT = 4 (3-4)	45% (placebo 19%) NNT = 4 (3-6)
Loss of ≥ 10% body weight (% of participants)	(see below)	25% (placebo 7%) NNT = 6 (4-8)	(see below)
Select Secondary Outcomes*			
Loss of ≥ 10% body weight (% of participants)	46% (placebo 8%)	(see above)	19% (placebo 6%)
Loss of ≥ 15% body weight (% of participants)	26% (placebo 3%)	N/A	N/A
Mean kg change in body weight	↓10 kg (placebo ↓4 kg)	↓6 kg (placebo ↓2 kg)	N/A

N/A = not available, NNT = number needed to treat [reported as NNT (95% CI)]. *Should be interpreted with caution and considered exploratory. *Note: For SCALE Insulin results see page 21.*

- Individual response to pharmacotherapy is heterogeneous.[19,20,27–31]
- There is an observed trend that less weight loss *may* occur in patients living with obesity and T2DM compared to those living with obesity without T2DM, although this is based on indirect comparisons.[19,20,27–31]
- In each of these trials, a notable proportion of patients discontinued therapy before the end of the trial, suggesting that some patients may not continue therapy long-term.[19,20,27–31]

➢ The **STEP-8** trial directly compared the efficacy of semaglutide 2.4 mg subcutaneously once weekly versus liraglutide 3.0 mg subcutaneously once daily for 68 weeks, in 338 adults with a BMI ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 with weight-related co-morbidities, and who did not have diabetes.[23]

- The semaglutide group had a statistically significantly greater mean reduction in body weight compared to the liraglutide group.[23]
  - Mean % change in body weight: absolute difference = -9.4% (95% CI, -12.0 to -6.8) [23]
- Discontinuation rates were notably higher in the liraglutide group compared to the semaglutide group (liraglutide = 27.6% versus semaglutide = 13.5%).[23]
  - This was likely due in part to a dose reduction being allowed for semaglutide, but not for liraglutide. Given the small sample size of the trial, this may have impacted the results and should be considered as a potential limitation of the study.

Is weight loss from obesity care pharmacotherapy sustained over time?

➢ Weight loss associated with semaglutide, liraglutide, and naltrexone/bupropion can start early in therapy.[19,27,30]

- In **STEP-1**, **SCALE Obesity and Prediabetes**, and **COR-1**, the mean % change in body weight observed in the treatment groups at week 4 was approximately -2% to -3%, and mean body weight continued to decrease after this time.[19,27,30]

➢ Most of the weight loss associated with semaglutide, liraglutide, and naltrexone/bupropion use occurs in the first 8-12 months of therapy, and then body weight appears to plateau.[19,27,30]

- In **STEP-1** (semaglutide), **SCALE Obesity and Prediabetes** (liraglutide), and **COR-1** (naltrexone/bupropion), change in body weight from baseline appears to plateau at approximately week 52, week 40, and week 36 respectively.[19,27,30]

- Semaglutide and liraglutide have been evaluated in weight loss RCTs for up to two and three years duration, respectively.[22,32]
    - The **STEP-5** trial (which had a very similar trial design and patient population to **STEP-1**, see page 14) followed 304 adults randomized to receive semaglutide 2.4 mg or placebo subcutaneously once weekly for 2 years.[22]
        - The primary outcomes evaluated weight loss at 2 years.[22]
        - Consistent with results of the **STEP-1** trial, weight loss with semaglutide appeared to plateau at ~52 weeks. [22]
        - Weight loss was maintained in the semaglutide arm at 2 years.[22]
        - The mean % body weight change from baseline to 2 years was: [22]
            - Semaglutide: -15.2%
            - Placebo: -2.6%
                - Absolute difference = -12.6% (95% CI, -15.3 to -9.8)
        - Of note, ~85% of patients in the semaglutide arm remained on treatment at 2 years.[22]
    - In the **SCALE Obesity and Prediabetes** trial, the participants who had prediabetes at baseline were asked to continue treatment for a total of 160 weeks (n = 2254).[32]
        - This study was not specifically designed to evaluate the durability of weight loss over 160 weeks.[32]
        - *Secondary outcomes* evaluated body weight changes at week 160. [32]
        - There was a high rate of discontinuation of therapy. Only ~50% of participants in the liraglutide group remained on therapy at week 160.[32]
        - The mean % body weight change from baseline to week 160 (*secondary outcome*) was: [32]
            - Liraglutide: -6.1%
            - Placebo: -1.9%
                - Absolute difference = -4.3% (95% CI, -4.9 to -3.7)
        - Because weight loss at 160 weeks was a secondary outcome and discontinuation rates were high, these 3-year follow-up results must be interpreted with caution.
- RCTs evaluating naltrexone/bupropion for weight loss were only ~1 year in duration.[17]
- Studies designed to evaluate the durability of weight loss with longer-term follow-up (i.e., >2-3 years) are required to confirm if weight loss with pharmacotherapy is sustained long-term.

Is weight regained when pharmacotherapy for obesity care is discontinued?

- Generally, it is believed that discontinuation of pharmacotherapy for obesity care results in weight regain.[15,33,34]
- Several studies have observed that when semaglutide or liraglutide are discontinued, mean body weight increases.[21,32,35]
- An observational extension phase of a subset of participants (N = 327) of the **STEP-1** trial observed that 1 year after discontinuing semaglutide and lifestyle interventions, ~2/3 of the body weight initially lost during therapy was regained.[35]
- The **STEP-4** RCT was designed to evaluate the effect of continuing semaglutide versus switching to placebo (both in combination with lifestyle interventions) on weight maintenance after initial semaglutide treatment.[21]
    - The **STEP-4** trial enrolled adults with a BMI ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 with weight-related co-morbidities (i.e., hypertension, dyslipidemia, OSA, or CV disease), who did not have diabetes, and who had at least one unsuccessful dietary effort to lose weight.[21]
    - All participants received semaglutide 2.4 mg subcutaneously once weekly (dose titrated over 16 weeks) for an initial 20-week run-in period.[21]
    - After the run-in period, participants (N = 803) were randomized to continue semaglutide 2.4 mg subcutaneously once weekly or switch to placebo for an additional 48 weeks.[21]
    - All participants had lifestyle modification counseling to support a reduced-calorie diet (500 kcal deficit per day) and increased physical activity (150 minutes per week) throughout the trial.[21]
    - The primary outcome was % change in body weight from randomization (week 20) to week 68.[21]
    - Most participants were white and female. The mean age of participants was 46 years, and mean baseline body weight was 107 kg. Almost all participants had a baseline BMI ≥ 30 kg/m^2.[21]
    - *Results: Weight Loss*
        - During the initial 20-week semaglutide therapy run-in period, the mean % change in body weight was -10.6%.[21]

Table 14. Weight loss results of STEP-4[21]

Outcomes	Semaglutide 2.4 mg weekly (n = 535)	Placebo (n = 268)	Absolute Difference Semaglutide vs. Placebo (95% CI)	P value
Primary outcome				
Mean % change in body weight from week 20 to 68	-7.9%	+6.9%	-14.8% (-16.0 to -13.5)	<0.001

CI = confidence interval, n = sample size

- *Observations:*
    - 48 weeks after being randomized to switch from semaglutide to placebo, ~50% of the body weight initially lost during the 20-week semaglutide therapy run-in period was regained.[21]
    - Weight regain may start soon after patients stop semaglutide.
        - In **STEP-4,** data indicated that within ~4-8 weeks of switching to placebo, mean body weight began to increase.

➢ The effect of stopping naltrexone/bupropion on body weight has not been reported.

Academic Detailing Comments: Weight regain after discontinuing GLP-1 agonist therapy

➢ Several studies have observed that when semaglutide or liraglutide are discontinued, mean body weight increases.[21,32,35]

➢ *But what if the individual continues with diet and exercise interventions to maintain weight loss after discontinuing GLP-1 receptor agonist therapy?*

- Data from the **STEP-4** RCT indicate that 48 weeks after switching from semaglutide to placebo, *in addition to lifestyle modification counseling*, about half of the body weight initially lost after 20-weeks of semaglutide therapy was regained.[21]
    - Unfortunately, an assessment of adherence to lifestyle interventions (diet and exercise) was not completed.[21] Therefore, we are unsure if the results of **STEP-4** are generalizable to individuals who are highly motivated to continue lifestyle interventions after discontinuing semaglutide therapy.
    - It is important to note that the run-in period of semaglutide in **STEP-4** was only 20 weeks, which may not reflect real world use.

Does baseline BMI impact the amount of weight loss expected with pharmacotherapy?

➢ Shi et al. completed a large systematic review (SR) and NMA of RCTs (N = 48,209) that assessed the efficacy and safety of pharmacotherapies for adults living with overweight and obesity. They completed a subgroup analysis of the effect of baseline BMI on weight loss outcomes.[17]

- Subgroup analysis found no statistically significant differences in mean % body weight change from baseline across different baseline BMI categories (overweight vs. mild vs. moderate to severe obesity) for all treatments assessed (including GLP-1 receptor agonists, orlistat, and naltrexone/bupropion).[17]
- The subgroup analysis did not assess severe obesity alone as a BMI category.

➢ A post-hoc subgroup analysis of the **STEP-1** trial examined the effects of semaglutide versus placebo in participants with a baseline BMI < 35 kg/m^2 versus ≥ 35 kg/m^2.[36]

- Results were similar across the two subgroups.[36]

Table 15. Results of STEP-1 BMI post-hoc subgroup analysis[36]

Outcome	Semaglutide 2.4 mg weekly	Placebo	Absolute Difference Semaglutide vs. Placebo (95% CI)	P value
Population	68 weeks			
Mean % change in body weight				
BMI < 35 kg/m^2 (n = 760)	-16.15%	-2.49%	-13.66% (-15.06 to -12.26)	<0.0001
BMI ≥ 35 kg/m^2 (n = 1201)	-14.03%	-2.37%	-11.67% (-12.74 to -10.59)	<0.0001

CI = confidence interval, BMI = body mass index, n = sample size

- A subgroup analysis of the **SCALE Obesity and Prediabetes** study reported that participants with a BMI of ≥ 40 kg/m^2 were less likely to have a loss of ≥ 10% body weight compared to those with a lower BMI.[27]
    - There was no statistically significant difference in % mean weight loss, or rates of ≥ 5% body weight loss between different BMI categories (BMI 27-29.9 kg/m^2, BMI 30-34.9 kg/m^2, BMI 35-39.9 kg/m^2, or BMI ≥ 40 kg/m^2). However, there was a statistically significant difference in rates of ≥ 10% body weight loss between different BMI categories (p value for test of no interaction = 0.02), with fewer patients with a BMI ≥ 40 kg/m^2 experiencing this outcome.[27]

Table 16. Results of SCALE Obesity and Prediabetes BMI subgroup analysis, loss of ≥ 10% body weight[27]

Outcome	Liraglutide 3.0 mg daily	Placebo	Absolute Difference	Odds Ratio	P value for test of no interaction
	56 weeks				
Loss of ≥ 10% body weight					
All participants (n = 3652)	32.8%	10.1%	22.7%	4.34	0.02
Participants with BMI 27-29.9 kg/m^2 (n = 108)	45.9%	9.1%	36.8%	8.46	
Participants with BMI 30-34.9 kg/m^2 (n = 1170)	33.8%	10.5%	23.3%	4.35	
Participants with BMI 35-39.9 kg/m^2 (n = 1161)	33.6%	7.2%	26.4%	6.50	
Participants with BMI ≥ 40 kg/m^2 (n = 1213)	29.9%	12.5%	17.4%	2.99	

BMI = body mass index, n = sample size

- Of the three analyses described above, the **SCALE Obesity and Prediabetes** subgroup analysis was the only one to specifically assess patients with a BMI ≥ 40 kg/m^2.[17,27,36]

Academic Detailing Comments: Baseline BMI impact on amount of weight loss expected

- Based on the available evidence (subgroup analyses), baseline BMI *may* not impact the % of body weight loss expected with use of pharmacotherapy for patients living with obesity and a baseline BMI < 40 kg/m^2.
- Unfortunately, there is limited evidence specifically assessing individuals living with obesity and a BMI > 40 kg/m^2. [17,27,36]

Do medications for obesity care improve quality of life and/or physical function?

