Canadian Adult Obesity Clinical Practice Guideline

obesity canada obésité canada

Pharmacotherapy for obesity management in adults

2025 clinical practice guideline update

Sue D. Pedersen MD, FRCPC, DABOM[i], Priya Manjoo MD, MSc, FRCPC, DABOM, CHS, [ii], Satya Dash MD, FRCPC[iii], Akshay Jain, MD, FRCPC, FACE, CCD, ECNU, DABOM[iv], Nicole Pearce, PMC, CPC(HC)[v], Megha Poddar, MD, FRCPC, DABOM[vi]

i. C-ENDO Diabetes & Endocrinology Clinic, and University of Calgary, Calgary, Alberta
ii. Department of Endocrinology, University of British Columbia & University of Victoria, Victoria, British Columbia
iii. Department of Medicine University of Toronto & University Health Network, Toronto, Ontario
iv. Dept of Endocrinology, University of British Columbia, TLC Diabetes and Endocrinology Clinic, Surrey, British Columbia
v. Obesity Canada, Edmonton, Alberta
vi. Department of Internal Medicine, McMaster University, Hamilton, Ontario

Cite this Chapter

Pedersen SD, Majoo P, Dash S, Jain A, Pearce N, Poddar M. Canadian Adult Obesity Clinical Practice Guideline: Pharmacotherapy for Obesity Management in Adults. Available from: obesitycanada.ca/healthcare-professionals/adult-clinical-practice-guideline. Accessed [date].

Update History

Version 3, August 11, 2025. Adult Obesity Clinical Practice Guideline are a living document.

Key Messages For Healthcare Professionals

- Pharmacotherapy is an effective and safe approach to treating obesity, and can facilitate health behavior changes for many people living with obesity. As with other chronic diseases such as type 2 diabetes or hypertension, pharmacotherapy is an important pillar in the management of obesity.
- The focus of obesity management should be the improvement of health parameters (metabolic, mechanical, mental, and/or quality of life), not solely weight reduction, and should include outcomes that the patient identifies as important. Obesity and overweight are defined by body mass index (BMI) in clinical trials, which itself does not adequately reflect body composition, fat distribution, or the presence of adiposity-related complications. The prescriber should interpret recommendations with ethnicity-specific BMI criteria and/or additional sex- and ethnicity-specific anthropometric assessments of adiposity in mind.
- There are six medications indicated for long-term obesity management in Canada as adjuncts to health behaviour changes: liraglutide (Saxenda®), naltrexone/bupropion (Contrave®), orlistat (Xenical®), semaglutide (Wegovy®), tirzepatide (Zepbound®), and setmelanotide (Imcivree®). All six medications are effective in achieving clinically significant, durable weight loss and providing important health benefits.
- The individual response to pharmacotherapy for obesity management is variable, due to the complex and heterogeneous nature of obesity. Efficacy (both for weight loss and management of adiposity-related health issues), mechanism of action, potential side effects/tolerability, contraindications, medication interactions, mode of administration, cost, access, and patient preference are all important considerations in choosing the most appropriate obesity pharmacotherapy.
- Obesity pharmacotherapy should be tailored to the individual, and medication should be titrated as tolerated to achieve the desired clinical effect. Some individuals may achieve their treatment goals with doses lower than the maximum dose of medication. Provided that the medication is well tolerated, patients should be treated for obesity-related complications at a dose that demonstrates benefit.
- Obesity medications are intended as part of a long-term treatment strategy. Clinical trials of pharmacotherapy for obesity management consistently demonstrate weight regain and regression of health improvements when treatment is stopped.
- Compounded medications are not currently approved as pharmacotherapy for obesity management in Canada and should not be used for this purpose.

Recommendations

1. We recommend the use of measures of central adiposity (using sex- and ethnicity-specific cut offs if applicable) such as waist circumference, waist-to-hip ratio and/or waist-to-height ratio, in addition to ethnicity-specific BMI thresholds and/or adiposity-related complications, to guide the decision to initiate pharmacotherapy. [1-4] [Level 3, Grade C]

2. We suggest the initiation of obesity pharmacotherapy for adults with excess adiposity be personalized to meet individual values, preferences and treatment goals to support an approach that is safe, effective, culturally acceptable, and affordable for long-term adherence. [Level 4, Grade D, Consensus]

3. Pharmacotherapy for obesity management should be offered to individuals with BMI ≥ 30 kg/m2 * or BMI ≥ 27 kg/m2 * with adiposity related complications, in conjunction with health behaviour changes:
   semaglutide 2.4 mg weekly (BMI ≥27 kg/m^{2*}) [Level 1a, Grade A] [5]
   tirzepatide 5 mg, 10 mg, or 15 mg weekly (BMI ≥27 kg/m^{2*}) [Level 1a, Grade A] [6]
   liraglutide 3 mg daily (BMI ≥27 kg/m^{2*}) [Level 2a, Grade B] [7]
   naltrexone/bupropion 16 mg/180 mg BID (BMI 27-45 kg/m^{2*}) [Level 2a, Grade B] [8]
   orlistat 120 mg TID (BMI 28-47 kg/m^{2*}) [Level 2a, Grade B] [9]

   *see recommendation #1

4. Pharmacotherapy for obesity management should be used long term, when effective, in conjunction with health behaviour changes to:
   - avoid weight regain and regression of health benefits achieved with pharmacotherapy
     semaglutide 2.4 mg weekly [Level 1a, Grade A] [10],
     tirzepatide 10 mg or 15 mg weekly [Level 1a, Grade A] [11],
     orlistat 120 mg TID [Level 2a, Grade B] [9]
   - maintain weight loss and prevent weight regain following health behavior changes
     liraglutide 3 mg daily [Level 2a, Grade B] [12]
     orlistat 120 mg TID [Level 2a, Grade B] [13]
     tirzepatide 10 mg or 15 mg [Level 2a, Grade B] [14]

5. Pharmacotherapy should be offered, in conjunction with health behaviour changes, to reduce the occurrence of major adverse cardiovascular events (MACE) in people with established atherosclerotic cardiovascular disease (ASCVD) and BMI ≥ 27 kg/m^{2*}, in addition to standard of care for ASCVD:
   semaglutide 2.4 mg weekly [Level 2a, Grade B] [15]

   *see recommendation #1

6. Pharmacotherapy should be offered in conjunction with health behavior changes in addition to standard of care in people living with heart failure with preserved ejection fraction (HFpEF) and BMI ≥ 30 kg/m^{2*}, for weight loss and:
   - a composite of reduction in cardiovascular death or a worsening heart failure event
     tirzepatide 15 mg weekly, [Level 1a, Grade A] [16]
   - improvement in heart failure symptoms
     semaglutide 2.4 mg weekly [Level 1a, Grade A] [17],
     tirzepatide 15 mg weekly [Level 1a, Grade A] [16]

   *see recommendation #1

7. Obesity pharmacotherapy, in conjunction with health behaviour changes, for people living with prediabetes should be offered for weight loss and to:
   - reduce the risk of progression to type 2 diabetes
     liraglutide 3 mg daily (BMI ≥27 kg/m^{2*}) [Level 2a, Grade B] [18]
     orlistat 120 mg TID (BMI ≥30 kg/m2*) [Level 2a, Grade B] [19]
     tirzepatide 5 mg, 10 mg or 15 mg weekly (BMI ≥27 kg/m^{2*}) [Level 2a, Grade B] [20]
   - achieve normoglycemia
     semaglutide 2.4 mg weekly (BMI ≥30 kg/m^{2*}) [Level 1a, Grade A] [21]

   *see recommendation #1

8. Obesity pharmacotherapy should be offered, in conjunction with health behaviour changes, in people living with type 2 diabetes (T2D) for weight loss and improvement in glycemic control:
   semaglutide 2.4 mg weekly (BMI ≥ 27 kg/m^{2*}) [Level 1a, Grade A] [22]
   tirzepatide 10 mg or 15 mg weekly (BMI ≥ 27 kg/m^{2*}) [Level 1a, Grade A] [23]
   liraglutide 3 mg daily (BMI ≥ 27 kg/m^{2*}) [Level 2a, Grade B] [24]
   naltrexone/bupropion 16 mg/180 mg BID (BMI 27-45 kg/m^{2*}) [Level 2a, Grade B] [25]
   orlistat 120 mg TID (BMI 27-43 kg/m^{2*}) [Level 2a, Grade B] [2]

   *see recommendation #1

9. Pharmacotherapy may be offered, in conjunction with health behaviour changes, in treating people living with metabolic dysfunction-associated steatohepatitis (MASH), for weight loss and:
   - resolution of MASH without worsening of fibrosis:
     semaglutide 2.4 mg weekly [Level 2a, Grade B] [27]
     liraglutide 1.8 mg daily (BMI ≥25 kg/m2*) [Level 3, Grade C] [28]
     tirzepatide 5 mg, 10 mg or 15 mg weekly (BMI 27-50 kg/m^{2*}) [Level 3, Grade C] [29]
   - improvement in fibrosis without worsening

of MASH:
semaglutide 2.4 mg weekly [Level 2a, Grade B] [27]
tirzepatide 5 mg, 10 mg or 15 mg weekly (BMI 27-50 kg/m^{2*}) [Level 3, Grade C] [29]

*see recommendation #1

10. Pharmacotherapy should be offered, in conjunction with health behaviour changes, for weight loss and improvement in apnea-hypopnea index in people who are living with moderate to severe obstructive sleep apnea (OSA) and BMI ≥ 30 kg/m^{2*}, and who are:
    - unwilling or unable to use positive airway pressure therapy
      tirzepatide 10 mg or 15 mg [Level 1a, Grade A] [30]
      liraglutide 3 mg daily [Level 2a, Grade B] [31]
    - using positive airway pressure therapy
      tirzepatide 10 mg or 15 mg [Level 1a, Grade A] [30]

    *see recommendation #1

11. Pharmacotherapy for obesity management should be offered, in conjunction with health behaviour changes, for individuals living with knee osteoarthritis and BMI ≥ 30 kg/m^{2*} for weight loss and reduction in knee pain:
    semaglutide 2.4 mg weekly [Level 1a, Grade A] [32]

    *see recommendation #1

12. Setmelanotide up to 3 mg daily may be offered for weight management for people with BMI ≥30 kg/m^{2*} and:
    - Bardet-Biedl syndrome [Level 2a, Grade B] [33]
    - genetically confirmed biallelic pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency due to variants interpreted as pathogenic, likely pathogenic, or of uncertain significance [Level 3, Grade C] [34]

    *see recommendation #1

13. We recommend against the use of compounded medications, prescription medications, or over-the-counter medications other than those approved in Canada for weight loss in people with excess adiposity [Level 4, Grade D, Consensus].

