Medications for Weight Loss in Adults

B.C. Provincial Academic Detailing (PAD) Service **March 2024**

Participants will have the opportunity to:

1. Apply current evidence to guide prescribing and deprescribing decisions for tirzepatide, semaglutide, liraglutide, naltrexone-bupropion and orlistat.
2. Compare clinical considerations when choosing between medications.
3. Discuss dosing, dose response, timing of weight loss effect, effect after stopping, and cost.

This session will focus on drug information applicable to adults who may be considering medications that reduce body weight. While important, the following are beyond the scope of this session: limitations of body mass index (BMI), pediatrics, nutrition, exercise interventions.

PAD acknowledges that there are differences in terminologies regarding body weight and will prioritize language that is respectful of individuals' preferences.

Brand name	Generic name	Year approved
TBD†	tirzepatide subcutaneous once a week	TBD†
Wegovy®	semaglutide subcutaneous once a week	2021
Saxenda®	liraglutide subcutaneous once a day	2015
Contrave®	naltrexone-bupropion oral twice a day	2018
Xenical®	orlistat oral three times a day	1999

† tirzepatide: Health Canada approval for type 2 diabetes in 2022 (Mounjaro®), US Food & Drug Administration approval for chronic weight management in 2023 (Zepbound™)

To book an academic detailing session and to subscribe to our PAD Refills newsletter:
www.bcpad.ca

Overview: pharmacology, contraindications, adverse events

Medication	Basic pharmacology	Contraindications & precautions	Important adverse events
tirzepatide subcutaneous Weight Loss: TBD Type 2 Diabetes: Mounjaro®	GIP and GLP1 receptor agonist hormone analogue: central and peripheral activity	▪ medullary thyroid cancer (MTC) ▪ Multiple Endocrine Neoplasia syndrome type 2 (MEN2) ▪ pregnancy, breastfeeding ▪ severe gastrointestinal disease ▪ type 1 diabetes: not indicated ▪ tirzepatide: reduces oral contraceptive absorption	▪ gastrointestinal: nausea > diarrhea > vomiting, constipation; delayed gastric emptying ▪ pancreatitis, gallbladder disease ▪ safety reviews ongoing: pulmonary aspiration during surgery; alopecia; suicide, suicidal ideation, self-harm
semaglutide subcutaneous Weight Loss: Wegovy® Type 2 Diabetes: Ozempic®	GLP1 receptor agonist hormone analogue: central and peripheral activity		
liraglutide subcutaneous Weight Loss: Saxenda® Type 2 Diabetes: Victoza®			
naltrexone-bupropion oral Contrave®	naltrexone: opioid antagonist bupropion: weak norepinephrine dopamine reuptake inhibitor central activity	▪ opioid use, including tramadol ▪ history or risk of seizures ▪ uncontrolled hypertension ▪ severe liver or kidney dysfunction ▪ pregnancy, breastfeeding	▪ gastrointestinal: nausea > constipation > vomiting, dry mouth ▪ agitation type adverse events, insomnia ▪ increased blood pressure & heart rate ▪ safety review ongoing: cardiovascular
orlistat oral Xenical®	gastrointestinal lipase inhibitor gastrointestinal activity only	▪ chronic malabsorption syndrome ▪ cholestasis ▪ pregnancy, breastfeeding ▪ lower gastrointestinal disease	▪ flatus, oily spotting, fecal incontinence ▪ oxalate kidney stones, nephropathy ▪ decreased fat soluble vitamin absorption
GIP: glucose-dependent insulinotropic polypeptide; **GLP1**: glucagon-like peptide-1			

A. Mechanism of action: proposed mechanisms of centrally-acting medications include regulation of appetite and caloric intake, but mechanisms are not fully understood

B. Effect on body composition: overall weight loss is the efficacy outcome required for regulatory drug approval; limited information from weight loss trials for tirzepatide, semaglutide, liraglutide, naltrexone-bupropion indicate that both fat and lean body mass are reduced with a larger medication effect on fat mass (subgroup analyses)

C. Relationship between gastrointestinal adverse events and weight loss: in semaglutide weight loss trials, weight loss occurs in people with and without gastrointestinal adverse events (exploratory posthoc analysis); this may also apply to tirzepatide and liraglutide, but information is currently more limited

See reference list

Weight loss outcomes: snapshot

Clinical trial participants in weight loss trials[1-4]