- Data on the effects of pharmacotherapy on quality of life and physical function are limited.
- Most of the available evidence evaluating these outcomes use self-reported health-related quality of life questionnaires.[17,37–39]
- The commonly used health-related quality of life questionnaires in obesity pharmacotherapy RCTs are:[19,27]
    - Impact of Weight on Quality of Life-Lite questionnaire (IWQOL-Lite) [19,27]
        - Designed to assess health-related quality of life in people living with obesity.[38]
    - 36-Item Short-Form Health Survey (SF-36) [19,27]
        - A general (non-disease-specific) health-related quality of life instrument. It has two summary measures: the physical component summary (PCS) and the mental component summary (MCS).[38]

> The IWQOL-Lite and SF-36 each evaluate several health-related quality of life domains, including physical function.[38]
>
> The CDA-AMC (formerly CADTH) defined the minimal important difference (MID) for IWQOL-Lite scores as 7.7 to 12 points, and the MIDs for the SF-36 PCS and SF-36 MCS as 2 points and 3 points respectively.[38]

Quality of Life:

- The large SR and NMA of RCTs by Shi et al (N = 48,209) evaluated mean quality of life score change from baseline.[17]
    - They found a statistically significantly greater increase in the mean quality of life score (benefit) with GLP-1 receptor agonists and naltrexone/bupropion compared to lifestyle modification alone. However, because the differences were small (below the MIDs), the benefits are “no better than lifestyle modification alone” (moderate certainty evidence).[17]
- The mean change in quality of life scores evaluated by Shi et al evaluated the effects of pharmacotherapy on a *population level*. Individual level response should also be considered.[17,37]
- A secondary analysis of the **SCALE Obesity and Prediabetes** trial evaluated the proportion of individuals who experienced meaningful improvement in quality of life scores at ~1 year. [37]
    - About 10% more people in the liraglutide group than the placebo group experienced meaningful improvement in the IWQOL-Lite [~50% vs. ~ 40%, OR = 1.59 (95% CI, 1.35 to 1.88)] and the SF-36 PCS [~45% vs ~35%, OR = 1.60 (95% CI, 1.35 to 1.90)]. There was no statistically significant difference between the liraglutide and placebo groups in the proportion of people experiencing a meaningful improvement in the SF-36 MCS.[37]

Physical Function:

- A 2023 SR and MA of RCTs assessed the effects of weight-lowering pharmacotherapies on physical activity and function in individuals living with obesity.[39]
    - The outcomes of interest of the SR and MA were any measure of self-reported or objectively measured physical activity, cardiorespiratory fitness, or physical function.[39]
    - Results:
        - Fourteen RCTs (N = 15,151) were included in the MA, and included studies evaluating semaglutide, liraglutide, and naltrexone/bupropion.[39]
        - The trial durations ranged from one to two years.[39]
        - The MA found a statistically significant difference in mean change in **self-reported** physical function outcomes between medication and placebo, however, the difference was less than the MID.[39]
            - Analysis of semaglutide, liraglutide, and naltrexone/bupropion individually found similar results.[39]
        - Only one study reported results of an **objective** physical function measure, the 6-minute walk test (6MWT).[39]
            - The study found no statistically significant improvement with liraglutide compared to placebo.[39]
- Mean changes in self-reported physical function scores evaluate the effects of pharmacotherapy on a population level. Individual level response should also be considered.
- The **STEP-1** trial reported that more patients in the treatment group achieved clinically important improvement in SF-36 physical function scores compared to those in the placebo group, however this was a supportive secondary outcome.[19]

Table 17. STEP-1 Results for Clinically Meaningful Improvement in SF-36 Physical Functioning[19]

Outcome	Semaglutide 2.4 mg weekly	Placebo	Absolute Difference	Odds Ratio Semaglutide vs. Placebo (95% CI)
	68 weeks			
Clinically meaningful improvement in SF-36 physical functioning*	40%	27%	13%	2.08 (1.60 to 2.70)

CI = confidence interval, SF-36 = 36-Item Short-Form Health Survey. *Supportive secondary endpoint analyses were not adjusted for multiplicity and P values are therefore not reported for these endpoints.

Academic Detailing Comments: Quality of Life and Physical Function

- Overall, the available evidence evaluating the effect of pharmacotherapy for obesity care on quality of life and physical function is limited.
- Differences in mean changes in self-reported quality of life or physical function measures between obesity care pharmacotherapy and placebo may not be clinically relevant.[17,39] However, **some** individuals may experience a clinically significant improvement.[19,37]
- It is important to note that RCTs were not designed to assess quality of life or physical function as primary outcomes; as such these results should be considered exploratory.

What is the available evidence for the effects of medications for obesity care on cardiovascular outcomes?

- Semaglutide (Wegovy) is currently the only Health Canada approved medication for obesity care that has been evaluated in CV outcome trials.
  - These trials include the large **SELECT** (2023) RCT, and the smaller **STEP-HFpEF** (2023),
  - and **STEP-HFpEF DM** (2024) RCTs.[24–26]

Major Adverse Cardiovascular Events:

- The **SELECT** trial was a large (n = 17,604) multicenter, double-blind, placebo-controlled, RCT. It evaluated the effects of semaglutide versus placebo (in addition to standard care) on the risk of major adverse cardiovascular events (MACE) in adults ≥ 45 years of age with BMI ≥ 27 kg/m^2 and established CV disease [previous myocardial infarction (MI), previous stroke, or symptomatic peripheral arterial disease (PAD)], without diabetes.[26]
  - Participants were randomized to receive either semaglutide 2.4 mg (dose titrated over 16 weeks) or placebo subcutaneously once a week.[26]
  - Participants also received standard of care management of CV disease, including medical treatment and healthy lifestyle counselling (including diet and physical activity).[26]
  - The primary outcome was a composite of death from CV causes, nonfatal MI, or nonfatal stroke.[26]
  - The exclusion criteria were similar to the **STEP-1** trial (page 14).[19,26]
    - Of note, people with a previous MI, stroke, hospitalization for unstable angina pectoris or transient ischaemic attack *within the past 2 months* were excluded from **SELECT**.
  - The mean age of participants was 62 years, and most (72%) were male. At baseline, the mean body weight was 97 kg, and the mean BMI was 33 kg/m^2. Most participants (~70%) had a baseline BMI ≥ 30 kg/m^2.[26]
  - Most participants were receiving lipid-lowering and antiplatelet drugs at baseline.[26]
  - At 104 weeks, most (77%) participants receiving semaglutide were taking the target dose of 2.4 mg once weekly.[26]
  - Participants were followed for a mean of 40 months.[26]

Table 18. Primary Outcome Results of SELECT [26]

Outcome	Semaglutide 2.4 mg weekly (n = 8803)	Placebo (n = 8801)	Absolute Risk Reduction	Hazard Ratio Semaglutide vs. Placebo (95% CI)	P value	NNT (95% CI)
	Mean 40 months					
Primary outcome						
MACE*	6.5%	8.0%	1.5%	0.80 (0.72 to 0.90)	<0.001	67 (44 to 136)

CI = confidence interval, MACE = major adverse cardiovascular event, n = sample size, NNT = number needed to treat. *Primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. NNTs calculated using GraphPad at https://www.graphpad.com/quickcalcs/NNT1/.

- Body weight was reported as a supportive secondary outcome.[26]
    - Participants in the semaglutide and placebo groups had a mean change in body weight of -9.39% and -0.88%, respectively, at 104 weeks.[26]
        - Absolute difference = -8.51% (95% CI, -8.75 to -8.27) [26]
            - Note: Body weight results were not adjusted for multiplicity, therefore, interpret the results of this outcome with caution.
- It is unknown if the mechanism of reduced risk of MACE is due to weight loss alone, or a combination of GLP-1 receptor agonist effects.[26]
- Approximately 25% of participants in the semaglutide and placebo groups discontinued therapy prematurely.[26]

Academic Detailing Comments: The SELECT Trial and MACE

- **SELECT** is the only RCT designed to evaluate a Health Canada approved obesity care medication (semaglutide) for effects on MACE.
- The **SELECT** trial population was <u>not</u> all comers.[26]
    - The **SELECT** trial enrolled adults ≥ 45 years of age with a BMI ≥ 27 kg/m^2 and history of *established CV disease,* without diabetes.[26]
        - Established CV disease = previous MI, previous stroke, or symptomatic PAD[26]
    - The results of **SELECT** would not be generalizable to individuals living with obesity who <u>do not have established CV disease.</u>
- Interpretation of the results of the **SELECT** Trial:
    - In adults ≥ 45 years of age with a BMI ≥ 27 kg/m^2 and established CV disease, semaglutide 2.4 mg once weekly (plus standard of care) reduced the absolute risk of experiencing a MACE over 40 months by 1.5% compared to placebo (plus standard of care).[26]
        - Number needed to treat (NNT): For every 67 adults ≥ 45 years of age with a BMI ≥ 27 kg/m^2 and established CV disease treated for 40 months, semaglutide 2.4 mg once weekly (plus standard of care) prevented one episode of MACE compared to placebo (plus standard of care) (NNT = 67).
            - The data show with 95% certainty that the number of people requiring treatment with semaglutide to avoid one episode of MACE was between 44 and 136 (95% CI around the NNT).
                - The wide confidence interval around the NNT suggests imprecision in the results.

- Liraglutide has not been evaluated in a large CV outcome trial.
    - A *post hoc* analysis of five of the **SCALE** trials (n = 5908) evaluated CV event risk.[40]
        - The primary composite outcome was CV death, nonfatal MI, or nonfatal stroke.

  - There was no statistically significant difference in risk of CV events between the liraglutide and placebo groups.
- The **SCALE** trials were not designed to evaluate CV outcomes, and rates of CV events were low in both the treatment and placebo groups.
- The patient population enrolled in the **SCALE** trials differed from those in **SELECT** (e.g., few participants had established CV disease).
- A larger, longer trial specifically designed to evaluate CV outcomes would be necessary to assess if liraglutide reduces the risk of MACE in people living with obesity.

➢ There is currently an RCT being conducted that is evaluating the effect of naltrexone/bupropion on MACE (the **INFORMUS** trial). It is expected to be completed in 2029.[41]

Heart Failure:

➢ The **STEP-HFpEF** and **STEP-HFpEF DM** trials evaluated the effects of semaglutide 2.4 mg subcutaneous once weekly in adults living with heart failure with preserved ejection fraction (HFpEF) and obesity. The **STEP-HFpEF DM** trial included patients living with T2DM, whereas the **STEP-HFpEF** trial did not.[24,25]

- The trials were multicenter, double-blind, placebo-controlled, RCTs.[24,25]
- The **STEP-HFpEF** and **STEP-HFpEF DM** trials enrolled 529 and 616 participants respectively.[24,25]
- Some of the key inclusion criteria for both studies included: age ≥ 18 years, left ventricular ejection fraction (LVEF) ≥ 45%, BMI ≥ 30 kg/m^2, and New York Heart Association (NYHA) functional class II – IV, a Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) of < 90 points, and a 6-minute walk distance of at least 100 m.[24,25] See Appendix 3 for more details on inclusion criteria.
- Participants were randomized to receive either semaglutide 2.4 mg (dose titrated over 16 weeks) or placebo subcutaneously once weekly for 52 weeks.[24,25] Participants were also offered individualized healthy lifestyle counselling (including diet and physical activity).[24,25]
- The dual primary outcomes were change in the KCCQ-CSS and % change in body weight at week 52.[24,25]

> The KCCQ measures symptoms, physical and social limitations, and quality of life in patients with heart failure.[42]
>
> It is a 23 item questionnaire with items related to 7 domains: symptom frequency; symptom burden; symptom stability; physical limitations; social limitations; quality of life; and self-efficacy (the patient's understanding of how to manage their heart failure).[42]
>
> Scores from the symptom frequency, symptom burden, and physical limitation domains are combined to create a clinical summary score (KCCQ-CSS).[42]

Scores are given on a 0-to-100 point scale, where lower scores represent more severe symptoms/limitations. A change in KCCQ scores of 5 points represents a small but clinically important change. A moderate to large change is 10 points, and a large to very large change is 20 points.[42]

- Participants across the two trials were similar at baseline.[24,25]
    - About half of the participants were female, and most were white. The median age of participants was 69 years. Median body weight was ~105 kg and the median BMI was 37 kg/m^2.[24,25]
    - Most participants were receiving diuretics, renin-angiotensin system blockers, and beta-blockers at baseline. About a third of participants were receiving a mineralocorticoid receptor antagonist at baseline.[24,25]
    - In the **STEP-HFpEF DM** trial most participants (~70%) were on metformin, ~30% were on a SGLT2 inhibitor, ~20% were on a sulfonylurea, and ~20% were on insulin at baseline.[25]
- *Results:*

Table 19. Results of STEP-HFpEF and STEP-HFpEF DM[24,25]

Outcome	Semaglutide 2.4 mg weekly	Placebo	Absolute Difference or Odds Ratio (OR) Semaglutide vs. Placebo (95% CI)	P value
	52 weeks			
STEP-HFpEF (n = 529)				
Primary outcomes				
Mean change in KCCQ-CSS from baseline	16.6 points	8.7 points	7.8 points (4.8 to 10.9)	<0.001
Mean % change in body weight from baseline	-13.3%	-2.6%	-10.7% (-11.9 to -9.4)	<0.001
Other select outcomes				
Mean change in 6-minute walk distance from baseline (meters, m)	21.5 m	1.2 m	20.3 m (8.6 to 32.1)	<0.001
≥ 5-point increase in KCCQ-CSS# (% of participants)	75.3%	63.7%	OR = 1.9 (1.3 to 2.8)	NA
STEP-HFpEF DM (n = 616)				
Primary Outcomes				
Mean change in KCCQ-CSS from baseline	13.7 points	6.4 points	7.3 points (4.1 to 10.4)	<0.001
Mean % change in body weight from baseline	-9.8%	-3.4%	-6.4% (-7.6 to -5.2)	<0.001
Other select outcomes				
Mean change in 6-minute walk distance from baseline (meters, m)	12.7 m	-1.6 m	14.3 m (3.7 to 24.9)	0.008
≥ 5-point increase in KCCQ-CSS# (% of participants)	73%	54.8%	OR = 2.3 (1.6 to 3.3)	NA

n = sample size, CI = confidence interval, KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire clinical summary score, NA = not available, OR = odds ratio. # p values were not reported for this outcome as results were not adjusted for multiplicity, therefore, interpret the results of this outcome with caution.

- Both trials found similar improvements in mean change in KCCQ-CCS from baseline.[24,25]

- As the KCCQ-CCS is not currently used in clinical practice, these results may be difficult for clinicians to interpret.[42]

- The mean change in 6-minute walk distance was less than the MID for a 6-minute walk test (6MWT). [43,44]

The MID for a 6MWT in patients with heart failure has been reported variably (e.g., 30 m and 54 m).[38,43,44]

- Several limitations to the **STEP-HFpEF** and **STEP-HFpEF DM** trials should be considered when interpreting the results.
  - They were relatively small and of short duration and were not powered to assess important hard clinical outcomes (e.g., mortality or hospitalization for heart failure).
  - Larger and longer trials are required to determine if semaglutide improves important clinical outcomes like mortality or hospitalization for heart failure in patients living with HFpEF and obesity.