Key Messages For People Living With Obesity

- Obesity medications are safe and effective for managing weight and weight-related health issues, often in combination with health behaviour changes, and/or psychological interventions.
- The goals in obesity management should include improving health, and should include outcomes that are important to you.
- When choosing a weight management medication with your healthcare professional, consider potential benefit to your obesity-related health conditions, effect on weight, potential side effects, form (injection vs. pill), dosing frequency, interaction with other medications, and cost.
- There are six medications approved by Health Canada for long-term obesity management: liraglutide (Saxenda®), naltrexone/bupropion (Contrave®), orlistat (Xenical®), semaglutide (Wegovy®), tirzepatide (Zepbound®), and setmelanotide (Imcivree®). These medications can help you to achieve and maintain improvements in weight and health complications associated with excess weight. These medications have been proven to be effective for obesity management in clinical trials.
- The dose of weight management medication should be tailored to you, depending on the goals of treatment, as needed and as tolerated. You may achieve your treatment goals with a dose that is lower than the maximum dose for that medication.
- Weight management medications are intended as part of a long-term treatment strategy. Stopping medication can lead to weight regain and a loss of the health benefits you've experienced.
- Compounded medications and medications that are not approved for obesity treatment may not be safe or effective for obesity management and should be avoided.

Introduction

Sustained weight loss is associated with improvements in health complications associated with obesity. [35-37] Health behaviour changes alone generally achieve only a 3% – 5% weight loss, which is most often not sustained over the long term and not sufficient to improve most adiposity-related complications. [38-40] Pharmacotherapy for obesity management should be utilized to decrease weight, optimize health and support adherence to health behaviour changes.

Despite the high prevalence of obesity, (see Epidemiology of Adult Obesity chapter) obesity medications are prescribed far less frequently than medications for other chronic medical conditions, such as type 2 diabetes (T2D) [41]. The adoption of novel diabetes medications is markedly greater and more rapid than the adoption rate of new pharmacotherapies for weight management. [42] Amongst people seeking or receiving obesity care in a US study between 2015-2023, only 8% had received a prescription for obesity pharmacotherapy. [41] Contributing factors include lack of public and limited private reimbursement of obesity pharmacotherapy, cost considerations, weight stigma and bias within the healthcare community and general public, internalized weight bias, time constraints within a busy clinical practice, insufficient financial and systemic support for obesity management, as well as clinician inexperience, and/or misperceptions about the efficacy and safety of available treatments. [43] (see Reducing Weight Bias in Obesity Management, Practice & Policy chapter)

This guideline chapter provides a review of the literature pertaining to the efficacy and safety of the obesity medications currently approved by Health Canada. This guideline is written with the primary care clinician as the main audience, but is also intended for all clinicians whose practices encompass adults with obesity with or without weight-related health complications. This guideline may also be used by policymakers, insurers, people living with obesity, and their families.

There are six medications approved for obesity management in Canada: liraglutide 3 mg subcutaneously daily, naltrexone/bupropion 16/180 mg orally BID, orlistat 120 mg orally TID, semaglutide 2.4 mg subcutaneously weekly, tirzepatide 5 mg, 10 mg, and 15 mg subcutaneously weekly, and setmelanotide up to 3 mg subcutaneously daily. It is recognized that some other medications available in Canada, though not approved for obesity management, are used off-label for this purpose. Thus, our literature search employed an open strategy to capture all pharmacotherapy agents studied for obesity management. However, except for metformin, which is recommended for prevention of antipsychotic-induced weight gain (see The Role of Mental Health chapter), we discourage healthcare professionals from using medications solely for obesity management if they lack regulatory approval for this indication or evidence-based recommendations for their use. Non-prescription treatments and supplements are reviewed separately in the Commercial Products and Programs in Obesity Management chapter.

This guideline addresses clinical questions regarding the efficacy of pharmacotherapy in people with obesity, for the management of weight and weight-related complications. Search strategies were employed to identify studies of pharmacotherapy in subpopulations with important adiposity-related complications including atherosclerotic cardiovascular disease, heart failure, prediabetes, type 2 diabetes, metabolic-associated steatotic liver disease and steatohepatitis, dyslipidemia, hypertension, obstructive sleep apnea, osteoarthritis, polycystic ovary syndrome, chronic kidney disease, gastroesophageal reflux disease, and depression. Search strategies were employed to identify studies of pharmacotherapy in these subpopulations with weight loss as a primary endpoint, and to identify studies of approved pharmacotherapies for obesity management in these subpopulations with complication-specific endpoints, whether or not weight was included as an endpoint. Reduction in cravings and improvement in quality of life are important patient outcomes that are intertwined with successful obesity management; as such, our search strategy included studies of approved pharmacotherapies for obesity management on cravings and quality of life as well.

The literature search was limited to randomized controlled trials (RCTs) or meta-analyses of at least six months' duration published since the time of the last literature review for this chapter (January 2022) until July 2024. We manually searched reference lists and included studies that were not included in our literature review. Randomized controlled clinical trials published between July 2024 and May 2025, as judged by unanimous consensus of the writing group and Obesity Canada, were included in the chapter. For medications newly approved in Canada since the last literature review (tirzepatide and setmelanotide), all literature until July 2024 was included. Setmelanotide, a melanocortin 4 receptor (MC4R) agonist, is approved for the treatment of extremely rare monogenic forms of obesity. As RCTs or meta-analyses are not feasible in these populations, the search strategy for setmelanotide was broadened to include any published clinical trial of at least 6 months' duration which encompassed a randomized period in which treatment initiation or withdrawal of treatment was compared to placebo. This guideline was developed in accordance with the AGREE II framework [44] and was supported by a team of independent methodologists from the McMaster Evidence Review and Synthesis Team, who conducted the evidence appraisal following the Shekelle framework [45] to assess levels of evidence and grading of recommendations.

The recommendations in this clinical practice guideline are based on clinical trials that use BMI to define obesity. In these trials, non-white ethnicities were generally underrepresented, and BMI criteria were utilized which were not ethnicity-specific (see the Assessment of People Living with Obesity chapter). In addition, BMI does not provide information on body composition (fat versus muscle), or fat distribution (visceral versus subcutaneous). Other anthropometric measures, such as waist circumference, waist-to-hip ratio, and waist-to-height ratio, correlate strongly with adiposity related complications, and vary by sex and ethnicity. [1-3,46,47] Recommendation 1 in this guideline underscores the importance of incorporating these anthropometric measures of central adiposity to inform decisions regarding the initiation of pharmacotherapy for weight management. Applying Recommendation 1 to BMI-informed recommendations in this guideline will ensure that individuals who do not meet ethnicity-specific BMI criteria for obesity but do meet other sex- and ethnicity-specific anthropometric criteria, are appropriately identified for treatment. The authors of this guideline also advocate for a complication-centred approach to weight management, which embraces the diverse ways in which excess adiposity can affect health. The Edmonton Obesity Staging System (EOSS) is a tool that encompasses a complication-centred approach to obesity management focusing on the burden of obesity-related complications (see the Assessment Chapter). This approach necessarily shifts the focus from weight alone toward managing obesity-related complications and overall health. In this clinical practice guideline, the term 'adiposity-related' is used interchangeably with terms such as 'weight-related' and 'obesity-related' to highlight the effect of excess body fat and its distribution on health conditions. [48]

This guideline makes evidence-based recommendations for medications which are licensed for weight management in Canada, even if the medication is not licensed for the specific recommendation. This off-label prescribing aligns with medical ethics and recommendations of Canada's Drug Agency (CDA-AMC). [49]

All recommendations in this chapter are either updated or new since the most recent guideline update in 2022, reflecting the rapid and impactful advancements in the field of obesity pharmacotherapy.