BMI ≥ 30
or BMI ≥ 27 plus comorbidity
hypertension
dyslipidemia
obstructive sleep apnea

age mid 40s
BMI 36 – 38
100 – 105 kg
average

Lifestyle modification counseling provided in addition to medication[1-4]

physical activity
≥ 150 minutes per week

diet
500 kcal deficit per day

Average weight loss at approximately 1 year[1-4]

lifestyle modification as a comparator
1% – 3%

tirzepatide 5 – 15 mg
15% – 21%

semaglutide 2.4 mg
15%

liraglutide 3 mg
8%

naltrexone-bupropion 32/360 mg
6%

these estimates reflect overall weight loss and do not differentiate fat versus muscle loss

International Obesity Collaborative Consensus Statement 2023:[5]

Success should be measured by health and quality of life goals established through shared decision making rather than by changes in BMI alone

Additional weight loss trials enrol people with type 2 diabetes and BMI ≥ 27 (HbA1c ~8%, age mid 50s).[6-8]

In these trials, HbA1c was also reduced:

tirzepatide 10 – 15 mg: ↓ 2%
semaglutide 2.4 mg: ↓ 1.6%
liraglutide 3 mg: ↓ 1.3%

vs

placebo group: ↓ 0.3% – 0.5%

[1]SURMOUNT-1 tirzepatide NEJM 2022; [2]STEP 1 semaglutide NEJM 2021; [3]SCALE liraglutide NEJM 2015; [4]COR-1 naltrexone-bupropion Lancet 2010; [5]International Obesity Collaborative BMI Consensus Statement 2023; [6]SURMOUNT-2 tirzepatide Lancet 2023; [7]STEP 2 semaglutide Lancet 2021; [8]SCALE diabetes liraglutide JAMA 2015; slide design images from Flaticon.com

Weight loss outcomes: details

Tirzepatide, semaglutide: exceed minimally important weight loss thresholds[1,2]

Liraglutide, naltrexone-bupropion: achieve part of the criteria for a minimally important effect (systematic & regulatory reviews)[1,3,4]

Orlistat: small effect which may not exceed minimally important thresholds[1]

Serious adverse events: lacking a systematic review comparing medications for serious adverse events (benefits & harms)

BMI ≥ 30 or a BMI ≥ 27 and at least one comorbidity[2,5-7]
principally hypertension, dyslipidemia, obstructive sleep apnea

Added to lifestyle modification counseling on a ↓ calorie diet (500 kcal deficit per day) and ↑ physical activity (minimum 150 minutes per week)

Minimally important effect required for regulatory drug approval[3,4,8,9]
- at least 5% more weight loss vs placebo on average; or
- at least 35% of people achieve 5% weight loss, doubling the placebo proportion
- tirzepatide, semaglutide: exceed both; liraglutide, naltrexone-bupropion: double the proportion achieving 5% weight loss

Effect at approximately 1 year[2,5-7]		Weight change (%) on average	Proportion of people who lose ≥ 5% weight	Proportion of people who lose ≥ 10% weight	Proportion of people who lose ≥ 20% weight	Proportion of people who discontinue due to adverse events
tirzepatide subcut 3 doses: 5, 10, 15 mg	majority BMI ≥ 30 average age mid 40s BMI 36 – 38 100 – 105 kg	↓ 15% – 21% ↓ 3% placebo	85% – 91% 35% placebo	69% – 84% 19% placebo	30% – 57% 3% placebo	4% – 7% 3% placebo
semaglutide subcut 1 dose: 2.4 mg		↓ 15% ↓ 2% placebo	86% 32% placebo	69% 12% placebo	32% 2% placebo	7% 3% placebo
liraglutide subcut 1 dose: 3 mg		↓ 8% ↓ 3% placebo	63% 27% placebo	33% 11% placebo	not reported	10% 4% placebo
naltrexone-bupropion 1 dose: 32 mg/360 mg		↓ 6% ↓ 1% placebo	48% 16% placebo	25% 7% placebo	not reported	20% 10% placebo

A. Orlistat: 3% more weight loss and 23% more people lose ≥ 5% weight compared to placebo; 2% of people remain on the medication at 2 years[1,10]

B. Discontinuations due to adverse events: liraglutide, naltrexone-bupropion, phentermine-topiramate had the highest risk in a 2022 systematic review & network meta-analysis of pharmacotherapies for weight loss (143 trials; 49,810 participants)[1]