Academic Detailing Comments: The STEP-HFpEF Trials and Heart Failure Outcomes

- The **STEP-HFpEF** and **STEP-HFpEF DM** trials evaluated the effects of semaglutide 2.4 mg subcutaneous once weekly in adults living with HFpEF and obesity. The **STEP-HFpEF DM** trial included patients living with T2DM, whereas the **STEP-HFpEF** trial did not.[24,25]
  - The **STEP-HFpEF** (n = 529) and **STEP-HFpEF DM** (n = 616) trials were small, much smaller than the **SELECT** trial (n = 17,604).[24–26]
  - **STEP-HFpEF** and **STEP-HFpEF DM** were not powered to assess important hard clinical outcomes (e.g., mortality or hospitalization for heart failure).
  - The primary outcomes were surrogate outcomes.
  - Larger and longer trials are required to determine if semaglutide improves important clinical outcomes like mortality or hospitalization for heart failure in patients living with HFpEF and obesity.
- The results of these two RCTs should not be extrapolated to adults living with heart failure with reduced ejection fraction and obesity.

What are the potential adverse events associated with pharmacotherapy for obesity care?

GLP-1 Receptor Agonists: Semaglutide & Liraglutide

- In this section, data from product monographs, RCTs, MAs, and observational studies are reported.
- Observational studies are useful in evaluating real-world effects of an intervention in a broader patient population.
    - Observational studies evaluating GLP-1 receptor agonist use in people living with obesity were reported when available. When this was not available, relevant observational studies of patients living with T2DM were reviewed.
- Many pharmacovigilance studies have investigated various potential adverse events.
    - As per the Canadian Network for Observational Drug Effect Studies (CNODES), although these studies are useful for signal generation, "pharmacovigilance analyses are subject to significant limitations, which include incomplete capturing of events, absence of information of the number of exposed subjects (no denominator), and inability to control for confounding variables."[45]
        - Due to these limitations, pharmacovigilance studies are not discussed in this evidence review.
- The evidence evaluating the safety of GLP-1 receptor agonists in obesity care is rapidly evolving.
- The potential adverse events reviewed here are not an exhaustive list.

Common Adverse Events:

- The most frequently reported adverse events (AEs) in RCTs were gastrointestinal (GI) related: nausea, diarrhea, vomiting, and constipation (see pages 14 to 23 for details on RCTs).[19,20,27,28]
    - Most GI AEs were mild-to-moderate in severity, transient, and did not result in discontinuation of therapy.[19,20,27,28]
    - Initial dose titration schedules (see Appendix 1) should be used to decrease the likelihood of experiencing GI AEs.[6,7]

Table 20. Most Frequently Reported Gastrointestinal GLP-1 Receptor Agonist Adverse Events[19,27]

Adverse Event	STEP-1[19]		SCALE Obesity and Prediabetes[27]	
	Semaglutide 2.4 mg weekly (% of participants)	Placebo (% of participants)	Liraglutide 3.0 mg daily (% of participants)	Placebo (% of participants)
Nausea	44.2%	17.4%	40.2%	14.7%
Diarrhea	31.5%	15.9%	20.9%	9.3%
Vomiting	24.8%	6.6%	16.3%	4.1%
Constipation	23.4%	9.5%	20%	8.7%

Drug Discontinuation Due to Adverse Events:

- GLP-1 receptor agonists are associated with more treatment discontinuation due to AEs compared to lifestyle modification alone.[17]
    - Discontinuation due to adverse events:
        - OR = 2.22 (95% CI, 1.74 to 2.84)
- Across most of the RCTs reviewed (see pages 14 to 23), about 1 in 10 clinical trial participants discontinued semaglutide or liraglutide therapy due to AEs. [19,20,27–29] For example:
    - In **STEP-1**, 7% of participants in the semaglutide group discontinued therapy due to AEs compared to 3% in the placebo group.[19]
    - In **SCALE Obesity and Prediabetes**, 10% of participants in the liraglutide group discontinued therapy due to AEs compared to 4% in the placebo group.[27]
    - Interestingly, higher rates of drug discontinuation due to AEs were reported in the **SELECT** trial, with 17% of participants in the semaglutide group discontinuing therapy due to AEs compared to 8% in the placebo group.[26]
        - The higher rate of drug discontinuation due to AEs in **SELECT** may be due to multiple factors, including the longer trial duration and the patient population enrolled (e.g., older individuals, history of CV disease).[26]
- Most AEs that led to drug discontinuation were GI-related. [19,20,26–28]

Serious Adverse Events:

- In the **STEP-1** and **SCALE Obesity and Prediabetes** trials, serious adverse events were reported more frequently in the treatment groups compared to placebo.[19,27]
    - Serious adverse events were events that resulted in death, a life-threatening event, new or prolonged hospitalization, persistent or significant disability, birth defect, or other important medical events. [19,27]
    - **STEP-1** serious adverse events:[19]
        - Semaglutide = 10% of participants
        - Placebo = 6% of participants
    - **SCALE Obesity and Prediabetes** serious adverse events in ≥ 0.2% of patients:[27]
        - Liraglutide = 6%
        - Placebo = 5%

Hypoglycemia:

- Hypoglycemia events have been reported with GLP-1 receptor agonists in patients without T2DM.[6]
    - The **STEP-1** and **SCALE Obesity and Prediabetes** trials did not require all participants to monitor blood glucose routinely at home.[19,27]

- **STEP-1:** Hypoglycemia events were reported by 0.6% and 0.8% of semaglutide and placebo participants respectively. No further details were provided.[19]
- **SCALE Obesity and Prediabetes**: Spontaneous hypoglycemia was reported by 1.3% and 1.0% of liraglutide and placebo participants respectively. **None of the events were serious or required third-party assistance**.[27]
    - Spontaneous hypoglycemia = symptoms of hypoglycemia (not biochemically confirmed)[27]

➢ Hypoglycemia events have been reported with GLP-1 receptor agonists in people living with obesity and T2DM. Risk of hypoglycemia may be higher in individuals taking concomitant SUs or insulin.[6,7]

- In the **STEP-2** and **SCALE Diabetes** trials participants were required to monitor blood glucose regularly at home and when they had symptoms of hypoglycemia.[20,28]
- **STEP-2:** Severe or blood glucose confirmed hypoglycemia events occurred in 5.7% of the semaglutide 2.4 mg group and 3.0% of the placebo group participants. Unfortunately, no further details were provided.[20]
- **SCALE Diabetes**:
    - *Severe hypoglycemia* events were only reported in participants in the liraglutide groups who were taking a SU as background medication.[28]
        - *Severe hypoglycemia* = An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
    - *Documented symptomatic hypoglycemia* events occurred most commonly in participants in the liraglutide groups who were taking a SU as background medication.[28]
        - *Documented symptomatic hypoglycemia*: Symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L.

Table 21: Hypoglycemia events in the SCALE Diabetes trial[28]

Type of Hypoglycemia Event	Liraglutide 3.0 mg (n = 422)		Placebo (n = 212)	
	% of participants	Number of events	% of participants	Number of events
Participants taking SU as background medication				
Severe	2.7%	5	0%	0
Documented symptomatic	43.6%	214	27.3%	41
Participants not taking SU as background medication				
Severe	0%	0	0%	0
Documented symptomatic	15.7%	115	7.6%	15

n = sample size, SU = sulfonylurea

- **SCALE Insulin:** There were similar rates of overall hypoglycemic events, severe hypoglycemia, and documented symptomatic hypoglycemia in the liraglutide and placebo groups.[29]
- It should be kept in mind that the **STEP-2**, **SCALE Diabetes**, and **SCALE Insulin** RCTs recommended dosage reductions of SU and insulin at baseline (see page 18). [20,28,29]
- When interpreting these results, consider that **STEP-2** and **SCALE Diabetes** participants had a baseline HbA1c between 7% and 10%, and in **SCALE Insulin** a baseline HbA1c between 6% and 10%.
    - Therefore, the proportion of patients who may experience hypoglycemia could be different in patients who have lower HbA1c at baseline.
- The Wegovy (semaglutide) product monograph suggests, at the initiation of Wegovy therapy, to consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas), or insulin to reduce the risk of hypoglycemia. It also recommends monitoring blood glucose prior to starting treatment and during treatment in patients with T2DM.[6]
- The Saxenda (liraglutide) product monograph suggests, at the initiation of Saxenda therapy, to consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) to reduce the risk of hypoglycemia. It also states that "Saxenda and insulin should not be used together".[7]

Acute Kidney Injury:

- Acute renal injury (AKI) has been reported in patients using semaglutide or liraglutide for obesity care (< 1%).[6,7]
- AKI events usually occurred in individuals who experienced GI AEs (e.g., nausea, vomiting, or diarrhea) that lead to volume depletion.[6,7]
    - Patients should be advised of the potential risk of dehydration in relation to GI AEs and take precautions to avoid fluid depletion.[6,7]
    - Monitor renal function in people who experience severe GI AEs.[6]
    - Use caution when initiating or escalating doses in patients with renal insufficiency.[7]
        - Note: Wegovy and Saxenda are not recommended to be used in individuals with severe renal insufficiency. [6,7]

Gallbladder-related disorders:

- The Wegovy (semaglutide) and Saxenda (liraglutide) product monographs report a possible increase in gallbladder-related events with use of these drugs.[6,7]
- In the **STEP-1** and **SCALE Obesity and Prediabetes** trials, gallbladder-related disorders occurred in about 2-3% of the individuals randomized to the treatment arms and ~1% of those receiving placebo. Unfortunately, these trials were not powered to adequately evaluate these AEs.[19,27]

- Two recent MAs of RCTs have found that use of GLP-1 receptor agonists for weight loss is associated with an increased risk of gallbladder or biliary diseases,[46,47] although, the absolute risk increase compared to placebo/control was small.[47]
    - A 2022 MA by He et al. evaluated the association of GLP-1 receptor agonist use with the risk of gallbladder or biliary diseases.[47]
        - The MA included RCTs that evaluated *any* GLP-1 receptor agonist (for *any* indication or dose) and reported adverse events of gallbladder or biliary diseases.
            - 76 RCTs were included (N = 103,371)
                - Most were diabetes trials. Thirteen RCTs were weight loss trials (n = 11,281), and three were for other indications.
        - Primary outcome results:
            - Risk of gallbladder or biliary diseases:
                - GLP-1 receptor agonists vs. control:
                    - **Absolute Risk Difference (ARD) = 27 events per 10,000 patients per year (95% CI, 17 to 38)**
                    - Relative Risk (RR) = 1.37 (95% CI, 1.23 to 1.52); I^2 = 0%
        - Subgroup analysis: Indication
            - The use of GLP-1 receptor agonists was associated with an increased risk of gallbladder or biliary disease compared to active control or placebo when used for weight loss or T2DM indications.
                - The subgroup analysis suggests higher risk when used for weight loss compared to T2DM (see table 22).

Table 22. Subgroup Analysis Results: Risk of Gallbladder or Biliary Diseases, GLP-1 Receptor Agonist vs Control, by Indication[47]

	Number of patients	Number of Trials	Relative Risk of Gallbladder or Biliary Diseases GLP-1 receptor agonist vs. control (95% CI)	I^2	P value for interaction
Indication					
Weight loss	11,282	13	2.29 (1.64 to 3.18)	0%	<0.001
T2DM/other	92,090	63	1.27 (1.14 to 1.43)	0%	

CI = confidence interval, T2DM = type 2 diabetes mellitus

- A 2024 MA by Singh et al. evaluated the efficacy and safety of GLP-1 receptor agonists in individuals living with obesity or overweight *without diabetes*.[46]
    - The MA included RCTs comparing a GLP-1 receptor agonist to placebo in adults living with overweight or obesity, without diabetes.
        - 10 RCTs were included (N = 29,325).

        - 9 trials evaluated liraglutide or semaglutide, and 1 trial evaluated tirzepatide.
        - Mean duration of follow-up was 19 months.
    - There were many primary clinical endpoints of interest, including gallbladder-related disorders.
    - Results:
        - Gallbladder-related disorders:
            - GLP-1 receptor agonists vs. placebo:
                - OR = 1.54 (95% CI, 1.07 to 2.21), I^2 = 45%

- Individuals using GLP-1 receptor agonists who experience a greater degree of weight loss may be at a higher risk of experiencing gallbladder or biliary disease.[48]
    - A 2024 MA found that a greater weight reduction difference between GLP-1 receptor agonist and placebo was significantly associated with the risk of gallbladder or biliary disease and cholelithiasis.[48]
- The exact mechanism(s) of increased risk of gallbladder and biliary disease is unknown.[48]
    - According to the product monographs, even after accounting for the amount of weight loss with semaglutide or liraglutide, the incidence of acute gallbladder disease was greater in the semaglutide or liraglutide-treated patients compared to placebo-treated patients.[6,7]
    - Other factors, including independent GLP-1 receptor agonist effects, may also contribute to the increased risk of gallbladder disease.[48]

Acute Pancreatitis:

- In both the **STEP-1** and **SCALE Obesity and Prediabetes** trials, acute pancreatitis was reported in 0.2% of participants in the GLP-1 receptor agonist groups, and in none of the participants in the placebo groups.[19,27]
- The 2024 MA by Singh et al. that evaluated the efficacy and safety of GLP-1 receptor agonists in individuals living with obesity or overweight *without diabetes* (described above on page 41), reported acute pancreatitis as one of the primary outcomes of interest.[46]
    - MA of data from 10 RCTs did not find an increased risk of acute pancreatitis with GLP-1 receptor agonists compared to placebo.
- A recent observational study by Sodhi et al. using data from the United States (US) evaluated GI AEs associated with GLP-1 receptor agonists used in weight loss. The cohort (n = 5,411) included new users of GLP-1 receptor agonists (semaglutide or liraglutide), and the active comparator naltrexone/bupropion. Patients with diabetes were excluded from the cohort.[49]
    - The incidence of pancreatitis was:
        - Semaglutide group = 4.6 events per 1000 person-years

- Liraglutide group = 7.9 events per 1000 person-years
- Naltrexone/bupropion = 1.0 event per 1000 person-years

- The use of GLP-1 receptor agonists was associated with an increased risk of pancreatitis compared to naltrexone/bupropion [adjusted hazard ratio (HR) 9.09 (95% CI, 1.25 - 66)].
  - The confidence interval is very wide, suggesting imprecision and uncertainty in the results.
  - The low event rates should also be considered when interpreting the results.
- There are many limitations to this study to consider, including:
  - There is potential for confounding.
    - Patients prescribed a GLP-1 receptor agonist may have different characteristics than those prescribed naltrexone/bupropion (e.g., different comorbidities, BMIs) which could impact the results.
  - There is uncertainty if all patients were using the prescribed GLP-1 receptor agonist for obesity versus other indications.
  - Most participants were using liraglutide, which may not be reflective of current prescribing practices.
  - The publication was not peer-reviewed.