Appendix 1. Pharmacotherapy for Obesity in Adults

	Liraglutide	Naltrexone/ Bupropion	Orlistat	Semaglutide	Tirzepatide
Mode of administration	Subcutaneous	Oral	Oral	Subcutaneous	Subcutaneous
Dose/frequency	3 mg daily	16/180 mg BID (8/90mg per tablet)	120 mg TID	2.4 mg weekly	5, 10, 15 mg weekly

Titration Schedule*	0.6mg daily x 1 week *then*
	1.2mg daily x 1 week *then*
	1.8mg daily x 1 week *then*
	2.4mg daily x 1 week *then*
	3.0 mg daily
		1 tablet daily x 1 week *then*
		1 tablet BID x 1 week *then*
		2 tablets in AM,1 tablet in PM x 1 week *then*
		2 tablets BID
			No titration	0.25mg weekly x 4 weeks *then*
				0.5mg weekly x 4 weeks *then*
				1mg weekly x 4 weeks *then*
				1.7mg weekly x 4 weeks *then*
				2.4mg weekly
					2.5mg weekly x 4 weeks *then*
					5mg weekly
					
					If increase indicated after 4 weeks at 5mg then
					7.5mg weekly x 4 weeks *then*
					10mg weekly
					
					If increase indication after 4 weeks at 10mg then
					12.5mg weekly x 4 weeks *then*
					15mg weekly

% weight loss, placebo subtracted	5.4% at 56 weeks [7]	4.8% at 56 weeks [8]	2.9% at 1 year [69]	12.4% at 68 weeks [5]	11.9% (5mg) 16.4% (10 mg) 17.8%(15 mg) at 72 weeks [6]
Effect on weight over longer term, placebo subtracted	4.3% at 3 years [18]	Not studied	2.8kg at 4 years [19]	12.6% at 104 weeks [78]	11% (5mg) 17.4% (10mg) 18.4% (15 mg) at 176 weeks [20]
% of patients achieving ≥ 5% weight loss	63.2% (vs. 27.1% with placebo) [7]	48% (vs. 16% with placebo) [8]	54% (vs. 33% with placebo) [69]	86.4% (vs 31.5% with placebo) [5]	85.1% (5mg) 88.9% (10mg) 90.9% (15mg) (vs 34.5% with placebo) [6]
% of patients achieving ≥ 10% weight loss	33.1% (vs. 10.6% with placebo) [7]	25% (vs. 7% with placebo) [8]	26% (vs. 14%with placebo) [69]	69.1% (vs 12% with placebo) [5]	68.5% (5mg) 78.1% (10mg) 83.5% (15 mg) (vs 18.8% with placebo) [6]
%of patients achieving ≥15% weight loss	14.4% (vs 3.5% with placebo) [7]	12% (vs. 2% with placebo) [8]	Not studied	50.5% (vs 4.9% with placebo) [5]	48.0 % (5mg) 66.6 %(10mg) 70.6 % (15mg) (vs 8.8 % with placebo) [6]

	Liraglutide	Naltrexone/ Bupropion	Orlistat	Semaglutide	Tirzepatide
% of patients achieving ≥20% weight loss	Not studied	Not studied	Not studied	Statistical significance not tested	30.0 % (5mg) 50.1 % (10 mg) 56.7 % (15mg) (vs 3.1% with placebo) [6]
Effect on maintenance of previous lifestyle-induced weight loss	6.2% additional placebo-subtracted weight loss at 1 year [12]	Not studied	2.4kg less weight regain vs. placebo over 3 years [13]	Not studied	94% patients able to maintain at least 80% of weight lost vs 43.8% with placebo [14]
Contraindications	• Personal or family history of medullary thyroid cancer • Personal history of MEN2 syndrome • Pregnancy, women attempting conception, breastfeeding	• Uncontrolled hypertension • Any opioid use • History of, or risk factors for, seizure • Abrupt discontinuation of alcohol • Concomitant administration of monoamine oxidase inhibitors (MAOI) • Severe hepatic impairment • End-stage renal failure • Pregnancy, women attempting conception, breastfeeding	• Cholestasis • Chronic malabsorption syndrome • Pregnancy, women attempting conception, breastfeeding	• Personal or family history of medullary thyroid cancer • Personal history of MEN2 syndrome • Pregnancy, women attempting conception, breastfeeding	• Personal or family history of medullary thyroid cancer • Personal history of MEN2 syndrome • Pregnancy, women attempting conception, breast-feeding
Common side effects	Nausea, constipation, diarrhea, vomiting	Nausea, constipation, headache, dry mouth, dizziness, diarrhea	Loose, oily stools, flatus	Nausea, diarrhea, constipation, vomiting	Nausea, diarrhea, constipation, dyspepsia, vomiting
Rare side effects	• Cholelithiasis • Pancreatitis	• Seizure • Worsening of depression	• Liver failure • Nephrolithiasis • Acute kidney injury	• Cholelithiasis • Pancreatitis	• Cholelithiasis • Pancreatitis
Drug interactions		Yes: See chapter text	• May reduce availability of oral contraceptives • Fat-soluble vitamins • Levothyroxine • Cyclosporine • Oral anticoagulants • Anticonvusants		• Reduces absorption of oral contraceptive during titration phase; switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation

*The medication can be titrated up more gradually and may need to be down-titrated if side effects or tolerance issues arise.

Appendix 2. Pharmacotherapy for Obesity in Adults: Effects on adiposity-related complications

	Liraglutide	Naltrexone/ Bupropion	Orlistat	Semaglutide	Tirzepatide
Effect on MACE	Cardiovascular safety demonstrated [104]	Not studied	Not studied	Reduction in MACE by 20% in people with ASCVD over 40 months [15]	Under Study
Effect on BP, placebo subtracted	−2.8; mm Hg SBP −0.9mmHg DBP [7]	+1.8 mmHg SBP +0.9 mmHg DBP [8]	+1.7 mm Hg SBP -0.71 mmHg DBP [114]	-5.1mm Hg SBP [5] -2.4mm Hg DBP [5]	SBP (mm Hg) -5.8 (5mg) -7.0 (10mg) -6.4(15mg) DBP (mm Hg) -4.2 (5mg) -4.5 (10mg) -3.6 (15 mg) [6]
Effect on lipids, placebo subtracted	percentage change: Total chol -2.3 LDL -2.4 HDL +1.9 non-HDL -3.9 Triglycerides -9.3 [7]	Percentage change: HDL +7.2% Triglycerides: - 9.6% [8]	LDL -0.23 mmol/L HDL -0.03 mmol/L [114]	Percentage change weighted mean difference: Total chol: -5.93% LDL: -6.55% Triglycerides: -18.34% [175]	Percentage change: Pooled Tirzepatide group Total chol -3.1% LDL -4.2% HDL +8.8% Triglycerides -20.3% [6]
Effect on HR, placebo subtracted	+2.4 BPM [7]	+1.4 BPM [8]	No change [114]	+4.2BPM [5]	+0.5 BPM (5 mg) +2.2 BPM (10 mg) +2.5 BPM (15 mg) [6]
Effect on HFpEF **(KCCQ-CSS score placebo subtracted)**	Not studied	Not studied	Not studied	Improvement of 7.8 points [17]	38% reduction of worsening HF event or CV death over 104 weeks Improvement of 9.8 points (pooled tirzepatide) [16]
Effect on prediabetes	79% reduction in risk of developing T2D at 3 years [18] 66% reversion to normoglycemia vs 36% with placebo [18]	Not studied	37.3% reduction in risk of developing T2D at 4 years [19]	81% reversion to normoglycemia vs. 14% with placebo at 52 weeks [21]	93% reduction in risk of developing T2DM at 176 weeks [20]

	Liraglutide	Naltrexone/ Bupropion	Orlistat	Semaglutide	Tirzepatide
Effect on type 2 diabetes (A1c, placebo subtracted)	-1.0% [24]	-0.5% [25]	-0.4% [26]	-1.2% [22]	−1·6% (10 mg) −1·6% (15 mg) [23]
Effect on MASH	Resolution of MASH without worsening of fibrosis (39% with liraglutide 1.8 mg vs. 9% with placebo) [28]	Not studied	No benefit [138]	Resolution of MASH without worsening of fibrosis (62.9% vs 34.3% with placebo) [27] Improvement in fibrosis without worsening of steatohepatitis (36.8% vs 22.4% with placebo) [27]	Resolution of MASH without worsening of fibrosis: 44% (5mg) 56% (10mg) 62% (15 mg) 10% (placebo) [29] Improvement in fibrosis without worsening of MASH: 55% (5 mg) 51% (10 mg) 51% (15 mg) 30% (placebo) [29]
Effect on OSA (Change in Apnea Hypopnea Index (AHI, placebo subtracted))	-6.1 events per hour [31]	Not studied	Not studied	Not studied	Patients not using Positive Airway Pressure (PAP): −20.0 events per hour Patients using PAP: −23.8 events per hour [30]
Effect on knee OA (Change in WOMAC pain scale, placebo subtracted)	No benefit [141]	Not Studied	Not Studied	Improvement of 14.2 points [32]	Not studied
Effect on PCOS	Not sufficiently studied	Not studied	Not studied	Not studied	Not studied
Effect on QoL	SF-36 – Improvement [170] IWQOL – Improvement [170]	IWQOL – Improvement [8]	Not studied	SF-36 - Improvement 5 IWQOL-Lite-CT – improvement [5]	SF-36v2 - improvement at all doses [171] IWQoL -Lite-CT improvement at all doses [171]
Effect on physical function	SF-36 – Improvement [170] IWQOL – Improvement [170]	IWQOL subscale– improvement [8]	Not studied	SF-36 - Improvement [5] IWQOL - improvement [5]	SF-36v2 -Improvement at all doses [171] IWQoL -Lite-CT improvement at all doses [171]
Effect on cravings (CoEQ)	Not studied	Improved [60]	Not studied	Improved [75]	Not studied

Key considerations in the use of pharmacotherapy for obesity management

The patient and healthcare professional should work together to identify clear goals of therapy prior to initiating obesity pharmacotherapy. The targets of treatment should be determined by the patient's values and preferences as they relate to their health and well-being, and should include a discussion around reasonable expectations of treatment, and potential benefits versus risks of pharmacotherapy. The treatment plan should acknowledge the cultural heterogeneity in what is considered acceptable or desirable in terms of body size and shape. In addition to weight loss, treatment targets can include reduction in cardiometabolic risk, improvement, remission, or resolution of adiposity-related complications, maintenance of weight loss, management of appetite and/or cravings, and improvement in quality of life.