C. Physical functioning, quality of life: improved statistically with tirzepatide, semaglutide, liraglutide, naltrexone-bupropion; clinical relevance of magnitude is unclear[1-4]

D. Weight loss trials: use different methodology designs & enrol different patient populations – these estimates are from the largest weight loss trial for each medication

[1]SHI LANCET 2022; [2]SURMOUNT-1 tirzepatide NEJM 2022; [3]US Food & Drug Administration Reviews Wegovy 2021, Saxenda 2014, Contrave 2014, Xenical 1998; [4]European Medicines Agency Reviews Wegovy 2021, Saxenda 2015, Contrave 2014; [5]STEP 1 semaglutide NEJM 2021; [6]SCALE liraglutide NEJM 2015; [7]COR-1 naltrexone-bupropion Lancet 2010; [8]US FDA 2007 Industry Guidance; [9]EMA 2016 Industry Guidance; [10]PADWAL Int J Obes 2007

Cardiovascular outcomes

Tirzepatide: cardiovascular and heart failure trials are ongoing

Semaglutide: reduces the risk of cardiovascular events in people with a history of cardiovascular disease (+ BMI ≥ 27) and improves heart failure symptoms, physical limitations in people with HFpEF (LVEF ≥ 45%, NYHA II-IV symptoms + BMI ≥ 30)

Naltrexone-bupropion: a cardiovascular trial and a cardiovascular safety review are ongoing

SELECT 2023

cardiovascular disease
BMI ≥ 27
without diabetes

semaglutide subcut
target dose 2.4 mg

77% achieved 2.4 mg

		placebo	semaglutide
17,604 participants with 3.3 years of follow up mean age 62, BMI 33, 72% male, 28% female, 84% White inclusion history MI 68%, stroke 18%, PAD 4%, ≥ 2 CVD 8%			
major cardiovascular events	ARR 1.5% ↓	8%	6.5%
		HR 0.80, 95%CI 0.72 to 0.90	
death from any cause	ARR 0.9% ↓	5.2%	4.3%
		HR 0.81, 95%CI 0.71 to 0.93	

- added to high rates background CVD medications
- ↓ serious adverse events: placebo 36% vs semaglutide 33% (ARR 3%)
- ↑ discontinuations due to adverse events: placebo 8% vs semaglutide 17% (ARI 9%)
- ↓ body weight: placebo ~1% weight loss vs semaglutide ~9% (difference ~8%)
- this is a very brief synopsis; there is currently no regulatory review of this trial; link to trial

STEP HFpEF 2023

LVEF ≥ 45%
NYHA II-IV
BMI ≥ 30
without diabetes

semaglutide subcut
target dose 2.4 mg

84% achieved 2.4 mg

		placebo baseline → at 1 year	semaglutide baseline → at 1 year
529 participants with 1 year of follow up median age 69, BMI 37, 44% male, 56% female, 96% White HFpEF 84%, HFmrEF 16%, NYHA II 66% & III-IV 34% median NT-proBNP level 451 pg/mL			
KCCQ-CCS range 0 – 100 points	8-point difference in change from baseline 95%CI 4.8 to 10.9 points	58 → 67 points	59 → 76 points
KCCQ-CCS: ≥ 5-point increase	NNT ~9	64%	75%
6-minute walk distance meters	20-meter difference in change from baseline 95%CI 8.6 to 32.1 meters	326 → 327 meters	316 → 338 meters

- added to high rates background CVD medications
- ↓ serious adverse events: placebo 27% vs semaglutide 13% (ARR 14%)
- ↑ discontinuations due to adverse events: placebo 5% vs semaglutide 13% (ARI 8%)
- ↓ body weight: placebo ~3% weight loss vs semaglutide ~13% (difference ~10%)
- modest sized trial with few heart failure events
- this is a very brief synopsis; there is currently no regulatory review of this trial; link to trial

major cardiovascular events: death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke; **ARR**: absolute risk reduction; **ARI**: absolute risk increase; **HFpEF**: heart failure preserved LVEF ≥ 50%; **HFmrEF**: heart failure mildly reduced LVEF 41-49%; **NT-proBNP**: N-terminal pro-B-type natriuretic peptide; **KCCQ-CCS**: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score: patient-reported outcome, higher scores indicate fewer symptoms, physical limitations – minimal clinically important difference: ≥ 5 point increase, moderate to large improvement: ≥ 10 point increase, large to very large improvement: ≥ 20 point increase; **NNT**: number of people who would need to take the medication for 1 year for 1 person to benefit