- Given the conflicting and limited available evidence, there is uncertainty if GLP-1 receptor agonists for obesity care increase the risk of pancreatitis.
- The Wegovy (semaglutide) and Saxenda (liraglutide) product monographs recommend that if acute pancreatitis is suspected, the GLP-1 receptor agonist should promptly be discontinued, and appropriate management should be initiated. If acute pancreatitis is confirmed, the drug should not be restarted.[6,7]
- Patients with a history of pancreatitis were excluded from **STEP-1** and **SCALE Obesity and Prediabetes** (see page 14-15),[19,27] therefore it is unknown whether these patients are at an increased risk of acute pancreatitis while using semaglutide or liraglutide in obesity care.

Gastroparesis

- GLP-1 receptor agonists may delay gastric emptying.[6,7,50]
- There is limited evidence available evaluating the risk of gastroparesis in this patient population.
- There are case reports of patients experiencing gastroparesis after initiating a GLP-1 receptor agonist for obesity care.[51,52]
- The observational study by Sodhi et al. (described on page 42) evaluated the incidence of gastroparesis.[49]
  - The incidence of gastroparesis was:
    - Semaglutide group = 9.1 events per 1000 person-years

- Liraglutide group = 7.3 events per 1000 person-years
- Naltrexone/bupropion = 3.1 events per 1000 person-years

- The use of GLP-1 receptor agonists was associated with an increased risk of gastroparesis compared to naltrexone/bupropion [adjusted HR 3.67 (95% CI, 1.15 to 11.9)].[49]
  - The confidence interval is wide, suggesting imprecision and uncertainty in the results.
  - The low event rates should also be considered when interpreting the results.
- The limitations to the study should be considered when interpreting the results (see page 42). In particular, there is risk of confounding as gastroparesis can occur due to other causes.

➢ Given the lack of high-quality evidence, there is uncertainty in the risk of gastroparesis associated with GLP-1 receptor agonist use in obesity care.

Intestinal Obstruction

➢ The Wegovy (semaglutide) product monograph notes that use of GLP-1 receptor agonists may be associated with severe GI disease (intestinal obstruction and ileus), and that post-market events have been reported.[6]

➢ Several observational studies have evaluated the risk of intestinal obstruction associated with GLP-1 receptor agonist use, and have found conflicting results.[49,53,54]

➢ Sodhi et al. evaluated the risk of bowel obstruction in patients using GLP-1 receptor agonists for obesity care.[49]

- The incidence of bowel obstruction was:
  - Semaglutide group = 0 events per 1000 person-years
  - Liraglutide group = 8.1 events per 1000 person-years
  - Naltrexone/bupropion = 1.7 events per 1000 person-year
- The use of GLP-1 receptor agonists was associated with an increased risk of bowel obstruction compared to naltrexone/bupropion [adjusted HR = 4.22 (95% CI, 1.02 to 17.40)].[49]
  - The confidence interval is wide, suggesting imprecision and uncertainty in the results.
  - The low event rates should also be considered when interpreting the results.
- The limitations to the study should be considered when interpreting the results (see page 42). In particular, there is risk of confounding as bowel obstruction can occur from other causes.

- The largest observational study identified by this evidence review evaluated the risk of intestinal obstruction of GLP-1 receptor agonists compared to SGLT2 inhibitors in adults in Sweden, Norway, and Denmark. [53]
    - Patients who filled their first prescription for a GLP-1 receptor agonist (*not including liraglutide with obesity indication*) or an SGLT2 inhibitor during the study period were included in the cohort and followed for up to 5 years.
    - 121,254 new users of GLP-1 receptor agonists and 185,027 new users of SGLT2 inhibitors were included in the cohort.
    - Results:
        - 0.2% of users in each group (GLP-1 receptor agonist and SGLT2 inhibitor) experienced intestinal obstruction.
        - There was no significant association between use of GLP-1 receptor agonists vs SGLT2 inhibitors and risk of intestinal obstruction:
            - Adjusted incidence rates 1.3 vs 1.6 events per 1000 person-years
                - HR = 0.83 (95% CI, 0.69 to 1.01)
        - Participants were followed for a median of ~1 year.
    - Limitation: This study primarily evaluated people using GLP-1 receptor agonists for diabetes. Results may not be generalizable to people using GLP-1 receptor agonists for obesity care, as the patient population and dosing would be different.
- Given the lack of high-quality evidence, and potential risk of confounding, there is uncertainty in the risk of intestinal obstruction associated with GLP-1 receptor agonist use in obesity care.

Aspiration Risk during Anesthesia:

- There are concerns that the use of GLP-1 receptor agonists in the perioperative period *may* increase risk of pulmonary aspiration due to delayed gastric emptying.[50,55]
- The current body of evidence evaluating the risk of pulmonary aspiration is limited to case reports, case series, and small observational studies.[55]
    - This makes it difficult to evaluate the risk and make evidence-informed recommendations for potential risk mitigation strategies.
- In 2023 The Canadian Anesthesiologists' Society (CAS) and the Institute for Safe Medication Practices (ISMP) Canada published Safety Bulletins on the topic, which include some guidance on management:[50,56]
    - CAS bulletin: https://www.cas.ca/CASAssets/Documents/Advocacy/Semaglutide-bulletin_final.pdf
    - ISMP bulletin: https://ismpcanada.ca/wp-content/uploads/ISMPCSB2023-i9-GLP-1.pdf

Breast Cancer

- In the **SCALE Obesity and Prediabetes** RCT (N = 3731) a numerical imbalance in the incidence of breast neoplasms (malignant and pre-malignant) was observed.[27]
    - 10 events in the liraglutide group versus 3 events in the placebo group.[27]
        - Most of the women with events had above average weight loss.[27]
    - The RCT was only ~1 year in duration and was not powered or designed to evaluate breast cancer as an outcome.[27] Given the low event rates reported, a larger study would be required to evaluate the potential risk of breast cancer with GLP-1 receptor agonists.
    - This imbalance was not observed in the **LEADER** trial, which was a CV outcome trial of liraglutide for T2DM that followed patients for a median of 3.8 years (N = 9340).[57]
- A 2021 SR and MA of RCTs evaluated the risk of breast cancer with GLP-1 receptor agonist use for T2DM or obesity.[58]
    - RCTs included in the MA compared a GLP-1 receptor agonist to a non-GLP-1 receptor agonist antihyperglycemic or weight loss medication or placebo, in adults with T2DM, prediabetes, obesity, overweight, or metabolic syndrome.[58]
    - 50 RCTs were included in the MA evaluating risk of breast cancer.[58]
        - 19 of these RCTs were open-label, the rest were double-blind.[58]
        - 16 RCTs evaluated liraglutide, 10 evaluated semaglutide, and 2 evaluated both drugs.[58]
        - BMI ranged across the studies, from 25.3 to 39.3 kg/m^2.[58]
        - *Results:*[58]
            - GLP-1 receptor agonists were not associated with an increased rate of breast cancer compared to placebo or comparator drugs.
                - RR = 0.98 (95% CI, 0.76 to 1.26, moderate certainty of evidence)
    - Limitations: Only 6 of the RCTs included in the breast cancer MA were conducted in individuals living with obesity or overweight.[58] This may limit the generalizability of the results. Also, these RCTs were not designed to evaluate breast cancer risk and may have been underpowered and too short in duration to evaluate this outcome.
- No observational studies specifically designed to investigate the use of GLP-1 receptor agonists and breast cancer risk in *obesity care* were identified.
    - The body of evidence available assessing GLP-1 receptor agonists and breast cancer risk is primarily in patients using GLP-1 receptor agonists in the management of T2DM.[58–60]
    - The doses of GLP-1 receptor agonists used in the management of T2DM are lower than those used in trials for obesity care, and patient populations and risk factors may be different. These factors may limit the generalizability of the results of the available observational evidence and should be considered when interpreting the results.

- A 2016 population-based cohort study conducted in the UK compared the rate of breast cancer in women with T2DM who used GLP-1 receptor agonists vs DPP-4 inhibitors.[57,59]
    - N = 44,984 women
        - ~95% and 65% of GLP-1 receptor agonist users and DPP-4 users respectively had a BMI ≥ 30 kg/m^2.
    - Follow-up duration = mean 3.5 years
    - *Results:*
        - GLP-1 agonists were not associated with an increased risk of breast cancer compared to DPP-4 inhibitors.
            - 4.4 vs 3.4 per 1000 person-years
            - Adjusted HR = 1.4 (95% CI, 0.91 to 2.16)
- A 2024 retrospective cohort study conducted in the US using data from 2005 to 2018 compared the rate of several obesity-associated cancers, including breast cancer, in women with T2DM who used GLP-1 receptor agonists vs insulin or metformin.[60]
    - Only ~1/3 of GLP-1 receptor agonist users were also living with obesity or overweight.
    - Mean follow-up duration was unclear.
    - *Results:*
        - GLP-1 receptor agonists were not associated with an increased risk of breast cancer compared to insulin or metformin.
            - GLP-1 receptor agonist vs. insulin (n = 13,768)
                - HR = 1.07 (95% CI, 0.93 to 1.23)
            - GLP-1 receptor agonist vs. metformin (n = 10,419)
                - HR = 1.02 (95% CI, 0.87 to 1.20)
- Overall, there is currently a lack of evidence available evaluating the potential association between GLP-1 receptor agonists for *obesity care* and breast cancer.
- Although a potential association between GLP-1 receptor agonists and breast cancer remains controversial, it has been speculated that weight loss with this class of agents may lead to improved detection of breast cancer.[57,61] For more information, see the 2023 Dalhousie Academic Detailing Service Topic, https://medicine.dal.ca/departments/core-units/cpd/programs/academic-detailing-service/AC-Service-Resources.html.[57]

Pancreatic Cancer

- An association between GLP-1 receptor agonists and pancreatic cancer has been raised as a potential concern. Animal studies have raised speculation that chronic over-stimulation of GLP-1 receptor agonists in exocrine pancreatic cells could induce pancreatitis, which may lead to an increased risk of pancreatic cancer.[62]

- The US Food and Drug Administration (FDA) and Health Canada have received reports of pancreatic cancer in patients using GLP-1 receptor agonists through their adverse event reporting systems.[62,63]
    - These reports are hypothesis generating only and require further investigation to determine if there is an association between the drug and the adverse event.
- There is limited evidence available evaluating the potential association between GLP-1 receptor agonist use for *obesity care* and pancreatic cancer risk.
    - Evidence from RCTs is limited by short follow-up durations.[62]
    - Most observational studies assessing GLP-1 receptor agonists and pancreatic cancer risk focus on patients living with T2DM, not obesity.
    - Almost all of the observational studies available to date have inadequate follow-up (<5-years) to evaluate pancreatic cancer risk.[62,64]
- A US retrospective cohort study evaluated the risk of pancreatic cancer in adults with *diabetes and/or obesity* who were newly treated with a GLP-1 receptor agonist or metformin.[62]
    - 369,360 patients were included in each of the GLP-1 receptor agonist and metformin groups for the main analysis and were matched to reduce risk of confounding.
    - The primary outcome was the incidence of pancreatic cancer.
    - *Results:*
        - Primary outcome: GLP-1 receptor agonist use was associated with a *lower* risk of pancreatic cancer compared to metformin use over ~ 3 years.
            - HR = 0.47 (95% CI, 0.42 to 0.52)
        - Liraglutide was the most frequently prescribed GLP-1 receptor agonist, followed by dulaglutide and then semaglutide.
    - Important limitations:
        - Mean follow-up duration was short.
            - 3 years for the GLP-1 receptor agonist group, and 4.5 years for the metformin group.
        - Indication and dose of GLP-1 receptor agonists were not reported, and less than 50% of the matched participants had overweight or obesity.
            - This may limit the applicability of the results.
- Additional observational studies in individuals living with obesity with longer term follow-up are required to monitor for the potential of this serious adverse event.
    - As the latency period for the development of pancreatic cancer is lengthy, long-term follow-up would be required to adequately evaluate risk.

- Obesity is a known risk factor for pancreatic cancer.[62] As such, it would be important to have studies specifically designed to evaluate the use of GLP-1 receptor agonists in this population.