The mechanism of action, efficacy, potential side effects/tolerability, and contraindications of each agent must be considered in the context of each patient's complications and pre-existing medications (see Appendix 1 and Appendix 2). The cost of medications, route of administration and frequency of dosing should be discussed, and must be acceptable to the patient to optimize compliance and adherence to long term treatment. It is important to assess concomitant medications as possible contributors to weight gain, and to consider alternatives where appropriate. (see Assessment of People Living with Obesity chapter)

Individualized goals of treatment are important in evaluating the success of pharmacotherapy. If goals of therapy have not been achieved, factors contributing to a suboptimal response such as cost, access, adequacy of dosing, challenges in adherence, barriers to health behaviour change, as well as psychosocial and medical issues should be reassessed. Consideration should be given to adding or substituting another obesity medication or intervention if treatment goals are not being achieved on the maximum tolerated dose.

Regulatory agencies have traditionally recommended discontinuing pharmacotherapy for weight management if weight loss of ≥ 5% has not been achieved after three months on a therapeutic dose. However, substantial health improvements and goals of therapy may be realized regardless of the magnitude of weight loss.

There is considerable heterogeneity in the response to any pharmacotherapeutic agent. Currently, we do not have the ability to predict which medication will be most effective for a patient. Preliminary data suggest that phenotypes of obesity [50] as well as metabolomic, proteomic, and genetic profiling [51] may be helpful in guiding the choice of pharmacotherapy in the future.

Obesity pharmacotherapy should be tailored to the individual, and medication should be titrated as tolerated to achieve the desired clinical effect. Some individuals may achieve their treatment goals with doses lower than the maximum dose of medication. Provided that the medication is well tolerated, patients should be treated for obesity-related complications at the dosage that demonstrates benefit in clinical trials. Patients may have more than one obesity-related health condition for which evidence supports use of different medications for each health condition. In the absence of definitive evidence for selection of medication in this situation, we support shared decision making informed by clinical priorities and patient preference.

Some individuals may experience adverse effects related to excessive weight loss. This can vary from feeling uncomfortable or unhappy with their weight being too low, feeling unwell, weakness, malnutrition, sarcopenia, and/or frailty. If an individual experiences excessive weight loss, it is important to assess for presence and severity of any gastrointestinal side effects of treatment, and whether investigations for other possible causes of weight loss are indicated. Ensuring adequate nutritional and protein intake and emphasizing the importance of physical activity to retain muscle mass is important for all patients at the onset of any weight management treatment strategy, and requires additional attention and emphasis for the patient experiencing excessive weight loss. In some cases, an assessment to explore body image constructs, the relationship between mental health and eating/activity behaviour changes, and the potential impact of weight loss on social relationships may be helpful. [52] In cases of excessive weight loss, weight management medication should be reduced to a dose where the patient is able to regain and maintain sufficient weight; in some cases, medication may need to be stopped.

Pharmacotherapy for obesity management should be considered early in the natural history of obesity, as weight and obesity-related health complications tend to increase and progress with time (see Assessment of People Living with Obesity chapter). Obesity medications are intended as part of a long-term treatment strategy. Clinical trials of pharmacotherapy for obesity management consistently demonstrate regain of weight and loss/regression of health benefits when treatment is stopped. [9-11,20]

The use of pharmacotherapy for obesity management is not recommended in pregnant or breastfeeding women, nor in women who are trying to conceive. There are no data available to inform on the timing of the discontinuation of pharmacotherapy for obesity management prior to conception (see discussion of individual medications below).

Approved pharmacotherapies for obesity management

Liraglutide 3 mg SC daily

Liraglutide is a daily, subcutaneously administered human glucagon-like peptide 1 (GLP-1) analog that acts centrally on the pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) neurons in the hypothalamus to improve satiety and reduce hunger. It also slows gastric emptying. [53,54] Liraglutide is approved for long-term obesity management as an adjunct to health behavior changes at a dose of 3 mg daily. [55] It is also indicated for the treatment of obesity in pediatric patients age 12 and older (see the Canadian Pediatric Obesity Clinical Practice Guideline). [56] The recommended starting dose of liraglutide is 0.6 mg daily, with up-titration by 0.6 mg each week as tolerated to a maximum dose of 3 mg daily.

In the SCALE obesity and prediabetes trial, among 3,731 people with BMI ≥30, or BMI ≥27 kg/m^2 with untreated dyslipidemia or hypertension, without diabetes, liraglutide 3 mg with health behaviour modification resulted in weight change of -8.0% vs -2.6% with placebo at 56 weeks.[7] Weight loss of ≥ 5% was seen in 63.2% of patients in the liraglutide group, compared with 27.1% of patients in the placebo group; 14.4% and 3.5% of participants lost more than 15% weight with liraglutide 3 mg and placebo, respectively. Placebo-subtracted change in waist circumference was -4.2 cm with liraglutide. Patients with prediabetes (n=2,254) were followed for 160 weeks, with weight change of -6.1% in the liraglutide group vs. -1.9% in placebo.[18] Mean weight plateaued after approximately week 50, with most of the weight loss maintained at 3 years.

In the SCALE IBT trial including 282 participants with BMI ≥30 kg/m^2, liraglutide 3 mg in addition to intensive behavioural therapy (IBT) resulted in -7.5% weight change at 56 weeks compared to -4.0% with placebo.[57]

In the SCALE maintenance study, amongst 422 participants with BMI ≥30, or BMI ≥27 kg/m^2 with obesity-related complications who achieved -6.0% weight change with a low-calorie diet, liraglutide 3 mg plus health behaviour counselling resulted in an additional weight change of -6.2% at 56 weeks compared with -0.2% in the placebo group. More patients were able to maintain the run-in weight loss of ≥ 5% (81.4%) with liraglutide 3 mg than with placebo (48.9%). Fewer patients on liraglutide 3 mg regained ≥ 5% body weight (1.9%) compared to placebo (17.5%).[12]

The most common side effects of liraglutide are nausea, diarrhea, constipation, vomiting and/or dyspepsia.[7,12,18,57] These were mostly transient, mild to moderate in severity, and occurred primarily during the dose-escalation period. More gradual titration can help mitigate gastrointestinal side effects. Liraglutide use is associated with a 1.4% higher risk of gallstones compared to placebo.[55] There may be a small increased risk of pancreatitis compared to placebo, with about half of cases seen in association with gallstones.[18] Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid cancer or a personal history of multiple endocrine neoplasia type 2 (MEN 2) because of an increased risk of medullary thyroid cancer seen in rodent studies. There have been no cases of medullary thyroid cancer in human studies.

Postmarketing cases of intestinal obstruction and ileus have been reported with liraglutide.[55] Rare case reports have raised concern that delayed gastric emptying from GLP1 receptor agonists may increase risk of pulmonary aspiration of gastric contents during general anesthesia and deep sedation. The safety of liraglutide has not been studied in gastroparesis and should not be used in this population.

Naltrexone/Bupropion 16 mg/180 mg BID

Naltrexone/bupropion is a combination extended-release tablet containing two medications. Bupropion is an antidepressant that induces satiety centrally by enhancing production and release of α-melanocyte stimulating hormone (α-MSH) and β-endorphin from the POMC cells in the hypothalamus. Naltrexone is an opioid receptor antagonist that disrupts the auto-inhibitory effect of *β*-endorphin on the POMC cells by blocking the μ-opioid receptors.[58] Naltrexone/bupropion also influences the mesolimbic reward system, resulting in a reduction in cravings.[8,59,60] Naltrexone/bupropion is approved for long-term obesity management as an adjunct to health behavior changes as a combined tablet containing 8 mg naltrexone and 90 mg bupropion, given as 2 tablets twice daily. The recommended titration schedule is one tablet daily for the first week, with an increase by one tablet each week as tolerated, to the maximum dose of two tablets twice daily (16 mg /180 mg BID).

In the COR-I study of 1,742 patients with BMI 30-45 kg/m^2 or BMI 27–45 kg/m^2 with dyslipidemia or hypertension, without diabetes, naltrexone/bupropion 16 mg/180 mg BID with health behavior changes was associated with weight change of -6.1% versus -1.3% with placebo at 56 weeks. Weight loss of ≥ 5% was seen in 48% of patients, and ≥ 15% weight loss was seen in 12% of patients with naltrexone/bupropion, compared with 16% and 2% in the placebo group, respectively. 8 Placebo-subtracted change in waist circumference was -3.7 cm with naltrexone/bupropion. Mean weight loss plateaued at approximately week 40.

In the COR-BMOD trial, 793 participants were randomized to receive naltrexone/bupropion or placebo as an adjunct to intensive behavior modification. Weight change at 56 weeks was -9.3% with naltrexone/bupropion vs -5.1% with placebo.[61]

A post-hoc analysis of six randomized controlled trials of 56, 78, and 208 weeks' duration included 10,198 participants with BMI 27-45 kg/m^2. Weight loss of ≥5% or ≥10% at week 16 of treatment with naltrexone/bupropion was associated with a greater likelihood of weight loss maintenance at up to 4 years.[62]

The most common side effects of naltrexone/bupropion include nausea, constipation, headache, vomiting, insomnia, dry mouth, dizziness, and diarrhea. Most nausea, constipation and vomiting events occur during the dose escalation period and are transient. Naltrexone/bupropion is contraindicated in patients with uncontrolled hypertension. Any opioid use is an absolute contraindication to the use of naltrexone/bupropion. Opioid therapy should be discontinued 7 to 10 days prior to initiation of naltrexone/bupropion to prevent the precipitation of opioid withdrawal.[63] As bupropion is associated with a slightly increased risk of seizure, naltrexone/ bupropion is contraindicated in seizure disorders, anorexia nervosa, bulimia, and patients undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates or antiepileptic drugs. Naltrexone/bupropion should be dosed with caution with any drugs that lower seizure threshold. Monoamine inhibitors (MAOIs) can increase the risk of hypertensive reactions, and naltrexone/bupropion should therefore not be used within 14 days of taking MAOI. Naltrexone/bupropion should not be taken with a high fat meal (≥ 55% fat), as this significantly increases systemic exposure to the medication.[64]

There are many potential drug interactions with naltrexone/bupropion, which stem from the effect of bupropion and its metabolites to inhibit the hepatic CYP2D6 enzyme system. Physicians and pharmacists must be aware of the importance of evaluating potential drug interactions prior to initiating naltrexone/bupropion. Among patients already receiving naltrexone/bupropion, medications metabolized by CYP2D6 should be started at the lower end of their recommended dosage range with cautious titration (e.g., selective serotonin reuptake

inhibitors, beta blockers, antipsychotic agents, type 1C antiarrhythmic agents and many tricyclic antidepressants, such as citalopram, metoprolol, risperidone, propafenone and desipramine, respectively). [65] For patients already receiving these medications, consideration should be given for dose reduction when starting naltrexone/ bupropion. Bupropion may result in reduced efficacy of tamoxifen and should therefore not be used in combination with it. Bupropion is primarily metabolized by the CYP2B6 enzyme system. Therefore, naltrexone/ bupropion dosing should not exceed one tablet twice daily when used with CYP2B6 inhibitors (e.g., ticlopidine, clopidogrel). [66] Naltrexone/bupropion should be avoided in patients taking CYP2B6 inducers as these may reduce efficacy of naltrexone/ bupropion by reducing bupropion exposure (e.g., ritonavir, lopinavir, efavirenz, carbamazepine, phenobarbital, phenytoin). [65] Central nervous system toxicity can occur when naltrexone/ bupropion is used concomitantly with dopaminergic drugs (e.g., levodopa, amantadine).