SELECT semaglutide NEJM 2023; STEP HFpEF semaglutide NEJM 2023; US FDA 2019 Heart Failure Endpoints; US FDA 2020 KCCQ Heart Failure; SPERTUS KCCQ JACC 2020

Tirzepatide, semaglutide, liraglutide: clinical considerations

Contraindications, precautions

- personal, family history MTC; personal history MEN2 (HC, FDA)
- evidence does not support causal link to thyroid cancer (EMA 2023)

- pregnancy or breastfeeding
- before planned pregnancy → discontinue
  - tirzepatide at least 1 month prior
  - semaglutide at least 2 months prior

- type 1 diabetes: not indicated

- avoid inadvertent duplication with DPP4 inhibitors “gliptins”, other GLP1 agonists
- other weight loss medications are not approved for concurrent use

Serious adverse events (SAEs)

- SAEs increased in people principally without CVD: semaglutide 9.3% vs placebo 6.4% (N=4179); liraglutide 6.3% vs placebo 4.6% (N=5325)
- SAEs were decreased in the semaglutide CVD and HF trials
- tirzepatide: SAE review not available

serious adverse events: death, life-threatening, disability, hospitalization, congenital anomaly

Gastrointestinal adverse events

- incidence: 60% – 70%
- dose related: nausea > diarrhea > vomiting, constipation
- abdominal pain: 10% – 20%
- most common reason for stopping particularly during initiation & dose titration, incidence reduces over time (eg, nausea with semaglutide at week 20: ~20%, at week 68: ~10%)
- severe or prolonged symptoms, abdominal pain → investigate

- cholelithiasis, cholecystitis: 1% – 2%
- risk increased with higher doses, longer treatment durations

---

- associated with increased risk of acute pancreatitis → discontinue & do not restart

---

- kidney function → monitor if reduced fluid intake & volume depletion

Contraceptive management

- tirzepatide transiently reduces oral contraceptive absorption → switch to a non-oral contraceptive or add a barrier method for 4 weeks at time of tirzepatide initiation and for 4 weeks after each dose increase

Perioperative management

- pulmonary aspiration: possibly secondary to delayed gastric emptying (case reports) → consider holding for a time-period equivalent to at least 3 half-lives
  - tirzepatide: hold 2 weeks preop
  - semaglutide: hold 3 weeks preop
  - liraglutide: hold 2 days preop
- safety reviews ongoing: FDA, EMA

Hypoglycemia, type 2 diabetes

- hypoglycemia: risk increased when coprescribed with insulin or sulfonylureas
- insulin → consider insulin dose reduction of 20%
- sulfonylurea → consider sulfonylurea dose reduction of 50%
- sulfonylureas were stopped in tirzepatide weight loss trials if already on the lowest dose

---

- blood glucose < 3 mmol/L: occurred in 1.5% of people without diabetes receiving tirzepatide

---

- history of diabetic retinopathy → monitor for progression

Suicide, suicidal ideation, self-harm

- preliminary evaluation does not suggest a causal link based on the small number of events in post-marketing case reports and clinical trials (FDA 2024)
- history of suicidal attempts or active ideation → avoid use
- monitor for depression, suicidal thoughts, unusual changes in mood or behaviour
- safety reviews ongoing: HC, FDA, EMA

Alopecia risk

- tirzepatide: females 7%, males 0.5%
- semaglutide, liraglutide: 3% – 5%; rate higher in patients who lose ≥ 20% of their body weight
- safety review ongoing: FDA

Cardiovascular monitoring

- ↓ SBP ↓ DBP ↑ HR ↑ PR interval
- caution: cardiac conditions that might be worsened by increase in HR, AV block, tachyarrhythmias
- hypotension: occurs in 1% – 2% of people receiving tirzepatide

See reference list; **MTC**: medullary thyroid cancer; **MEN2**: Multiple Endocrine Neoplasia syndrome type 2; **HC**: Health Canada; **FDA**: US Food & Drug Administration; **EMA**: European Medicines Agency; **N**: # of people in safety dataset