Thyroid Cancer

- Wegovy (semaglutide) and Saxenda (liraglutide) are contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).[6,7]
- The Wegovy (semaglutide) and Saxenda (liraglutide) product monographs report that semaglutide and liraglutide cause dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposure in rodents, and it is unknown whether semaglutide and liraglutide cause thyroid C-cell tumors (including MTC) in humans. [6,7]
- The FDA and Health Canada have received reports of thyroid cancer in patients using GLP-1 receptor agonists through their adverse event reporting systems.[63,65]
- Establishing a potential increase in risk of MTC and duration of GLP-1 receptor agonist use is challenging due to the low rate of MTC (estimated incidence of 0.2 cases per 100,000 patient-years).[57]
- Several recently published MA of RCTs have investigated the potential association between GLP-1 receptor agonists and thyroid cancer, and have found conflicting results.[66–68] There are several important limitations to the RCTs included in these MA, therefore results are not reported in this evidence review. Limitations include:
    - RCTs were not designed to evaluate thyroid cancer.
    - Most of the RCTs evaluated GLP-1 receptor agonists in T2DM management, not obesity care, and this may limit the generalizability of the results.
    - RCTs are of short duration and do not provide long-term safety data.
    - People with a personal or family history of MTC were excluded from the trials, therefore high-risk populations were excluded.
    - Very few cases of MTC have been documented in RCTs which makes it difficult to evaluate this outcome. [68]
- No observational studies were identified that specifically evaluated the potential association between thyroid cancer and use of GLP-1 receptor agonists *for obesity care*.
    - The body of evidence available assessing GLP-1 receptor agonists and thyroid cancer risk is primarily in patients using GLP-1 receptor agonists in the management of T2DM.[69]
    - The doses of GLP-1 receptor agonists used in the management of T2DM are generally lower than those used in trials for obesity care, and patient populations and risk factors may be different. These factors may limit the generalizability of the results of the available observational evidence.
- Observational studies evaluating the potential association between GLP-1 receptor agonists and thyroid cancer have conflicting results and important limitations.[60,65,69–73]

- One prospective[70] and one retrospective cohort study[60] using data from US databases and one retrospective cohort study using nationwide register data from Sweden, Denmark, and Norway[65] did not find an increased risk of thyroid cancer associated with GLP-1 receptor agonist use compared to other antihyperglycemic agents.
- A nested case-control study using a French database found an increased risk of thyroid cancer in individuals with T2DM using a GLP-1 receptor agonist compared to individuals with T2DM using other second-line antihyperglycemic agents.[71]
    - 2,562 cases (new thyroid cancer) were matched to 45,184 controls.
    - *Results:*
        - All thyroid cancer: adjusted HR = 1.46 (95% CI, 1.23 to 1.74)
        - MTC: adjusted HR = 1.76 (95% CI, 1.16 to 2.69)
        - Absolute risk increases were not reported, so it is difficult to interpret these results given the rarity of MTC.
    - Results should be interpreted with caution due to several significant limitations to the study, including the potential risk of confounding. Unlike the US and Scandinavian cohort studies[60,65,70], this study did not adjust for body weight as a potential confounder.[71]
- A retrospective cohort study using data from a US database found an increased risk of thyroid cancer in patients with T2DM receiving a GLP-1 receptor agonist compared to metformin for *up to* 5 years of follow-up (*mean follow-up time not reported*).[72]
    - Adjusted OR = 1.65 (95% CI, 1.31 to 2.05)
    - Of the 64,230 GLP-1 receptor agonist users about half were receiving liraglutide and none were receiving semaglutide. When individual drugs were evaluated, there was no statistically significant increased risk of thyroid cancer associated with liraglutide use.
        - It has been suggested that the potential associations between GLP-1 receptor agonists and cancer may be drug-dependent and not a feature of the entire class.[74]
- The mean duration of follow-up across observational studies was short (e.g., 17 months and 3.9 years) or was not clearly reported.[60,65,69–72] Longer-term studies are required to evaluate risk of thyroid cancer.

➢ In 2023, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) investigated the potential risk of thyroid cancer associated with GLP-1 receptor agonists. They concluded that the available evidence does not support a causal association, and no updates to the product monograph were warranted at the time.[65,75]

Suicidality and Self Harm:

- Reports of suicidal thoughts and self-harm behavior have recently been reported in people using liraglutide and semaglutide. This has caused concern about a potential association between GLP-1 receptor agonists and an increased risk of suicidality and self-harm.[45]
- The **STEP** and **SCALE** clinical trial program RCTs were not designed to evaluate the risk of suicide, suicidal ideation, or self-harm.[19,27,45,76]
    - Suicide, suicidal ideation, and self-harm were not prespecified study end points, and this could have resulted in incomplete reporting of these events. [19,27,45,76]
    - The trials would have been underpowered to evaluate these rare events. [19,27,45]
    - The trials excluded people with a history of major depressive disorder within 2 years or history of other severe psychiatric disorder or history of suicide attempt.[19,27,45,76]
        - This excludes a potentially higher-risk population.
        - Evidence evaluating the effect of GLP-1 receptor agonists in people living with psychiatric conditions is limited to small, short-term trials.[76]
- A 2024 MA of RCTs evaluated the effects of GLP-1 receptor agonists on the incidence of psychiatric disorders and the risk of suicidal behaviour.[76]
    - The RCTs included in the MA were at least 52 weeks long and evaluated GLP-1 receptor agonists versus control (placebo or active comparator) in adults for any indication (T2DM or obesity). [76]
    - *Results:*
        - 31 RCTs, N = 84,713 patients.[76]
            - 9 RCTs evaluated GLP-1 receptor agonists in obesity care.[76]
        - There was no statistically significant difference in the incidence of any psychiatric disorder or suicidal behaviour between the GLP-1 receptor agonist and control groups.[76]
            - Any psychiatric disorder: OR = 0.97 (95% CI, 0.83 to 1.15) [31 studies]
            - Suicidal behaviour: OR = 0.86 (95% CI, 0.47 to 1.56) [11 studies]
    - Given the limitations of the available RCTs to evaluate risk of suicide, suicidal ideation, and self-harm, as described above, the results of this MA must be interpreted with caution.
- At the request of Health Canada, the Canadian Network for Observational Drug Effect Studies (CNODES) completed a critical appraisal of available real-world evidence to evaluate the association between GLP-1 receptor agonists and the risk of suicidality and self-harm among patients living with *obesity or T2DM*.[45]
    - Two relevant comparative observational studies were identified: Gamble et al. (2018) and Wang et al. (2024).[45]

- Gamble et al. completed a retrospective cohort study in patients with T2DM using a primary care database in the United Kingdom (UK).[45,77]
    - The cohort included 501 patients exposed to a GLP-1 receptor agonist and 16,409 patients exposed to a SU.
    - Mean duration of follow-up = ~1 year.
    - Patients were excluded from the cohort if they had a history of depression, self-harm, anxiety, or other serious psychiatric condition in the previous year.
    - 94% of patients exposed to a GLP-1 receptor agonist had a BMI ≥ 30 kg/m^2.
    - Primary outcome: composite of new-onset depression or self-harm (including suicide and suicidal ideation).
    - *Results:* There was no statistically significant association between GLP-1 receptor agonist use and risk of depression or self-harm when compared to SU use.
        - Primary outcome: GLP-1 receptor agonists vs SU
            - HR = 1.25 (95% CI, 0.63 to 2.50)
            - The confidence interval is wide, suggesting imprecision in the results.
- Wang et al. completed a retrospective cohort study using a US health records database.[45]
    - Two cohorts were studied.
        - Cohort 1: 105,566 patients with overweight or obesity prescribed semaglutide or a non-GLP-1 receptor agonist weight loss drug.
        - Cohort 2: 55,542 patients with T2DM who were prescribed semaglutide or a non-GLP-1 receptor agonist antihyperglycemic agent.
    - Mean duration of follow-up = ~5-6 months
    - Study outcome: Suicidal ideation
    - *Results:* In Cohort 1 and Cohort 2, GLP-1 receptor agonists were associated with a *decreased* risk of suicidal ideation compared to comparator drugs.
- There are *many* limitations to these studies, including:
    - Short follow-up time (Gamble and Wang)
    - Small sample size of GLP-1 receptor agonist users (Gamble)
    - Patients who may be at the highest risk of the outcome were excluded (Gamble)
    - Potential inappropriate comparator drugs, potential for confounding (Wang)
    - Potential for selection bias and outcome misclassification (Wang)

- The CNODES report concluded that there is limited evidence to demonstrate whether or not there is a link between the use of GLP-1 receptor agonists for obesity or T2DM and the risk of suicidality and self-harm.

➢ Since the publication of the CNODES critical appraisal, additional observational studies evaluating the potential risk of suicidal ideation or behaviors associated with GLP-1 receptor agonists have been published.[78,79] The identified studies were designed to evaluate patients prescribed GLP-1 receptor agonists for T2DM, *not obesity care*. [78,79]

- One of the observational studies did not report baseline BMI or rates of comorbid obesity[78], and in the other study only ~30% of participants had comorbid obesity.[79]
    - This may limit the generalizability of the results of these studies to obesity care.

➢ Government Agency Safety Reviews:

- Health Canada and the FDA are currently conducting safety reviews to investigate the risk of suicidality and self-harm associated with GLP-1 receptor agonist use.[45,80]
- The EMA has completed a safety review.
    - The EMA's Pharmacovigilance Risk Assessment Committee concluded that current evidence is insufficient evidence to establish a causal relationship between suicidal ideation and GLP-1 receptor agonists and that no updates to the product information are warranted at this time.[81]

➢ The Wegovy (semaglutide) and Saxenda (liraglutide) product monographs recommend to:

- Monitor patients for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.[6,7]
- Discontinue therapy in patients who experience suicidal thoughts or behaviors.[6,7]
- **Avoid** using these drugs in patients with a history of suicidal attempts or active suicidal ideation. [6,7]

Diabetic Retinopathy:

➢ The Wegovy (semaglutide) product monograph states that "retinal disorders, including diabetic retinopathy, have been reported in Wegovy treated patients. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. The effect of long-term glycemic control with semaglutide on diabetic retinopathy complications has not been studied. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy."[6]

➢ The Saxenda (liraglutide) product monograph does not mention diabetic retinopathy.[7]

➢ It is difficult to draw any conclusions regarding event rates of diabetic retinopathy or worsening diabetic retinopathy from the GLP-1 receptor agonist obesity trials.

- The **STEP-2** and **SCALE Diabetes** trials were not designed or powered to evaluate diabetic retinopathy, and some patients with diabetic retinopathy would have been excluded from the trials (see page 17).[20,28]

- Diabetic retinopathy was a "safety area of interest" adverse event in **STEP-2**.[20]
    - Diabetic retinopathy was recorded in 4% of participants in the semaglutide 2.4 mg arm, and 2.7% of participants in the placebo arm.
- Diabetic retinopathy was not recorded in **SCALE Diabetes.** [28]

- No observational studies were identified in the evidence review that specifically evaluated a potential association between diabetic retinopathy and GLP-1 receptor agonists in *obesity care*.
- Previous studies of people with T2DM and people undergoing bariatric surgery have suggested that early and rapid glucose lowering may result in an initial increase in diabetic retinopathy yet prevent or delay the development of this complication over longer periods of time.[57]
- A review of evidence evaluating the risk of diabetic retinopathy with GLP-1 receptor agonists in the management of T2DM was reported in the 2023 Dalhousie Academic Detailing Service Topic, https://medicine.dal.ca/departments/core-units/cpd/programs/academic-detailing-service/AC-Service-Resources.html.[57]
- The **FOCUS** trial, which is expected to be completed in 2027, is evaluating the effects of semaglutide compared to placebo on diabetic eye disease in people living with T2DM.[82]
    - Results may be helpful to further evaluate this relationship.

Nonarteritic Anterior Ischemic Optic Neuropathy (NAION):

- NAION is a relatively rare event with an incidence of 2-10 cases per 100 000 persons. It is the second most common form of optic neuropathy and remains a significant cause of blindness among adults. The pathogenesis of NAION remains unknown.[83]
- A recently published observational study by Hathaway et al reported on a potential association between GLP-1 receptor agonist exposure and the development of NAION in both people living with T2DM or obesity or overweight.[83]
    - The study included a cohort of people from a single site Neuro-ophthalmology subspecialty clinic in Boston, MA, from December 2017 to November 2023.
        - There was a higher risk of NAION [HR 4.28 (95% CI, 1.62 to 11.29)] observed in people with T2DM receiving a GLP-1 receptor agonist vs other antihyperglycemics.
        - There was a higher risk of NAION [HR 7.64 (95% CI, 2.21 to 26.36)] observed in people with obesity or overweight receiving a GLP-1R receptor agonist vs other medications for weight loss.
            - The confidence intervals are wide, suggesting imprecision in the results.
    - Strengths of the study:
        - All diagnoses of NAION were made by experienced neuro-ophthalmologists and then manually reviewed by the study authors.

- Propensity score matching was used to address potential confounders such as sex, age, systemic hypertension, T2DM, OSA, obesity, hyperlipidemia and coronary artery disease.

- There are several limitations to this study. In particular, the study was conducted in a single site subspecialty clinic, thus limiting the generalizability of the findings to a broader population.