Orlistat 120mg TID

Orlistat is a potent and selective orally administered inhibitor of pancreatic lipase which inhibits the breakdown of dietary triglycerides into absorbable free fatty acids. As a result, approximately 30% of ingested triglycerides are excreted, primarily in the feces, creating a caloric deficit. [67] Orlistat does not target appetite or satiety mechanisms. It is approved as a long-term obesity pharmacotherapy in adults in conjunction with health behavior changes at a dose of 120 mg three times daily, taken during or up to 1 hour after meals. [68] It is also indicated for the treatment of obesity in pediatric patients age 12 and older (see the Canadian Pediatric Obesity Clinical Practice Guideline). [56]

A systematic review and meta-analysis of randomized controlled trials of orlistat 120 mg three times daily including 10,631 participants reported a mean placebo subtracted weight change of -2.9% at one year. [69] Weight loss of ≥ 5% and ≥ 10% was achieved with orlistat by 54% and 26% of patients, respectively, compared to 33% and 14% with placebo. [69] Placebo-subtracted change in waist circumference was -2.1 cm with orlistat. In a 4-year study including 3,305 participants, mean weight change in addition to health behavior changes was -5.8 kg with orlistat vs -3 kg with placebo. Mean weight plateaued after 52 weeks, followed by gradual weight regain. [19] Orlistat has been shown to be effective in maintaining weight loss after a very low energy diet for eight weeks, with less weight regain in the orlistat arm compared to placebo over three years (4.6 kg vs. 7.0 kg). [13]

Orlistat therapy is associated with prevalent gastrointestinal effects due to reduced absorption of dietary fat, including oily spotting and loose stools, flatus with discharge, fecal urgency and increased defecation. [69] These adverse effects may cause patients who do not lower their dietary fat intake to discontinue therapy. A long-term analysis of obesity medications in Canada demonstrated six-month, one-year and two-year persistence rates with orlistat therapy of 18%, 6% and 2%, respectively. [70] Orlistat therapy may interfere with the absorption of fat-soluble vitamins (A, D, E and K), and patients should thus be counselled to take a multivitamin at least two hours before or after taking orlistat. [69,71] Orlistat is contraindicated in patients with chronic malabsorption syndrome or cholestasis. Some patients may develop increased levels of urinary oxalate with orlistat; cases of oxalate nephropathy with renal failure have been reported. [72] There have also been rare cases of severe liver injury or acute liver failure. [73]

As orlistat may interfere with vitamin K absorption, the international normalized ratio (INR) should be monitored closely when oral anticoagulants are co-administered. Orlistat may affect absorption of levothyroxine and/or iodine salts; patients on levothyroxine should be monitored for changes in thyroid hormone levels. Orlistat may indirectly reduce the availability of oral contraceptives. [68] A reduction in plasma cyclosporine levels has been observed when orlistat is co-administered; thus, it is recommended to monitor cyclosporine levels more frequently. Orlistat may affect absorption of anticonvulsants, therefore patients on anticonvulsants and orlistat should be monitored for possible changes in the frequency and/or severity of seizure.

The modest weight loss with orlistat above placebo, as well as its frequent gastrointestinal side effects, limit its use in management of obesity.

Semaglutide 2.4 mg SC weekly

Semaglutide is a once weekly, subcutaneously administered GLP-1RA that acts centrally on the pro-opiomelanocortin POMC/CART neurons to improve satiation and satiety, reduce hunger, and reduce cravings. [74,75] It also slows gastric emptying. [74] It is indicated for long-term obesity management in adults at a dose of 2.4 mg weekly as an adjunct to health behaviour changes. [76] It is also indicated for the treatment of obesity in pediatric patients age 12 and older (see the Canadian Pediatric Obesity Clinical Practice Guideline). [56] The recommended starting dose of semaglutide is 0.25 mg weekly, with up-titration every 4 weeks as tolerated to 0.5 mg weekly, 1 mg weekly, 1.7 mg weekly, then to the maximum dose of 2.4 mg weekly.

In the STEP 1 study of 1,961 people with BMI ≥30 kg/m^2 or BMI ≥ 27 kg/m^2 with at least one weight-related coexisting condition, without diabetes, semaglutide 2.4 mg with health behaviour modification resulted in a weight change of -14.9% at 68 weeks, compared to -2.4% with placebo. In terms of categorical weight loss, 86.4% of patients lost ≥5% weight with semaglutide, vs 31.5% with placebo; 50.5% of patients lost ≥ 15% weight with semaglutide vs 4.9% with placebo. 5 Placebo-subtracted change in waist circumference was -9.4 cm with semaglutide. An off-treatment extension of 327 participants for an additional year [77] demonstrated that following treatment withdrawal, participants previously treated with semaglutide (who had -17.3% weight change at 68 weeks) had regained 11.6% weight. Placebo participants (who had -2.0% weight change at 68 weeks) regained 1.9% weight. The weight increase had not plateaued in the group previously randomized to semaglutide at the end of the extension study (week 120).

Longer term efficacy and safety of semaglutide 2.4 mg in addition to behavioural intervention over 104 weeks was evaluated for weight management in 304 people with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with at least one weight-related complication in the STEP 5 trial. 78 The mean change in body weight was -15.2% with semaglutide vs -2.6% with placebo. Mean weight plateaued after approximately week 60 and was maintained for the remainder of the study. Though not a weight management trial, the SELECT cardiovascular outcome trial

demonstrated that weight loss with semaglutide 2.4 mg was sustained over 4 years, with a safety profile similar to that of previously conducted studies with semaglutide 2.4 mg. [79]

In the STEP 3 study, which included 611 participants with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with at least one weight-related complication, in addition to a low-calorie diet for eight weeks followed by intensive behavioural therapy for 68 weeks, weight change with semaglutide 2.4 mg was -16.0% vs −5.7% with placebo. [80]

In the STEP 4 trial, 803 individuals with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with at least one weight-related complication who completed a 20-week run-in with semaglutide 2.4 mg weekly achieved a mean weight change of -10.6%. These individuals were then randomized to either continue treatment with semaglutide or switch to placebo for an additional 48 weeks. At the end of the study, individuals that continued with semaglutide experienced an additional weight change of -7.9%. Those that were switched to placebo regained 6.9% weight, [10] and this weight increase had not plateaued at the end of the study.

In the open-label randomized STEP 8 study of semaglutide 2.4 mg weekly vs liraglutide 3 mg daily in 338 people with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with at least one weight-related complication, without diabetes, mean weight change at 68 weeks was -15.8% with semaglutide vs -6.4% with liraglutide. Gastrointestinal side effects were seen in similar proportions of patients with semaglutide and liraglutide, though more events occurred with semaglutide than liraglutide. Proportions of participants discontinuing treatment for any reason were 13.5% with semaglutide vs 27.6% with liraglutide. [81]

The most common side effects of semaglutide are gastrointestinal, including nausea, vomiting, diarrhea, constipation, and heartburn. These were mostly transient, mild to moderate in severity, and occurred primarily during the dose-escalation period. More gradual titration can help mitigate gastrointestinal side effects. Semaglutide use is associated with a 0.9% higher risk of gallstones compared to placebo. [76] There may be a small increased risk of pancreatitis. [5] Semaglutide is contraindicated in patients with a personal or family history of medullary thyroid cancer or in patients with MEN 2 because of an increased risk of medullary thyroid cancer in rodent studies. [76] There have been no cases of medullary thyroid cancer in human studies of semaglutide 1.0 mg nor semaglutide 2.4 mg. In the SELECT cardiovascular outcome trial, fractures of the femur and pelvis were reported in 1.0% of females in the semaglutide 2.4 mg group vs 0.2% of females in the placebo group. In people aged 75 and older, fractures of the femoral neck, femur, hip and pelvis were reported in 2.4% of patients in the semaglutide group vs 0.6% of patients in the placebo group. [76]

Semaglutide could potentially influence absorption of concomitantly administered oral medications due to slowing of gastric emptying. In clinical pharmacology trials, no clinically relevant drug-drug interactions with semaglutide 1 mg were observed based on the evaluated medications. The manufacturer recommends discontinuation of semaglutide at least two months before a planned pregnancy. [76]

Postmarketing cases of ileus and intestinal obstruction have been reported with semaglutide. [76] Rare case reports have raised concern that delayed gastric emptying from GLP1 receptor agonists may increase risk of pulmonary aspiration of gastric contents during general anesthesia or deep sedation. Semaglutide has not been studied in people with gastroparesis.