Naltrexone-bupropion: clinical considerations

Contraindications, precautions

- opioid use: agonist or partial agonist, including tramadol
- opioid withdrawal

- seizure disorder, bulimia, anorexia nervosa, abrupt alcohol or sedative discontinuation

- uncontrolled hypertension: patients with SBP > 140 or DBP > 90 excluded from naltrexone-bupropion weight loss trials
- Brugada syndrome

- severe hepatic impairment
- end stage kidney disease

- pregnancy, breastfeeding

- avoid inadvertent duplication with other bupropion formulations (Wellbutrin®, Zyban®)

Serious adverse events (SAEs)

- SAEs in people principally without CVD (N=3558): 2.3% vs placebo 1.3%
- SAEs in people with co-occurring T2DM (N=502): 3.9% vs placebo 4.7%

serious adverse events: death, life-threatening, disability, hospitalization, congenital anomaly

Opioid antagonist: naltrexone

- can precipitate opioid withdrawal
- opioid-free interval → at least 7 to 10 days before initiating naltrexone-bupropion (at least 14 days for methadone, buprenorphine)
- pain management: the threshold to safely overcome antagonistic effects of naltrexone for acute and surgical pain is not defined → consult with anesthesiologist is recommended
- advise patient: an attempt to overcome opioid blockade with administration of large doses of opioids risks opioid overdose

Epileptogenic: bupropion

- consider risk factors for seizures: head trauma, CNS tumor, renal or hepatic impairment, insulin, hypoglycemic agents, medications that lower seizure threshold
- minimize seizure risk → do not exceed recommended dose: total daily dose provides 360 mg of bupropion sustained release in two divided doses

Neuropsychiatric: bupropion

- agitation-type adverse events → monitor for suicidal ideation and behavior, depression and agitation–type adverse events (eg, anxiety, aggression, mania) when initiating therapy or changing dose (HC)
- insomnia, headache, dizziness, tremor

Gastrointestinal adverse events

- incidence: 55%
- nausea > constipation > vomiting, dry mouth, abdominal pain
- more common during dose escalation phase, incidence reduces over time in clinical trials

Renal impairment

- moderate-severe renal impairment (15 – 59 mL/min) → reduce dose to *one tablet twice a day*

Hepatic impairment

- mild-moderate hepatic impairment (Child-Pugh Class A or B) → reduce dose to *one tablet once a day*

Cardiovascular monitoring

- effect on cardiovascular morbidity and mortality has not been established
- two cardiovascular safety trials were stopped early and a third trial is currently ongoing
- safety review ongoing: EMA

- monitor: BP, HR
- risk of increase may be greatest during initial 3 months
- small mean ↑ SBP 1 to 3 mmHg and ↑ DBP 1 mmHg in clinical trials
- case reports of hypertensive crisis

Clinical toxicology: bupropion

- risk of morbidity and mortality increased relative to SSRIs: case series, observational studies of acute overdoses, poisonings

- urine toxicology: potential positive for amphetamine

Immune system effects

- anaphylaxis ~1 to 3 per 1000
- onset of cutaneous lupus erythema
- exacerbation of systemic lupus erythema

See reference list; **HC**: Health Canada; **EMA**: European Medicines Agency; **N**: # of people in safety dataset; **T2DM**: type 2 diabetes

Dosing, timing of weight loss effect, dose response, cost

Medication	Initial dosing & titration	Onset & plateau	Dose response	Annual cost	Stopping
tirzepatide half-life: 5 days	initial: 2.5 mg subcut once a week 4 – 20 week titration: ↑ every 4 weeks in 2.5 mg increments up to 5 mg, 10 mg or 15 mg once a week	onset: within 4 weeks plateau: 60 – 72 weeks	10 mg vs 5 mg: 5% additional weight loss 15 mg vs 10 mg: 1% additional weight loss	5 mg: $4300† 10 mg: $4300† 15 mg: $4300†	on average, weight loss achieved does not persist after the medication is stopped
semaglutide half-life: 7 days	initial: 0.25 mg subcut once a week 16 week titration: ↑ every 4 weeks to 0.5 mg, 1 mg, 1.7 mg, up to 2.4 mg once a week	onset: within 4 weeks plateau: 52 – 60 weeks	2.4 mg vs 1 mg: 3% additional weight loss 2.4 mg vs 1.7 mg: 4% additional weight loss	1 mg: $2960†† 2.4 mg: TBD	4 weeks after stopping tirzepatide or semaglutide ~1% – 2% of weight may be regained
liraglutide half-life: 13 hours	initial: 0.6 mg subcut once a day 4 week titration: ↑ weekly in 0.6 mg increments up to 3 mg once a day	onset: within 2 weeks plateau: 34 – 40 weeks	3 mg vs 1.8 mg: 1% additional weight loss	3.0 mg: $5300	1 year after stopping ~1/2 to 2/3 weight may be regained
naltrexone-bupropion half-life: naltrexone 5 hours with active metabolite 13 hours; bupropion 21 hours	initial: 1 tab (8/90 mg) once a day 3 week titration: ↑ weekly by 1 tab (8/90 mg) up to 2 tabs BID (32/360 mg)	onset: within 4 weeks plateau: 28 – 36 weeks	relevant dose response information is absent	32/360 mg: $3700	not reported