Alopecia:

- Alopecia is listed as a potential adverse effect in the Wegovy (semaglutide) product monograph.[6]
  - Across the **STEP 1-3** trials, 3.3% of semaglutide participants and 1.4% of placebo participants reported hair loss.[6]
  - Alopecia was reported more frequently in semaglutide treated adults who lost ≥ 20% of initial body weight compared to those who lost < 20% of initial body weight (5.3% vs 2.5%).[6]
- Several cases of alopecia in individuals using semaglutide have been reported to Health Canada's Canada Vigilance Program.[63]
- Alopecia is not mentioned in the Saxenda (liraglutide) product monograph.[7]
- RCTs were not specifically designed to evaluate this adverse event.[19,27]
- Given the lack of available evidence, further investigation exploring this potential association is required.
- The FDA is currently conducting a safety review to investigate the risk of alopecia associated with GLP-1 receptor agonist use.[84]

Table 23. Select Potential GLP-1 Receptor Agonist Adverse Events

Confirmed	Probably Associated	Uncertain or Unknown Association
• Nausea *(common)* • Vomiting *(common)* • Diarrhea *(common)* • Constipation *(common)* • Gallbladder-related disorders *(rare; people who experience a greater degree of weight loss may be at higher risk)*	• AKI *(volume depletion from GI AEs may ↑ risk of AKI)* • Hypoglycemia *(concomitant SU or insulin therapy may ↑ risk of hypoglycemia - consider dose adjustments*)*	• Acute pancreatitis • Alopecia • Aspiration risk during anesthesia • Breast cancer *(may improve detection)* • Diabetic retinopathy • Gastroparesis • Intestinal obstruction • Nonarteritic anterior ischemic optic neuropathy • Pancreatic cancer • Suicidality and self-harm • Thyroid cancer**

AEs = adverse events, AKI = acute kidney injury, GI = gastrointestinal, SU = sulfonylurea
*Recommended dose adjustments in RCTs (page 18): ↓ SU dose by 50%, ↓ basal insulin by 15-20% if HbA1c ≤ 8% at baseline
**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.

Naltrexone/bupropion

- Data from product monographs and RCTs are reported in this section.

Note: Contrave (bupropion/naltrexone) should not be administered with a high-fat meal, due to a significant increase in systemic drug exposure and increased risk of AEs.[8]

Common Adverse Events

- The most commonly reported AEs that occurred more frequently with naltrexone/bupropion compared to placebo ($p<0.05$) were: nausea (30%), constipation (16%), headache (14%), vomiting (10%), dizziness (9%), dry mouth (8%), and hot flush (5%).[8,30]
    - Nausea was generally mild-to-moderate in intensity, transient (usually first reported during dose titration), and did not result in discontinuation in most participants.[30]

Discontinuation Due to Adverse Events

- In the **COR-1** trial, significantly more participants in the naltrexone/bupropion 16 mg/180 mg BID group discontinued therapy due to an AE compared to placebo.[30]
    - AEs leading to discontinuation:
        - Naltrexone/bupropion vs placebo: 20% vs. 10% ($p < 0.05$)
    - The most frequently reported AE leading to discontinuation was nausea (6%).

Serious Adverse Events

- In the **COR-1** trial, there were similar rates of serious AEs in the naltrexone/bupropion 16 mg/180 mg BID (1.6%) and placebo (1.4%) groups.[30]
    - Serious adverse events were defined the same as reported above on page 38.

Opioid Antagonist Related Effects

- Naltrexone is a pure opioid antagonist.[8]
- Naltrexone/bupropion is **contraindicated** in people "with chronic opioid or opiate agonist (e.g., methadone) or partial agonist (e.g., buprenorphine) use, or acute opiate withdrawal."[8]
- To prevent a precipitated opioid withdrawal or an exacerbation of pre-existing subclinical withdrawal symptoms, people should be opioid-free before starting naltrexone/bupropion treatment.[8]
    - The product monograph recommends an opioid-free interval of a minimum of 7 to 10 days for patients previously dependent on short-acting opioids, and those patients transitioning from buprenorphine or methadone may need as long as two weeks.[8]
- The Contrave product monograph recommends that in people requiring intermittent opiate treatment, naltrexone/bupropion therapy should be temporarily discontinued, and lower doses of opioids may be needed.[8]
    - Patients should be alerted that they may be more sensitive to opioids, even at lower doses, after naltrexone/bupropion treatment is discontinued.[8]

- Inform patients that attempts to overcome any naltrexone opioid blockade by administering large amounts of opioids may lead to overdose.[8]
- Patients who require opioids should be monitored closely in a hospital setting.[85]
- Patients should be advised to inform other health care providers if they are taking naltrexone.[85]

Seizures

- Naltrexone/bupropion is **contraindicated** in individuals: [8]
    - with a seizure disorder or history of seizures.
    - with a current or prior diagnosis of bulimia or anorexia nervosa, because of a higher incidence of seizures noted in patients treated for bulimia with the immediate release formulation of bupropion.
    - using other bupropion hydrochloride-containing products, because the incidence of seizure is dose dependent.
    - undergoing an abrupt discontinuation of alcohol, benzodiazepines or other sedatives, and antiepileptic drugs.
- An individual's risk of seizure should be considered before selecting therapy.[8]
    - Consider individual patient risk factors for seizure (e.g., history of head trauma, central nervous system tumor or infection, metabolic disorders, concomitant medications that lower the seizure threshold, etc.) and use caution if prescribing naltrexone/bupropion to individuals with risk factors.[8]
- To reduce the risk of seizures, the Contrave product monograph recommends adhering to dosing recommendations, including the following: [8]
    - The total daily dose does not exceed 360 mg of the bupropion component
    - The daily dose is administered in divided doses (twice daily)
    - The dose is escalated gradually
    - No more than two tablets are taken at one time
    - Co-administration of Contrave with high-fat meals should be avoided
    - If a dose is missed, a patient should wait until the next scheduled dose to resume the regular dosing schedule

Mental Health

- As with other bupropion-containing products, the Contrave product monograph has a serious warning and precautions box, warning prescribers of an “increased risk of self-harm, harm to others, suicidal thinking and behaviour with antidepressant use.” [8]
    - The product monograph recommends to “closely monitor all patients for emergence of depression, agitation-type and/or suicidal thoughts and behaviours”.[8]

- Individuals with a history of serious psychiatric illness were excluded from the **COR-1** and **COR-DM** RCTs.[30,31]

Cardiovascular

- The long-term CV safety of naltrexone/bupropion has not been established.
    - A 2016 CV outcome RCT was terminated early due to public release of confidential interim data by the study sponsor.[86]
    - A new CV outcome trial (**INFORMUS**) is currently underway, but is not expected to be completed until 2029.[41]
- People living with CV disease were excluded from the **COR-1** and **COR-DM** trials.[30,31]
- Blood pressure and pulse should be monitored prior to starting therapy, and should be monitored at regular intervals.[8]
    - In **COR-1** (see page 14 for details) a *transient increase* in mean systolic blood pressure (SBP) and diastolic blood pressure was observed in the naltrexone/bupropion groups during the first 8 weeks of therapy. Blood pressure returned to baseline after week 12, then decreased below baseline for the rest of the study.[30]
    - The product monograph recommends that if patients experience clinically relevant and sustained increases in blood pressure or heart rate, therapy should be discontinued.[8]
- Naltrexone/bupropion is **contraindicated** in patients with uncontrolled hypertension, and it is recommended to use with caution in patients with controlled hypertension.[8]

Hepatic

- Hepatitis and clinically significant liver dysfunction have been observed with naltrexone exposure.[8]
- Patients should be advised of the symptoms of acute hepatitis (e.g., fatigue, anorexia, nausea, and vomiting) and to seek medical attention and stop treatment if symptoms appear.[8,85]
- Contrave is **contraindicated** in severe hepatic impairment, and dose adjustments are recommended for patients with mild or moderate hepatic impairment (see Appendix 1).[8]

Cutaneous lupus erythematosus (CLE)/Systemic lupus erythematosus (SLE)

- According to the product monograph, naltrexone/bupropion use has been associated with the development of CLE (which has resolved following withdrawal of medication), and exacerbation of SLE.[8]
    - Symptoms including arthralgia, myalgia, rash, swelling and positive autoantibodies have been observed.[8]
    - If individuals experience these AEs, therapy should be discontinued, and the patient should be carefully evaluated for appropriate clinical management.[8]

Orlistat

- Data from product monographs, guidelines, and evidence synthesis resources are reported in this section.

Common Adverse Events

- The most commonly reported AEs are GI related and include:[9]
    - Oily spotting (26%), flatus with discharge (24%), fecal urgency (22%), oily stool (20%), and increase defecation (11%).[9]
        - The incidence of these GI AEs is related to the amount of dietary fat ingested. Patients should be advised that a low-fat diet will decrease the likelihood of experiencing GI AEs.[9]

Discontinuation of Therapy

- In general, most individuals do not continue orlistat long-term. Persistence rates with orlistat therapy at 6 months, 1 year, and 2 years, was 18%, 6%, and 2%, respectively.[15]

Absorption of fat-soluble vitamins

- Orlistat can reduce the absorption of some fat-soluble vitamins and beta-carotene.[9]
    - Patients should be advised to take a multivitamin supplement that contains fat-soluble vitamins.[9] The supplement should be taken at least two hours before or after the administration of orlistat.[9,15]

Liver Injury

- Severe liver injury and acute liver failure have been rarely reported with orlistat.[9]
    - Patients should be advised to report any symptoms of hepatic dysfunction (anorexia, itching, jaundice, dark urine, pale stools, or right upper quadrant pain) while taking orlistat, and the drug should be discontinued immediately and the patient should be evaluated for liver injury. [9,34]
- Orlistat is **contraindicated** in individuals with cholestasis.[9]

Renal Calculi and Oxalate-induced AKI

- Cases of hyperoxaluria and oxalate nephropathy with renal failure have been reported. [9]
    - Orlistat-induced fat malabsorption may cause an increase in intestinal oxalate absorption and urinary oxalate excretion. Free oxalate can be deposited in the kidney parenchyma, resulting in AKI. [9,34]

What is the place in therapy of pharmacotherapy in obesity care?

- The Canadian Adult Obesity Clinical Practice Guidelines from Obesity Canada suggest that pharmacotherapy in obesity care should be considered when healthy eating and physical activity alone have been ineffective, insufficient or without sustained benefit.[15]
- The Canadian Adult Obesity Clinical Practice Guidelines recommend:
  - "Pharmacotherapy for obesity management can be used for individuals with BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 with adiposity-related complications, in conjunction with medical nutrition therapy, physical activity and/or psychological interventions (semaglutide 2.4 mg weekly [Level 1a Grade A], liraglutide 3.0 mg daily [Level 2a, grade B], naltrexone/ bupropion 16 mg/180 mg BID [Level 2a, Grade B], orlistat 120 mg TID [Level 2a, Grade B])."[15]
    - Level 1a = Evidence from meta-analysis of RCTs
    - Level 2a = Evidence from at least 1 controlled study without randomization
    - Grade A = Directly based on level 1 evidence
    - Grade B = Directly based on level 2 evidence or extrapolated recommendation from category 1 evidence
- The Canadian Adult Obesity Clinical Practice Guidelines note that "obesity medications are intended as part of a long-term treatment strategy".[15]
- International guidelines also provide recommendations for pharmacotherapy in obesity care.
  - American Gastroenterological Association (AGA) 2022 Clinical Practice Guidelines:[87]
    - "In adults with obesity or overweight with weight-related complications, who have had an inadequate response to lifestyle interventions, the AGA recommends adding pharmacological agents to lifestyle interventions over continuing lifestyle interventions alone." (strength of recommendation, strong; quality of evidence, moderate)[87]
    - The AGA provide individual recommendations for use of pharmacological agents including, semaglutide, liraglutide, and naltrexone/bupropion, however, they suggest against the use of orlistat in most patients due to the small magnitude of benefit and high rate of discontinuation due to AEs.[87]
    - See guidelines for full recommendations: https://www.gastrojournal.org/article/S0016-5085(22)01026-5/fulltext.
  - National Institute for Health and Care Excellence (NICE) 2023 Clinical Guideline:[88,89]
    - "Consider pharmacological treatment [liraglutide, orlistat, and semaglutide] only after dietary, exercise and behavioural approaches have been started and evaluated. NICE has not recommended naltrexone/bupropion."[88]
    - NICE provide individual recommendations for each of the drugs. [88]
    - See guidelines for full recommendations and rationale:

- Obesity: identification, assessment and management:[88] https://www.nice.org.uk/guidance/cg189/resources/obesity-identification-assessment-and-management-pdf-35109821097925
- Naltrexone–bupropion for managing overweight and obesity:[89] https://www.nice.org.uk/guidance/ta494

Academic Detailing Comments: Place in Therapy

- Pharmacotherapy recommendations from the Canadian Adult Obesity Clinical Practice Guidelines and the Health Canada approved indications for semaglutide, liraglutide, and naltrexone/bupropion are reflective of the inclusion criteria of the pivotal trials for each of these drugs (see pages 14 to 23).[6–8,15,19,27,30]
  - In general, RCTs included adults with a BMI ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 with weight-related co-morbidities.[19,27,30]
  - Guideline recommendations for initiating pharmacotherapy using a BMI cutoff alone (i.e., BMI ≥ 30 kg/m^2 could potentially include some individuals who do not have abnormal or excess body fat (adiposity) impairing health.[15]
    - This is important to consider in practice, as the current understanding of obesity as a chronic disease requires more than the recognition of abnormal or excessive body fat, but whether abnormal or excessive body fat is impairing health (see "Screening and Assessing Obesity" page 9).[1]
- Metabolically healthy obesity
  - The association between obesity and cardiometabolic and other obesity-related complications is strong but may not be present for all individuals.[1]
  - Several studies have identified a subgroup of individuals with obesity who remain free of cardiometabolic health consequences, a phenomenon that has been described as metabolically healthy obesity (MHO).[12]
  - The reported prevalence of MHO varies amongst studies due to differences in age, ethnicity, environmental factors and a lack of standardized definition of metabolic health.[12]
  - Some studies with long-term follow up have reported that MHO may be a temporary or transition state, thus underscoring the importance of re-evaluation of risk factors and health implications over time.[12]
  - Canadian Guidelines suggest that individuals with MHO may not be "fully medically healthy", as these patients are more likely to suffer other non-metabolic conditions associated with obesity such as sleep apnea, depression and joint/back pain which should also be considered when assessing individuals for obesity.[1]

Pharmacotherapy in the Pipeline

- Several medications are in the pipeline for obesity care, including oral semaglutide and tirzepatide injection.
    - Tirzepatide is a glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist.[90] GIP regulates energy balance through mechanisms in the brain and adipose tissue.[91]
- Oral semaglutide and tirzepatide injection do **not** have Health Canada approved indications for weight management or obesity care. [90,92]
    - They have been evaluated in recent RCTs for use in people living with obesity.[91,93]
    - A brief summary of the main weight loss trials for each of these drugs is provided below.