Tirzepatide 5 mg, 10 mg, 15 mg SC weekly

Tirzepatide is a once-weekly subcutaneously administered dual GIP/GLP1 receptor agonist. The GLP-1 component acts centrally on the POMC/CART neurons to improve satiation and satiety and reduce hunger. [82] Tirzepatide also slows gastric emptying. [83] Like GLP-1, glucose-dependent insulinotropic polypeptide (GIP) is a nutrient-stimulated hormone that regulates energy balance through cell-surface receptor signaling in the brain and adipose tissue. The GIP component is hypothesized to act centrally to enhance GLP-1-induced weight loss. [84] Tirzepatide is approved for use for chronic weight management, including weight loss and weight maintenance, as an adjunct to health behavior changes at doses of 5 mg, 10 mg and 15 mg weekly. The recommended starting dose of tirzepatide is 2.5 mg weekly, with up-titration by 2.5 mg every 4 weeks as needed and tolerated to achieve the desired treatment goals, to a maximum dose of 15 mg weekly. [85]

In the SURMOUNT-1 study, 2,539 adults with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with at least one weight-related complication, without diabetes, were randomized to receive tirzepatide 5 mg, 10 mg, 15 mg or placebo for 72 weeks, in addition to health behavior changes. [6] At 72 weeks, the mean weight change with 5 mg, 10 mg and 15 mg was −15.0%, −19.5%, and −20.9% respectively, compared with −3.1% with placebo. The proportion of participants achieving at least 5% weight reduction in the 5 mg, 10 mg and 15 mg groups were 85%, 89% and 91% respectively, vs 35% in the placebo group. Fifty percent of participants in the 10 mg and 57% of participants in the 15 mg groups achieved weight loss of ≥20%, vs 3% in the placebo group. Placebo-subtracted change in waist circumference was -10.0 cm, -13.7 cm, and -14.5 cm with tirzepatide 5 mg, 10 mg, and 15 mg, respectively. Patients with prediabetes (n=1,032) were followed for 176 weeks, with weight change of -12.3%, -18.7%, and -19.7% with tirzepatide 5 mg, 10 mg, and 15 mg vs. -1.3% with placebo. [20] Mean weight plateaued after approximately week 60 (5 mg), week 72 (10 mg), and week 85 (15 mg) and was maintained for the remainder of the study.

Tirzepatide use was evaluated in 579 participants with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with at least one weight-related complication, who were able to achieve at least 5% weight loss with a 12-week intensive lifestyle intervention (ILI) in the SURMOUNT-3 trial. [14] Following an average -6.9% change in body weight with ILI, there was a further weight change of -18.4% at 72 weeks with tirzepatide at maximum tolerated dose (10 mg or 15 mg), compared to a weight change of +2.5% with placebo. In the tirzepatide group, 94% of participants were able to maintain ≥80% of weight lost during the 12-week ILI vs 43.8% of patients in the placebo group.

In the SURMOUNT-4 study, 670 participants with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with at least one weight-related complication who completed a 36-week lead-in period with tirzepatide at maximum tolerated dose (10 or 15 mg) achieved a mean weight change of -20.9%. [11] Following a subsequent 52-week double-blind period where participants were randomly assigned to either continue

tirzepatide or switch to placebo, participants continuing tirzepatide experienced a further weight change of -5.5%. Those who switched to placebo regained 14.0% of their weight, and this weight increase had not plateaued at the end of the study.

The SURMOUNT-5 trial was an open label randomized trial in which 751 adults with BMI ≥30 kg/m² or ≥27 kg/m² with at least one weight-related comorbidity, without diabetes, were randomized 1:1 to receive either maximum tolerated dose of tirzepatide (10 mg or 15 mg weekly) or semaglutide (1.7 mg or 2.4 mg weekly) for 72 weeks.[86] The mean weight change was -20.2% with tirzepatide compared with -13.7% with semaglutide. Weight loss of at least 10% was experienced by 81.6% of people with tirzepatide vs 60.5% with semaglutide. Weight loss of at least 25% was experienced by 31.6% of people in the tirzepatide group vs 16.1% with semaglutide. Tirzepatide also resulted in a greater change in waist circumference (−18.4 cm vs. −13.0 cm) compared with semaglutide. Serious adverse events occurred in 4.8% of tirzepatide-treated and 3.5% of semaglutide-treated participants. Gastrointestinal side effects were the most common side effects in both groups, generally mild to moderate in severity, and occurred mostly during dose escalation. Treatment discontinuation related to gastrointestinal side effects occurred more commonly in the semaglutide group (5.6%) compared with tirzepatide (2.7%). Injection site reactions were more common with tirzepatide (8.6%) compared with semaglutide (0.3%).[86]

The most frequently reported adverse events with tirzepatide were gastrointestinal (nausea, diarrhea, and constipation). These were mostly transient, mild to moderate in severity, and occurred primarily during the dose-escalation period. More gradual titration can help mitigate gastrointestinal side effects. While no increased risk of pancreatitis has been noted in obesity trials, a slightly increased risk was noted in clinical trials of tirzepatide among patients with T2D.[85] Tirzepatide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with MEN 2 because of an increased risk of medullary thyroid cancer in rodent studies. No cases of medullary thyroid cancer have been reported in human studies. 6,11,14,23 There is a small increased risk of acute gallbladder disease (cholelithiasis 1.1% with tirzepatide vs 1.0% with placebo, cholecystitis 0.6% with tirzepatide vs 0.2% with placebo).[85]

Tirzepatide delays gastric emptying, which could potentially influence absorption of concomitantly administered oral medications. For patients using oral contraceptives, it is recommended to switch to a non-oral contraceptive method, or to add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation.[85] The manufacturer recommends discontinuation of tirzepatide at least one month before a planned pregnancy.

Postmarketing reports of ileus have been reported with tirzepatide.[85] Rare case reports have raised concern that delayed gastric emptying from GLP1 receptor agonists may increase risk of pulmonary aspiration of gastric contents during general anesthesia or deep sedation. Available data are insufficient to inform recommendations to mitigate the risk of pulmonary aspiration during general anesthesia or deep sedation in patients using tirzepatide. Tirzepatide has not been studied in people with severe gastroparesis and is not recommended in these patients.

Setmelanotide 3 mg daily

Setmelanotide is a daily, subcutaneously administered melanocortin 4 receptor (MC4R) agonist. It is designed to restore impaired MC4R activity caused by extremely rare genetic deficits leading to hyperphagia (an overwhelming, heightened, pathological, and often insatiable hunger accompanied by preoccupation with food and abnormal food-seeking behaviors)[87,88] and early onset severe obesity.[89] Setmelanotide is indicated for long-term weight management in patients with obesity due to Bardet-Biedl syndrome (BBS) or genetically confirmed biallelic pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency that are pathogenic, likely pathogenic, or of unknown significance, at a dose of up to 3 mg daily.[90] Setmelanotide is also indicated for the treatment of these rare genetic conditions causing obesity in pediatric patients age 6 and older (see the Canadian Pediatric Obesity Clinical Practice Guideline).[56] Patients with clinical features of monogenic or syndromic obesity should be considered for genetic testing. The recommended starting dose of setmelanotide for adults is 1 mg daily, with titration by 0.5 mg every 2 weeks as tolerated to a maximum of 3 mg daily.

Due to the rarity of monogenic and syndromic causes of obesity, conducting large randomized controlled trials in these populations is not feasible.

Bardet-Biedl syndrome (BBS) is a rare autosomal recessive syndromic cause of obesity. Clinical diagnosis is based on features such as intellectual disability, retinal dystrophy, polydactyly, renal malformations and microorchidism in men.[91] Approximately 72-92% of people with BBS have obesity,[92] which is often driven by hyperphagia.[93] A randomized, 14-week, double-blind, placebo-controlled trial followed by a 52-week open-label setmelanotide treatment period (up to 3 mg daily) was conducted in 32 patients with Bardet-Biedl syndrome and obesity (BMI in adults ≥30 kg/m^2).[33] Mean weight change amongst adults who completed 52 weeks of treatment was -9.1%. Nine of 15 adults (60%) achieved at least 5% weight reduction, and 7 of 15 (47%) achieved at least 10% reduction. Amongst participants aged 12 or older who reported hunger scores, 8/14 (57%) achieved at least 25% reduction in hunger score after 52 weeks with setmelanotide, with a mean percentage change in maximal hunger score of -30.5%. Ten of 14 patients (71%) achieved a meaningful reduction of 1 point or more in their maximum hunger score.

Rare monogenic autosomal recessive loss of function mutations in POMC, PCSK1 or LEPR can result in severe early-onset obesity due to hyperphagia.[94,95] Other characteristics may include delayed puberty, variable stature and growth trajectories, and concomitant endocrine disorders.[96] Ten patients aged 6 years or older (4 adults with BMI ≥30 kg/m^2) with POMC deficiency (homozygous or compound heterozygous variants in POMC or PCSK1) were treated with open-label setmelanotide for 12 weeks to achieve a target weight loss of 2-3 kg/week, up to a maximum dose of 3 mg/day.[34] Those who lost ≥5 kg (or ≥5% weight loss in those with baseline weight <100 kg) entered an 8-week double-blind withdrawal phase consisting of 4 weeks of treatment with setmelanotide and 4 weeks with placebo, followed by a 32-week open-label treatment phase. At one year, 80% of patients achieved ≥10% weight loss, with a mean weight change of -25.6%. Hunger scores decreased by 27.1% in the 7 patients with available data. During the withdrawal phase, the mean weight change was −3.0 kg with

setmelanotide vs +5.5 kg with placebo. Hunger scores showed no significant change during this phase. In this same study, amongst 11 participants (including eight adults with BMI ≥30 kg/m^2) with LEPR deficiency, 45% achieved ≥ 10% weight loss at one year, with a mean weight change of -12.5%. Hunger scores decreased by 43.7% in the 7 patients with available data. During the withdrawal phase, mean weight change was -2.1 kg with setmelanotide and +5.0 kg with placebo, and was associated with a reduction in hunger scores.