Titration: (tirzepatide, semaglutide, liraglutide) dose escalation can be slowed or paused; the time required for titration in clinical practice may take longer than in clinical trials which inform prescribing information; 12.5 – 25% of people in clinical trials had their dose reduced or titration paused (semaglutide, liraglutide)

Onset: earliest time point reported in clinical trials where the weight loss difference between drug and placebo emerges; effect may occur earlier

Plateau: approximate time point when the weight loss difference between drug and placebo begins to level off

Dose response: estimates from clinical trials where more than one dose was used but may not apply to all patient populations

Drug cost: approximate drug cost excluding mark up and professional fee; †tirzepatide estimated from Mounjaro single dose vials; ††semaglutide estimated from Ozempic 1 mg dose/4 mg pen; costs may be subject to change

Stopping: medication was discontinued if BMI reached ≤ 18.5 in the tirzepatide weight-loss trials

Health Canada Drug Health Product Portal; US FDA Approved Drugs; SURMOUNT-1 tirzepatide NEJM 2022; SURMOUNT-4 tirzepatide JAMA 2024; STEP 1 semaglutide NEJM 2021; STEP 1 semaglutide extension Diabetes Obes Metab 2022; STEP 2 semaglutide diabetes Lancet 2021; STEP 4 semaglutide maintenance JAMA 2021; STEP 6 semaglutide East Asia; SELECT semaglutide NEJM 2023; SCALE liraglutide NEJM 2015; SCALE liraglutide adolescents NEJM 2020; SCALE liraglutide diabetes JAMA 2015; COR-1 naltrexone-bupropion Lancet 2010; US FDA Reviews Wegovy 2021, Saxenda 2014, Contrave 2014; McKesson Canada Pharmaclick (accessed March 1, 2024); WHARTON Post Grad Med 2022

Drug interactions

Drug Interaction Key
contraindicated
dose or timing modification
caution and monitor

Pharmacodynamic Interactions	tirzepatide	semaglutide, liraglutide	naltrexone-bupropion	orlistat
Opioids including tramadol: naltrexone is an opioid antagonist			opioid antagonism	
Inadvertent duplication: other bupropion or naltrexone medications			Wellbutrin®, Zyban® REVIA®	
Glucose lowering medications	consider dose reduction of sulfonylureas, insulin; avoid co-prescribing a DPP4 inhibitor or another GLP1 agonist		severe hypoglycemia increases seizure risk	
Medications associated with weight gain: mirtazapine, antipsychotics, valproate, gabapentinoids, TCAs, insulin, sulfonylureas				
Medications that lower seizure threshold or increase seizure risk: antipsychotics, lithium, theophylline, corticosteroids, TCAs			bupropion lowers seizure threshold	

Pharmacokinetic Interactions	tirzepatide	semaglutide, liraglutide	naltrexone-bupropion	orlistat
Prodrug requiring CYP2D6 activation: tamoxifen			tamoxifen efficacy reduced	
CYP2D6 substrates may require dose reductions: aripiprazole, atomoxetine, carvedilol, metoprolol, vortioxetine, dextromethorphan, metoclopramide, risperidone			pimozide, thioridazine bupropion inhibits CYP2D6	
CYP2B6 inhibitors reduce the clearance of bupropion: clopidogrel, ticlopidine			decrease naltrexone-bupropion dose 50%	
CYP2B6 inducers increase the clearance of bupropion: carbamazepine, phenytoin, rifampin, ritonavir			may decrease concentration of bupropion component	
Narrow therapeutic index medications: antiretrovirals, digoxin, antiepileptics, warfarin, amiodarone, levothyroxine, cyclosporine	possible modified absorption due to delayed gastric emptying		may decrease digoxin levels: monitor	cyclosporine: space 3 hrs levothyroxine: space 4 hrs
Oral contraceptives: switch to a non-oral contraceptive or add a barrier method of contraception when tirzepatide is initiated or increased	for 4 weeks at initiation and after each dose increase			in cases of severe diarrhea
Fat soluble vitamins: Vitamins A, D, E, beta carotene				separate by 2 hours