How much weight loss would be expected with oral semaglutide in people living with obesity?

Table 24. Summary of OASIS 1 [93]

<table>
<tr><th colspan="2">OASIS 1[93]</th></tr>
<tr><td>Design</td><td>Multicenter, double-blinded, placebo-controlled RCT (N = 667)</td></tr>
<tr><td>Patients</td><td>Inclusion Criteria: Adults with a BMI of ≥ 30 kg/m², or ≥ 27 kg/m² with ≥ 1 bodyweight-related complication or comorbidity (hypertension, dyslipidemia, OSA, or CV disease), and with at least one unsuccessful dietary effort to lose weight, and no history of DM.
Baseline Characteristics: Mean age 50 years, 73% female, 74% white, mean body weight 105 kg, mean BMI 38 kg/m^2, 92% had BMI ≥ 30 kg/m^2</td></tr>
<tr><td>Intervention</td><td>Semaglutide 50 mg orally once daily (dose titrated over 16 weeks) + lifestyle counseling*
Note: The formulation of oral semaglutide used in OASIS was designed to enhance the bioavailability of semaglutide, and it is not currently available in Canada.</td></tr>
<tr><td>Comparator</td><td>Placebo orally once daily + lifestyle counseling*</td></tr>
<tr><td>Outcomes</td><td>Coprimary outcomes: % change in body weight and loss of ≥ 5% body weight</td></tr>
<tr><td>Tx Duration</td><td>68 weeks</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th></th><th>Oral Semaglutide 50 mg daily (n = 334)</th><th>Placebo (n = 333)</th><th>Absolute Difference or Odds Ratios (OR) Semaglutide vs. Placebo (95% CI)</th><th>p-value</th></tr>
<tr><th></th><th colspan="2">68 weeks</th><th></th><th></th></tr>
<tr><td colspan="5">Primary Outcomes</td></tr>
<tr><td>Mean % change in body weight</td><td>-15.1 %</td><td>-2.4%</td><td>-12.7% (-14.2 to -11.3)</td><td><0.0001</td></tr>
<tr><td>Loss of ≥ 5% body weight (% of participants)</td><td>85%</td><td>26%</td><td>OR = 12.6 (8.5 to 18.7)</td><td><0.0001</td></tr>
<tr><td colspan="5">Select Secondary Outcomes</td></tr>
<tr><td>Loss of ≥ 10% body weight (% of participants)</td><td>69%</td><td>12%</td><td>OR = 14.7 (9.6 to 22.6)</td><td><0.0001</td></tr>
<tr><td>Loss of ≥ 15% body weight (% of participants)</td><td>54%</td><td>6%</td><td>OR = 17.9 (10.4 to 30.7)</td><td><0.0001</td></tr>
<tr><td>Loss of ≥ 20% body weight (% of participants)</td><td>34%</td><td>3%</td><td>OR = 18.5 (8.8 to 38.9)</td><td><0.0001</td></tr>
</table>
</td></tr>
</table>

Adverse Events:

	Oral Semaglutide 50 mg	Placebo
Any AE	92%	86%
Serious AE	10%	9%
AE leading to tx discontinuation	6%	4%
Some common AE		
Nausea	52%	15%
Constipation	28%	15%
Diarrhea	27%	17%
Vomiting	24%	4%

AE = adverse event, BMI = body mass index (kg/m^2), CI = confidence interval, CV = cardiovascular, DM = diabetes mellitus, n = sample size, OR = odds ratio, OSA = obstructive sleep apnea, RCT = randomized controlled trial, Tx = treatment. * lifestyle counseling to support a reduced-calorie diet (500 kcal deficit/day) and increased physical activity (150 minutes/week)

How much weight loss would be expected with tirzepatide injection in people living with obesity?

Table 25. Summary of SURMOUNT-1 [91]

SURMOUNT-1[91]		
Design	Multicenter, double-blinded, placebo-controlled RCT (N = 2539)	
Patients	*Inclusion Criteria:* Adults with a BMI ≥ 30 kg/m^2, or ≥ 27 kg/m^2 and ≥ 1 weight-related complication (e.g., hypertension, dyslipidemia, OSA, or CV disease), and who reported one or more unsuccessful dietary effort to lose weight, and no history of DM. *Baseline Characteristics:* Mean age 45 years, 68% female, 71% white, mean body weight 105 kg, mean BMI 38 kg/m^2, 95% had BMI ≥ 30 kg/m^2	
Intervention Groups	Tirzepatide 5 mg subcutaneously once weekly (dose titrated over 4 weeks)	+ lifestyle intervention*
	Tirzepatide 10 mg subcutaneously once weekly (dose titrated over 12 weeks)	
	Tirzepatide 15 mg subcutaneously once weekly (dose titrated over 20 weeks)	
Comparator	Placebo subcutaneously once weekly + lifestyle intervention*	
Outcomes	Coprimary outcomes: % change in body weight and loss of ≥ 5% body weight	
Tx Duration	72 weeks	

Results

	Tirzepatide 5 mg# (n = 630)	Tirzepatide 10 mg (n = 636)	Tirzepatide 15 mg (n = 630)	Placebo (n = 643)
	72 weeks			
*Primary Outcomes**				
Mean % change in body weight [% (95% CI)]	-15% (-15.9 to -14.2)	-19.5% (-20.4 to -18.5)	-20.9% (-21.8 to -19.9)	-3.1% (-4.3 to -1.9)
Loss of ≥ 5% body weight (% of participants)	85%	89%	91%	35%
*Select Key Secondary Outcomes**				
Loss of ≥ 10% body weight (% of participants)	69%	78%	84%	19%
Loss of ≥ 15% body weight (% of participants)	48%	67%	71%	9%
Loss of ≥ 20% body weight (% of participants)	30%	50%	57%	3%

* The outcomes reported in this table for comparisons of tirzepatide 5 mg, 10 mg, or 15 mg to placebo were significant at p<0.001. #tirzepatide 5 mg results were analyzed as key secondary outcomes.

Adverse Events:

	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo
Any AE	81%	82%	79%	72%
Serious AE	6%	7%	5%	7%
AE leading to tx discontinuation	4.3%	7.1%	6.2%	2.6%
Some common AE				
Nausea	25%	33%	31%	10%
Diarrhea	19%	21%	23%	7%
Constipation	17%	17%	12%	6%
Vomiting	8%	11%	12%	2%

AE = adverse event, BMI = body mass index (kg/m2), CI = confidence interval, CV = cardiovascular, DM = diabetes mellitus, n = sample size, OSA = obstructive sleep apnea, RCT = randomized controlled trial, Tx = treatment. * lifestyle intervention included lifestyle counseling to support a 500 kcal deficit/day diet and ≥ 150 minutes/week of physical activity.

- Tirzepatide has also been evaluated in people living with obesity and T2DM in the **SURMOUNT-2** trial.[94]
  - In addition to other inclusion criteria, participants in **SURMOUNT-2** had to have T2DM with a baseline HbA1c of 7-10% and on stable T2DM therapy of diet and exercise alone or oral antihyperglycemic agents.
  - Although indirect comparisons, the mean % change in body weight was numerically less in **SURMOUNT-2** (obesity and T2DM) compared to **SURMOUNT-1** (obesity without T2DM).
    - This is similar to trends observed for semaglutide and liraglutide (pages 14-16),
    - ***SURMOUNT-2*** *Results:* Mean % change in body weight: absolute difference
      - Tirzepatide 10 mg vs. placebo = -9.6% (95% CI, -11.1 to -8.1), p<0·0001
      - Tirzepatide 15 mg vs. placebo = -11.6% (95% CI, -13.0 to -10.1); p<0.001
- Tirzepatide is currently being evaluated in a CV outcome trial, **SURMOUNT-MMO** [95]
  - The trial is enrolling adults ≥ 40 years of age with a BMI ≥ 27 kg/m^2 and established CV disease, similar to the SELECT trial. The trial is anticipated to be completed in 2027.[95]

LOCAL CLINICAL RESOURCES

- HealthyNS: https://library.nshealth.ca/HealthyLiving/Home
  - Free online group health and wellness programs for residents of Nova Scotia. Topic areas include Self-Management, Reducing Your Health Risks, Healthy Eating, Physical Activity, and Mental Wellness.
  - Free online one-on-one coaching offered for physical activity, and health goals.
- Community Health Teams: https://www.nshealth.ca/clinics-programs-and-services/community-health-teams or (902) 460-4560
  - Free in-person (greater Halifax area) and online group health and wellness programs for residents of Nova Scotia and the greater Halifax area (see program descriptions for regional availability). Topic areas include Healthy Eating, Mental Wellness, Physical Activity, and Managing Risk Factors.
- Hants Health and Wellness Team: https://www.nshealth.ca/clinics-programs-and-services/hants-health-and-wellness-team
  - Free in-person group health and wellness programs in West Hants. Topic areas include physical activity, chronic disease management, and nutrition education.
- Northern Zone Mobile Health and Wellness Team: https://www.nshealth.ca/clinics-programs-and-services/northern-zone-mobile-health-and-wellness-team-0
  - Provide teaching and support for healthy living. Topics include healthy eating, and physical activity.
- Obesity Care Clinic (Eastern Zone): https://www.nshealth.ca/clinics-programs-and-services/obesity-care-clinic-eastern-zone
- Valley Metabolic Health: https://www.valleymetabolichealth.com/
- Halifax Obesity Network: https://www.cdha.nshealth.ca/obesity-network
- Nova Scotia Health Dietitians: https://www.nshealth.ca/clinics-programs-and-services/nutrition-education-and-counselling-dietitians
- Nova Scotia Dietitians: https://www.dietitiansnovascotia.com/fulldietitiandirectory

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Appendix 1*: Drug Tables*

<table>
<tr><th></th><th colspan="2">Semaglutide (Wegovy)</th><th colspan="2">Liraglutide (Saxenda)</th></tr>
<tr><td>Mechanism of Action</td><td colspan="4">GLP-1 receptor agonists (semaglutide and liraglutide) stimulate receptors in multiple areas of the body, including the brain and pancreas. Semaglutide and liraglutide act in the brain to improve satiation and satiety and reduce appetite. They also regulate insulin and glucagon secretion and may delay gastric emptying.</td></tr>
<tr><td>Adult Health Canada Approved Indications</td><td colspan="4">Adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adults with BMI of:
• 30 kg/m^2 or greater (obesity) or
• 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity
• and who have failed a previous weight management intervention – liraglutide only</td></tr>
<tr><td>Route</td><td colspan="4">Subcutaneous Injection</td></tr>
<tr><td>Marketed Products</td><td colspan="2">Five different pre-filled, fixed-dose, multi-use pens
• 0.25 mg dose pen [1 mg/pen (0.68 mg/mL)]
• 0.5 mg dose pen [2 mg/pen (1.34 mg/mL)]
• 1 mg dose pen [4 mg/pen (1.34 mg/mL)]
• 1.7 mg dose pen [6.8 mg/pen (2.27 mg/mL)]
• 2.4 mg dose pen [9.6 mg/pen (3.2 mg/mL)]</td><td colspan="2">A pre-filled, multi-dose pen (6 mg/mL, 3 mL pen)
• The pen delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg.</td></tr>
<tr><td>Usual Adult Dose</td><td colspan="2">Usual Dose Titration:
The following doses are administered once weekly
<table><tr><th>Week 1-4</th><th>Week 5-8</th><th>Week 9-12</th><th>Week 13-16</th><th>Week 17 - onward</th></tr><tr><td>0.25 mg</td><td>0.5 mg</td><td>1 mg</td><td>1.7 mg</td><td>2.4 mg</td></tr></table>Usual Maintenance Dose: 2.4 mg once weekly</td><td colspan="2">Usual Dose Titration:
The following doses are administered once daily
<table><tr><th>Week 1</th><th>Week 2</th><th>Week 3</th><th>Week 4</th><th>Week 5 - onward</th></tr><tr><td>0.6 mg</td><td>1.2 mg</td><td>1.8 mg</td><td>2.4 mg</td><td>3.0 mg</td></tr></table>Usual Maintenance Dose: 3.0 mg once daily</td></tr>
<tr><td>Common Adverse Events</td><td colspan="4">Nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue</td></tr>
<tr><td>Drug Interactions
(Not an exhaustive list)</td><td colspan="4">• GLP-1 receptor agonists should not be used in combination with another GLP-1 receptor agonist.
• Oral drugs: GLP-1 receptor agonists may delay gastric emptying and could potentially influence the absorption of concomitantly administered oral drugs.
○ Use caution and monitor with use of narrow therapeutic index drugs (e.g., digoxin, warfarin, levothyroxine…)
• Other drugs that ↑ heart rate: use caution.
• Other drugs that cause PR interval prolongation (e.g., calcium channel blockers, beta-adrenergic blockers, digoxin, and HIV protease inhibitors): use caution.
• Glucose lowering drugs: consider reducing the dose of concomitantly administered insulin or sulfonylureas.
○ Saxenda (liraglutide) product monograph states that “Saxenda and insulin should not be used together”.</td></tr>
<tr><td>Contraindications</td><td colspan="4">• Hypersensitivity to the drug or to any ingredient in the formulation.
• Personal or family history of Medullary Thyroid Cancer or Multiple Endocrine Neoplasia syndrome type 2.
• Pregnancy or breast-feeding</td></tr>
<tr><td>Precautions
(Not an exhaustive list)</td><td colspan="2"><u>Renal impairment:</u>
• Use not recommended in people with ESRD