The most common side effects with setmelanotide include skin hyperpigmentation, injection site reactions, nausea and vomiting. Spontaneous penile erections were also reported. It is recommended to perform a full body skin examination prior to starting treatment and periodically thereafter to monitor pre-existing and for new pigmented skin lesions. Setmelanotide should not be used in people with a personal or family history of melanoma or pre-melanoma skin lesions.[90] Setmelanotide is contraindicated in pregnancy, women attempting pregnancy, and breastfeeding.

Setmelanotide is under investigation as a potential treatment for other monogenic forms of obesity associated with impaired MC4R signaling, 97 as well as acquired hypothalamic obesity.[98,99] Topline results in people with acquired hypothalamic obesity have suggested benefit, though these data are not yet published.[99]

Efficacy of pharmacotherapy on health parameters

The efficacy of obesity pharmacotherapy in improving complications associated with obesity such as cardiovascular disease, heart failure with preserved ejection fraction (HFpEF), hypertension, dyslipidemia, prediabetes, type 2 diabetes, metabolic dysfunction-associated steatotic liver disease and metabolic dysfunction-associated steatohepatitis (MASLD/MASH), obstructive sleep apnea, and osteoarthritis, highlights their potential benefits beyond weight reduction (see Appendix 2). The information in this section can assist healthcare professionals in tailoring treatments to individual patients based on their unique health profiles and presence of obesity-related complications. The beneficial effects of weight management medications on these complications may reduce healthcare costs associated with these complications and support the role of these medications in the comprehensive management of patients with obesity.

Atherosclerotic cardiovascular disease

Obesity is strongly associated with cardiovascular risk factors and is a major driver of cardiovascular disease (CVD), which remains a leading cause of morbidity and mortality worldwide.[100-102]

The SELECT study evaluated semaglutide 2.4 mg vs placebo in addition to standard of care in 17,604 participants with BMI ≥27 kg/m^2 and cardiovascular disease, without diabetes. 15 The primary endpoint was a composite of major adverse cardiovascular events (MACE) (death from CV causes, nonfatal myocardial infarction, or nonfatal stroke). Over a mean of 40 months of follow-up, the risk of a cardiovascular event was reduced by 20% with semaglutide vs placebo. Death from any cause was reduced by 19%, and heart failure was reduced by 18%. Mean weight change was -9.4% with semaglutide over the first 2 years vs -0.9% with placebo, and weight loss was maintained through the duration of the trial. Based on these results, Health Canada has approved semaglutide 2.4 mg for reduction in risk of non-fatal myocardial infarction in adults with established CVD and BMI ≥27 kg/m^2.[76]

In patients with type 2 diabetes, liraglutide 1.2 –1.8 mg has been shown to reduce cardiovascular events and mortality in people with T2D.[103] These data have been accepted as sufficient safety data by the U.S. Food and Drug Administration to reassure the cardiovascular safety of liraglutide in people with obesity without T2D, at the therapeutic dose of 3 mg daily. The cardiovascular safety of liraglutide 3 mg was evaluated post hoc using data from five randomized, double-blind, placebo-controlled clinical trials comprising 5,908 patients, 97% of whom did not have diabetes. Liraglutide 3 mg was not associated with excess cardiovascular risk.[104]

The Cardiovascular Outcomes Study of Naltrexone SR/Bupropion SR in Overweight and Obese Subjects with Cardiovascular Risk Factors (LIGHT) study was a cardiovascular outcome trial undertaken to assess the cardiovascular safety of naltrexone/bupropion. Interim results were released after 25% of the planned MACE events occurred, compromising the integrity of the trial. Although the trial was terminated upon the recommendation of the lead investigator, the results of the preplanned 50% interim analysis were released and did not demonstrate increased cardiovascular risk.[105] These results could not be used to establish non-inferiority due to the compromise of the trial. A meta-analysis including 12 RCTs comprising 19,176 patients was conducted which showed no significant effect of bupropion, naltrexone, or naltrexone/bupropion on MACE.[106] A randomized, double-blinded, placebo controlled study intended to capture CV outcomes during real-world use of naltrexone/bupropion is currently underway.[107]

Tirzepatide is currently under investigation in cardiovascular outcome trials in people with obesity without diabetes,[108] and in people with T2D.[109]

There are no cardiovascular outcome trials for orlistat.

Cardiovascular risk factors: Hypertension and Lipids

Obesity is a major risk factor for hypertension,[110] due to metabolic, hemodynamic and molecular changes which differ based on body fat distribution.[111] Hypertension is a highly prevalent complication amongst people with obesity.[112] Obesity is associated with dyslipidemia, typically resulting in elevated triglycerides and low HDL cholesterol levels.[113]

Among patients with obesity and prediabetes, change in systolic blood pressure with liraglutide was -2.8 mmHg compared with placebo at three years. There were beneficial effects on lipid parameters.[7]

Naltrexone-Bupropion did not demonstrate improvement in blood pressure (BP) and can increase BP on initiation;

as such, it is contraindicated in patients with uncontrolled hypertension.[63] Naltrexone-Bupropion demonstrated beneficial effects on cholesterol profiles.[8]

In a meta-analysis including 17 trials of orlistat vs placebo of minimum 1 year duration (n=10,702), orlistat demonstrated a minimal effect on BP and lipid profiles.[114]

Change in systolic BP with semaglutide was -5.1 mmHg compared with placebo at 68 weeks,[5] with improvement in lipid parameters.[5] Most of the blood pressure reduction was observed during the titration phase of medication.

Change in systolic and diastolic BP with tirzepatide was -5.8 to -7.0 mm Hg and -3.6 to -4.5 mmHg respectively in the pooled tirzepatide groups (5 mg, 10 mg, and 15 mg) compared with placebo.[6] Of note, the change in systolic BP was greatest during the first 24 weeks of the trial. Tirzepatide was also shown to have beneficial effects on all aspects of the lipid profile.

Liraglutide, semaglutide, and tirzepatide have all demonstrated a small increase in heart rate, in keeping with what is known of GLP1 RA-containing medications (see Appendix 2).

Weight loss is associated with reductions in BP.[115] Persons with hypertension being treated with weight loss pharmacotherapy should be monitored for changes in blood pressure, and antihypertensive medication should be adjusted where clinically appropriate.

Heart failure with preserved ejection fraction (HFpEF)

Obesity is a particularly common phenotype in people with HFpEF, with reported prevalence of up to 84%.[116] The relationship between obesity and HFpEF is complex, and is mediated not only by the excess of adipose tissue, but also by complications associated with obesity.[117] As weight loss has been shown to improve HFpEF,[118] it is of interest whether pharmacotherapy for obesity management may be of benefit in people with HFpEF.

The SUMMIT Trial[16] evaluated the safety and efficacy of tirzepatide in 731 patients aged 40 or older, with HFpEF [left ventricular ejection fraction (LVEF) ≥50%] and BMI ≥30 kg/m^2 (48% with T2D). Participants were randomized to receive tirzepatide titrated to maximum tolerated dose (maximum 15 mg) or placebo. At 104 weeks, the composite endpoint of death from cardiovascular causes or a worsening heart failure event was reduced by 38% in the tirzepatide group vs placebo. A worsening HF event, and worsening HF event resulting in hospitalization were reduced with tirzepatide by 46% and 56% respectively vs placebo. The Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS), a questionnaire that measures symptoms, physical and social limitations, and quality of life in people with heart failure, improved by 19.5 points in the tirzepatide group vs 12.7 points in the placebo group at 1 year. Weight change was -13.9% with tirzepatide vs -2.2% with placebo. The mean six-minute walk distance was improved by 26 m in the tirzepatide group versus 10.1 m with placebo.

The STEP HFpEF trial included 529 people with HFpEF (LVEF ≥45%) and BMI ≥30 kg/m^2 without diabetes and randomized them to receive either semaglutide 2.4 mg weekly or placebo for one year.[17] At one year, the mean improvement in the KCCQ-CSS score was 16.6 points with semaglutide vs 8.7 points with placebo. Weight change was -13.3% with semaglutide vs -2.6% with placebo. The mean six-minute walk distance was improved with semaglutide by 21.5 m vs 1.2 m with placebo. Similar placebo-subtracted benefit in KCCQ-CSS score was seen in a similar study undertaken in people with HFpEF and T2D.[119]

No studies of liraglutide, naltrexone/bupropion, or orlistat in patients with HFpEF were identified.

Heart failure with reduced ejection fraction (HFrEF)

Obesity may increase the risk of HFrEF based on some, but not all, data. Data are lacking to support that weight loss affects heart failure outcomes in people with obesity and HFrEF.[120-122]

The SELECT trial included 1347 patients with BMI ≥27kg/m^2 and HFrEF. In a prespecified subgroup analyses, semaglutide 2.4 mg weekly did not reduce the HF composite outcome but did reduce major adverse cardiovascular events by 35%.[123]

Liraglutide 1.8 mg has been evaluated in people with established HFrEF. In the 24-week LIVE trial, liraglutide 1.8mg did not improve LVEF, and was associated with an increase in heart rate and risk of serious cardiac side effects (10% vs 3% with placebo).[124] In the FIGHT trial, treatment with liraglutide 1.8 mg resulted in no improvement in outcomes in patients with HFrEF who were recently hospitalized.[125]

No studies specifically evaluating obesity pharmacotherapy in people with HFrEF were identified.