See reference list; not intended as an exhaustive drug interaction list; consult a drug interaction resource

Evidence ongoing: trials, safety reviews

Weight loss trials	Cardiovascular trials	Safety trials, reviews
tirzepatide subcut (SURMOUNT-5) ▪ versus semaglutide 2.4 mg	tirzepatide subcut (SURMOUNT-MMO) ▪ cardiovascular disease + BMI ≥ 27	pulmonary aspiration during surgery ▪ GLP1 agonists, including tirzepatide ▪ agency review: FDA & EMA
semaglutide subcut (STEP UP) ▪ 7.2 mg once a week	tirzepatide subcut (SUMMIT) ▪ HFpEF + BMI ≥ 30	alopecia ▪ GLP1 agonists, including tirzepatide ▪ agency review: FDA
semaglutide oral (OASIS trials) ▪ 25 – 50 mg once a day	semaglutide subcut (STEP UP HFpEF DM) ▪ HFpEF + T2DM + BMI ≥ 30	suicide, suicidal ideation, self harm ▪ GLP1 agonists, including tirzepatide ▪ agency review: HC, FDA & EMA
Osteoarthritis	naltrexone-bupropion (INFORMUS) ▪ cardiovascular disease or high cardiovascular risk + BMI ≥ 27	cardiovascular safety ▪ naltrexone-bupropion ▪ agency review: EMA
tirzepatide subcut (STOP KNEE-OA) ▪ osteoarthritis of the knee + BMI ≥ 30		diabetic retinopathy ▪ semaglutide subcut ▪ safety trial: FOCUS
semaglutide subcut (STEP 9) ▪ osteoarthritis of the knee + BMI ≥ 30		sarcopenia, nutritional deficiencies ▪ no ongoing safety reviews were identified

See reference list; not an exhaustive list: includes trials, safety reviews relevant to topic scope with patient important outcomes; **HC**: Health Canada; **FDA**: US Food & Drug Administration; **EMA**: European Medicines Agency

Updates: after March 2024

Medications for weight loss: evidence for practice

	Tirzepatide	Semaglutide	Naltrexone-bupropion	Orlistat
Weight loss in people with a BMI ≥ 30 or a BMI ≥ 27 and at least one comorbidity	▪ ≥ 15% weight lost on average ▪ majority of people experience ≥ 5% body weight loss ▪ weight loss achieved with medication does not persist after the medication is discontinued, on average		▪ partially achieves minimally important weight loss effects	▪ small weight loss effect ▪ few people remain on it long term
Cardiovascular	▪ semaglutide reduces the risk of cardiovascular events in people with a history of cardiovascular disease (+ BMI ≥ 27) ▪ semaglutide improves heart failure symptoms and physical limitations in people with HFpEF (LVEF ≥ 45%, NYHA II-IV symptoms + BMI ≥ 30)		▪ cardiovascular safety is being evaluated in an ongoing trial	
Gastrointestinal adverse events	▪ dose related; more common during medication initiation and titration: dose escalation schedules can be slowed or paused ▪ severe or prolonged symptoms, abdominal pain should be investigated			
More evidence to come & drug interactions	▪ efficacy: doses, formulations, osteoarthritis, cardiovascular, heart failure, tirzepatide versus semaglutide direct comparison ▪ safety: perioperative pulmonary aspiration; alopecia; suicide, suicidal ideation, self harm; diabetic retinopathy		▪ potential for several pharmacokinetic and pharmacodynamic drug interactions	

Link to the survey for this academic detailing session

Reference list is available upon request. Materials are designed to be used in conjunction with an academic detailing session provided by a PAD pharmacist.

For more information, or to schedule an academic detailing session, please contact: BC Provincial Academic Detailing Service Email: PAD@gov.bc.ca Web: www.bcpad.ca

v. March 7, 2024