<u>Hepatic insufficiency</u>:
• Use not recommended (liraglutiude)
• Use with caution (semaglutide)</td><td>• Breast cancer
• ↑ heart rate & PR interval prolongation
• Heart Failure (NYHA Class IV for semaglutide; NYHA Class III-IV for liraglutide)
• Hypoglycemia
• Acute kidney injury</td><td>• Delayed gastric emptying
• Acute pancreatitis
• Acute gallbladder disease
• Retinal disorders
• Suicidal behavior and ideation
• Risk of thyroid C-Cell tumours</td></tr>
<tr><td>Cost/30 days*</td><td colspan="2">~ $420</td><td colspan="2">~ $450</td></tr>
<tr><td>Nova Scotia Pharmacare Status</td><td colspan="4">Not a benefit</td></tr>
</table>

<table>
<tr><th colspan="2">Naltrexone/Bupropion (Contrave)</th></tr>
<tr><td>Mechanism of Action</td><td>Together, naltrexone (opioid antagonist) and bupropion (weak inhibitor of dopamine and norepinephrine reuptake) may reduce food intake by targeting the hypothalamus (appetite regulatory center) and the mesolimbic dopamine circuit (reward system) which are both involved in regulating food intake.</td></tr>
<tr><td>Adult Health Canada Approved Indications</td><td>Adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of:
30 kg/m^2 or greater (obese) or
27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity.</td></tr>
<tr><td>Route</td><td>Oral</td></tr>
<tr><td>Products</td><td>naltrexone 8 mg / bupropion 90 mg extended-release oral tablets</td></tr>
<tr><td>Usual Adult Dose & Administration Notes</td><td>Usual Dose Titration:
<table>
<tr><th></th><th>Morning Dose</th><th>Evening Dose</th></tr>
<tr><td>Week 1</td><td>1 tablet</td><td>None</td></tr>
<tr><td>Week 2</td><td>1 tablet</td><td>1 tablet</td></tr>
<tr><td>Week 3</td><td>2 tablets</td><td>1 tablet</td></tr>
<tr><td>Week 4 - onward</td><td>2 tablets</td><td>2 tablets</td></tr>
</table>
Usual Maintenance Dose: Two tablets orally BID

Renal dose adjustment: moderate or severe renal impairment, max dose = 1 tablet BID

Hepatic dose adjustment: mild or moderate hepatic impairment, max dose = 1 tablet AM

<u>Administration Notes:</u>
Swallow tablets whole. Do not cut, chew, or crush.
Do not take with a high-fat meal, due to a significant ↑ in systemic exposure.</td></tr>
<tr><td>Common Adverse Events</td><td>Nausea, constipation, headache, vomiting, dizziness, dry mouth, and hot flush</td></tr>
<tr><td>Drug Interactions
(Not an exhaustive list)</td><td>Many (consult other drug information resources for a more comprehensive list)
<u>Avoid concomitant use</u> with opioids.
Some common medications to <u>consider therapy modification</u>: Aripiprazole, Risperidone, Tamoxifen, Citalopram, Atomoxetine, Metoclopramide, Vortioxetine</td></tr>
<tr><td>Contraindications</td><td>Current seizure disorder or history of seizures
Use of other bupropion containing products
Current or prior diagnosis of bulimia or anorexia nervosa
Chronic opioid or opiate agonist or partial agonists use, or acute opiate withdrawal
Undergoing abrupt discontinuation of alcohol, benzodiazepines or other sedatives, and antiepileptic drugs
Uncontrolled hypertension
Concomitant administration of MAOI. At least 14 days should elapse between discontinuation of MAOI and initiation of treatment with Contrave
Use of thioridazine
Pregnancy
Severe hepatic impairment
End-stage renal failure
Hypersensitivity to the drug or any ingredient in the formulation</td></tr>
<tr><td>Precautions
(Not an exhaustive list)</td><td>Increased risk of self-harm, harm to others, suicidal thinking and behavior
Opioid antagonist related effects
Seizure risk
Brugada syndrome
Increase in BP and HR
Hypoglycemia
Hepatotoxicity
CLE/SLE
Serotonin syndrome
Angle closure glaucoma
Breastfeeding (should not be used)</td></tr>
<tr><td>Cost / 30 days*</td><td>~$300</td></tr>
<tr><td>Nova Scotia Pharmacare Status</td><td>Not a benefit</td></tr>
</table>

Orlistat (Xenical)	
Mechanism of Action	A reversible inhibitor of pancreatic and gastric lipases. Prevents triglycerides from being broken down into absorbable fats, which leads to ↓ fat absorption.
Adult Health Canada Approved Indications	In conjunction with a mildly hypocaloric diet, is indicated for: • Obesity management including weight loss and weight maintenance • Reducing the risk of weight regain in obese patients after prior weight loss. These indications apply to obese patients with a BMI ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 in the presence of other risk factors (e.g. hypertension, T2DM, dyslipidemia, excess visceral fat).
Route	Oral
Products	120 mg oral capsules
Usual Adult Dose & Administration Notes	**Usual Dose**: one 120 mg capsule orally TID with each main meal (during or up to 1 hour after the meal). *Administration Note:* If a meal is occasionally missed or contains no fat, the dose of may be omitted.
Common Adverse Events	Oily spotting, flatus with discharge, fecal urgency, oily stool, and increase defecation
Drug Interactions ***(Not an exhaustive list)***	Orlistat may ↓ absorption of oral drugs including: • Fat-soluble vitamins, which may also impact anticoagulants • Anticonvulsants • Cyclosporine • Levothyroxine • Oral contraceptives (an additional contraceptive method is recommended in case of severe diarrhea) • Antiretrovirals • Amiodarone There are case reports of reduced efficacy of antidepressants, antipsychotics, and benzodiazepines.
Contraindications	• Chronic malabsorption syndrome • Cholestasis • Pregnancy or breast-feeding • Hypersensitivity to the drug or to any ingredient in the formulation
Precautions ***(Not an exhaustive list)***	• *Absorption of fat-soluble vitamins:* Patients should be advised to take a multivitamin supplement that contains fat-soluble vitamins. The supplement should be taken at least two hours before or after the administration of orlistat. • Hypothyroidism • Disease of the large bowel or rectum • Severe liver injury • Renal calculi
Cost / 30 days*	~$180
Nova Scotia Pharmacare Status	Not a benefit

This document is not intended to be all-inclusive. Please refer to the Health Canada Product Monographs and drug interaction databases.
BMI = body mass index, BP =blood pressure, HR = heart rate, OSA = obstructive sleep apnea , T2DM = type 2 diabetes mellitus, TID = three times daily, GLP-1 = glucagon-like peptide 1, MAOI = Monoamine Oxidase Inhibitor, ESRD = end-stage renal disease, CLE = cutaneous lupus erythematosus, SLE = systemic lupus erythematosus, NYHA = New York Heart Association. *Pricing is approximate from www.mckesson.ca
References: Health Canada product monographs: https://health-products.canada.ca/dpd-bdpp/; Lexi-Drugs: https://online.lexi.com; Canadian Pharmacists Association: http://www.e-cps.ca or http://www.myrxtx.ca; Medications for Weight Loss, British Columbia Provincial Academic Detailing: www.bcpad.ca; Canadian Adult Obesity Clinical Practice Guidelines: https://obesitycanada.ca/guidelines/pharmacotherapy.

Appendix 2*: Main Inclusion Criteria of STEP-HFpEF and STEP-HFpEF DM*

Trial	*Main Inclusion Criteria*
STEP-HFpEF	Patients 18 years of age or older were eligible to participate if they had: • a left ventricular ejection fraction of at least 45%, • a BMI of at least 30, • a New York Heart Association functional class II -IV, • a Kansas City Cardiomyopathy Questionnaire clinical summary score of less than 90, • a 6-minute walk distance of at least 100 m, • No hospitalizations due to HF between screening and admission, and at least one of the following findings: ○ elevated left ventricular filling pressures (on the basis of direct invasive measurements) or ○ elevated natriuretic peptide levels (with thresholds stratified according to the BMI at baseline) plus echocardiographic abnormalities, or ○ hospitalization for heart failure in the 12 months before screening plus ongoing treatment with diuretics or echocardiographic abnormalities.
STEP-HFpEF DM	Same as above for **STEP-HFpEF**, and • diagnosis of T2DM ≥ 90 days before screening, • HbA1c of ≤ 10%, and • treated with diet, exercise, and/or glucose-lowering treatment such as oral antihyperglycemic agents or insulins.

BMI = body mass index (kg/m^2), HbA1c = hemoglobin A1c, T2DM = type 2 diabetes mellitus

APPENDIX 3: *Glossary of Evidence Based Medicine Terms*

Number Needed to Treat (NNT) [1]
The number of subjects who need to be treated for one subject to have a favorable outcome. **Note:** It is the inverse of absolute risk reduction (1 ÷ absolute risk reduction). Thus, if the results of a study indicate that the probability of death in a control group is 25% and the probability of death in a treatment group is 10% the number needed to treat would be 1.0 ÷ (0.25 - 0.10) = 6.7, therefore 7 subjects.

Risk Difference (RD) (synonym: Absolute Risk Reduction, Absolute Difference) [1]
The value of the difference between the probability that an event will occur in the group exposed to a given factor and the probability that this event will occur in the group not exposed to this factor.
Note: For example, if the results of a trial were that the probability of death was 25% in the control group and 10% in the experimental group, the absolute risk reduction would be 0.25 – 0.10 = 0.15.

Relative Risk (RR) (synonym Risk Ratio) [1]
The ratio (quotient) of the risk that an event will occur among the subjects exposed to a given factor and the risk that this event will occur among the subjects not exposed to this factor. **Note:** A relative risk (RR) of 1 indicates that the risk is equal in the groups compared, and RR > 1 indicates that the factor increases the risk, and an RR < 1 indicates that the factor decreases the risk.

Odds Ratio (OR) [1]
The odds ratio is a measure of the effect of treatment that compares the probability of suffering an event in the treatment group with the probability of suffering it in the control group. For example, if the results of a trial indicate that the probability of death in the control group is 25% and the probability of death in the treatment group is 10%, the odds ratio would be 0.10 ÷ (1.0 – 0.10) ÷ (0.25 ÷ (1.0 – 0.25) = 0.33.

95% Confidence Interval (95% CI) [1]
A 95% confidence interval indicates that there is a 95% probability that the confidence interval calculated from a particular study includes the true value of the parameter. If the interval includes a null value (a difference in means of 0, and odds ratio or a relative risk of 1, or a correlation coefficient of 0, for example), the null hypotheses cannot be rejected. A narrow confidence interval around a point estimate indicates a more precise estimate than a wide confidence interval.

P-Value[2]
The P-value is used in hypothesis testing. The P value is the probability of obtaining the observed effect (or larger) under a null hypothesis, which is an assumption of no effect of the intervention. A P value that is very small indicates that the observed effect is unlikely to have arisen purely by chance, and therefore provides evidence against the null hypothesis. It is common practice to interpret a P value by examining whether it is smaller than a particular threshold value. P values less than 0.05 are often reported as statistically significant and interpreted as being small enough to justify rejection of the null hypothesis.

Hazard Ratio (HR)[3]
A hazard describes how many times more or less likely a participant is to suffer the event at a particular point in time if they receive the treatment rather than the comparator intervention. The intervention effect is expressed as a hazard ratio.

Mean Difference (MD)[3]
The mean difference measures the absolute difference between the mean value in two groups of a randomized trial. It estimates the amount by which the experimental intervention changes the outcome on average compared with the comparator intervention.

Meta-analysis[4]
Meta-analysis is the statistical combination of results from two or more separate studies. Potential advantages of meta-analyses include an improvement in precision, the ability to answer questions not posed by individual studies, and the opportunity to settle controversies arising from conflicting claims. However, they also have the potential to mislead, particularly if specific study designs, within-study biases, variation across studies, and reporting biases are not carefully considered.

Network Meta-analysis[5]
A network meta-analysis is a technique for comparing three or more interventions simultaneously in a single analysis by combining both direct and indirect evidence across a network of studies. A network meta-analysis produces estimates of the relative effects between any pair of interventions in the network, and usually yields more precise estimates than a single direct or indirect estimate. It also allows estimation of the ranking and hierarchy of interventions. However, they also have the potential to mislead, particularly if specific study designs, within-study biases, variation across studies, and reporting biases are not carefully considered.

References:
1. HtaGlossary.net | Reception
2. Chapter 15: Interpreting results and drawing conclusions | Cochrane Training
3. Chapter 6: Choosing effect measures and computing estimates of effect | Cochrane Training
4. Chapter 10: Analysing data and undertaking meta-analyses | Cochrane Training
5. Chapter 11: Undertaking network meta-analyses | Cochrane Training