Prediabetes

Although the exact prevalence of prediabetes in people with obesity is not known, studies suggest that between 14.3% to 36.9% of adults with obesity may have prediabetes.[126,127] People with prediabetes are at high risk of developing T2D, with about 25% of individuals with either impaired fasting glucose or impaired glucose tolerance (IGT) progressing to T2D over three to five years.[128] In individuals with prediabetes, one kilogram of weight loss is associated with a 16% relative risk reduction in the development of T2D.[35]

The SCALE Obesity and Prediabetes trial randomized 2,254 patients with prediabetes and BMI ≥30 kg/m^2 or ≥27 kg/m2 with dyslipidemia and/or hypertension, to receive liraglutide 3 mg daily (n=1,505) or placebo (n=749), in addition to health behaviour change.[18] The time to onset of T2D over 160 weeks was 2.7 times longer with liraglutide 3 mg vs. placebo, and the risk of developing T2D was reduced by 79% with liraglutide. At the end of the trial, 66% of those in the liraglutide 3 mg group had reverted from prediabetes to normoglycemia compared to 36% in the placebo group.[18]

The XENDOS study randomized 3,305 patients with BMI ≥30 kg/m2 and normal (79%) or impaired (21%) glucose tolerance (IGT), to receive Orlistat 120 mg TID (n= 1,640) or placebo (n= 1,637), in addition to health behaviour change.[19] At 208 weeks, progression to diabetes was observed in 6.2% in the orlistat group vs

9.0% in the placebo group. People with IGT at baseline derived the greatest benefit in terms of decreased rate of progression to T2D.

The SURMOUNT-1 study randomized 1,032 adults with prediabetes and BMI ≥30 kg/m or BMI ≥27 kg/m^2 with at least one obesity-related complication to receive tirzepatide 5 mg, 10 mg, 15 mg weekly (n=762) or placebo (n=270), in addition to health behaviour change.[20] At 176 weeks, the risk of progression to T2D was decreased by 93% with tirzepatide vs placebo. Following the subsequent 17 week off-treatment period, 8 new cases of type 2 diabetes were observed in the groups previously treated with tirzepatide, in parallel with weight regain off treatment.

The STEP 10 study randomized 207 individuals with BMI ≥30 kg/m^2 and prediabetes to receive semaglutide 2.4 mg (n=138) or placebo (n=69), in addition to health behaviour change.[21] At 52 weeks, 81% of participants reverted to normoglycemia with semaglutide vs 14% with placebo. Following the subsequent 28 weeks off treatment, a decrease in the proportion of patients remaining normoglycemic was observed amongst those previously treated with semaglutide, along with weight regain and regression of cardiometabolic risk factors.

No studies of naltrexone/bupropion in people with prediabetes were identified.

Type 2 diabetes

Obesity in people with T2D is associated with poorer glycemic control, blood pressure control and lipid profiles, as well as an increased use of lipid-lowering and antihypertensive medications, compared to those with T2D who do not have obesity.[129]

The effect of glucose-lowering pharmacotherapy on weight should be considered when choosing the most appropriate medication(s) for glycemic control. GLP1 receptor agonists, GIP/GLP1 receptor agonists, and sodium/glucose cotransporter 2 (SGLT2) inhibitors not only improve glycemic control but also promote weight loss. Metformin, dipeptidyl peptidase-4 (DPP4) inhibitors, and acarbose are typically weight neutral. Insulin, insulin secretagogues, and thiazolidinediones are associated with weight gain.[130] Pharmacotherapy for obesity can be of benefit for weight management, improved diabetes control, and reduction in need for other glucose-lowering medications.

In the STEP 2 study, 22 1,210 people with BMI ≥ 27 kg/ m^2 and T2D managed with 0-3 oral agents were randomized to semaglutide 2.4 mg weekly, 1 mg weekly, or placebo, in addition to health behaviour change. At 68 weeks, weight change was superior with semaglutide 2.4 mg at -9.6% at 68 weeks, vs -7.0% with 1.0 mg, and -3.4% with placebo. Change in hemoglobin A1c (HbA1c) was similar with semaglutide 2.4 mg (-1.6%) and 1 mg (-1.5%), both superior to placebo (-0.4%).

In the SURMOUNT-2 study, the efficacy of tirzepatide for weight loss was evaluated among 938 adults with BMI ≥ 27 kg/ m^2 and T2D managed with 0-3 oral medications.[23] Participants were randomized to receive tirzepatide 10 mg or 15 mg weekly, or placebo, in addition to health behaviour change. At 72 weeks, the mean change in body weight with 10 mg and 15 mg of tirzepatide was −12.8% and −14.7% respectively, both superior to placebo (−3.2%). Change in HbA1c was similar with tirzepatide 10 mg and 15 mg (-2.1%), both superior to placebo (-0.5%).

In the SCALE diabetes trial, liraglutide 3 mg daily was compared to 1.8 mg daily and placebo, in addition to health behaviour changes, in 846 people with BMI ≥ 27 kg/ m^2 and T2D managed with 0-3 oral agents. At 52 weeks, weight change was -6.0% with liraglutide 3 mg, -4.7% with liraglutide 1.8 mg, and -2.0% with placebo. Change in HbA1c was -1.3% with liraglutide 3 mg and -1.1% with liraglutide 1.8 mg, vs -0.3% with placebo.[24] In the SCALE Insulin trial, 396 participants with BMI ≥27 kg/m^2 and T2D treated with basal insulin and up to 2 oral glucose-lowering agents were randomized to receive liraglutide 3 mg daily vs placebo, combined with intensive behavioural therapy. At 56 weeks, weight change was -5.8% with liraglutide 3 mg, vs -1.5% with placebo. Liraglutide 3 mg was associated with significantly greater change in HbA1c (-1.1% vs -0.6%) and less need for insulin compared with placebo.[131]

The Contrave Obesity Research Diabetes (COR-Diabetes) trial evaluated naltrexone/bupropion 16 mg/180 mg BID in addition to health behaviour changes amongst 505 adults with BMI 27-45 kg/m^2 and T2D managed with oral agents or lifestyle.[25] Weight change was -5.0% with naltrexone/bupropion vs -1.8% in the placebo group. Change in HbA1c was superior with naltrexone/bupropion (-0.6%) vs placebo (-0.1%).

A meta-analysis comprising 2,550 patients with T2D and BMI 27-43 kg/m^2 randomized to orlistat 120 mg TID or placebo found that patients treated with orlistat had significantly greater mean change in HbA1c compared with placebo (-0.7% vs. -0.3%, respectively).[26] Weight change in the orlistat group was -3.8 kg compared to -1.4 kg with placebo.

Metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH)

MASLD (previously NAFLD) is the most prevalent chronic liver disease, affecting approximately 25% of adults globally.[132] The spectrum of MASLD includes steatosis, metabolic dysfunction-associated steatohepatitis (MASH, previously NASH), fibrosis, and cirrhosis.[133] MASLD is strongly associated with cardiometabolic risk factors, particularly T2D. 134 In people living with obesity, the prevalence of MASLD has been estimated to be approximately 75%, and the prevalence of MASH about 34%.[135] The management of MASLD is focused on weight loss in people with obesity,[136] optimization of cardiometabolic risk factors, prevention/delay of progression/regression of MASH and/or fibrosis, and prevention/management of outcomes such as cirrhosis, hepatocellular carcinoma and liver transplantation.[133]

The ESSENCE trial is an ongoing phase 3 trial evaluating semaglutide 2.4 mg weekly in people with MASH and stage 2 or 3 (moderate or advanced) liver fibrosis. The results of a planned interim analysis conducted at 72 weeks (Part 1) involving the first 800 patients demonstrated resolution of steatohepatitis without worsening of fibrosis amongst 62.9% of participants in the semaglutide

group vs 22.4% with placebo.[27] Part 2 of this trial is currently in progress and will evaluate the effects of semaglutide on cirrhosis-free survival at 240 weeks.[137]

The SYNERGY-NASH STUDY was a phase 2 study which investigated the efficacy and safety of tirzepatide in 190 patients with BMI 27-50 kg/m^2 and MASH with stage F2 or F3 (moderate or severe) fibrosis.[29] At 52 weeks, resolution of MASH without worsening of fibrosis occurred in 44%, 56% and 62% of participants receiving tirzepatide 5 mg, 10 mg and 15 mg respectively vs 10% with placebo. Improvement of at least one fibrosis stage without worsening of MASH occurred in 55%, 51%, and 51% of participants in the 5 mg, 10 mg, and 15 mg groups respectively, vs 30% with placebo.

A 48-week randomized, double-blind, placebo-controlled study assessed the efficacy of liraglutide 1.8 mg daily in 52 adults with MASH and BMI ≥25 kg/m^2.[28] The primary endpoint of histological resolution of MASH without worsening of fibrosis was met in 39% of the liraglutide group vs 9% in the placebo group. Additionally, 36% of those in the placebo group had progression of fibrosis compared to 9% with liraglutide.

Fifty people with BMI ≥27kg/m^2 and MASH were randomized to receive a 1,400 Kcal/day diet plus vitamin E (800 IU) daily with or without orlistat (120 mg TID) for 36 weeks. Orlistat did not enhance weight loss or improve liver enzymes, measures of insulin resistance, or histopathology compared to placebo.[138]

There are no obesity medications that have been shown to reduce the occurrence of hard liver outcomes such as cirrhosis, hepatocellular carcinoma or liver transplantation.

No studies of naltrexone/bupropion in patients with MASH or MASLD were identified.

Obstructive sleep apnea

Obstructive sleep apnea (OSA) is a common, yet underdiagnosed chronic disorder characterized by obstructive apneas and hypopneas due to repetitive collapse of the upper airway during sleep, with excess weight being a leading risk factor. Weight reduction can reduce OSA severity and improve related health outcomes.[139]

In the SURMOUNT-OSA trial, tirzepatide (10 mg and 15 mg) combined with health behavior changes was evaluated in 469 adults with BMI ≥30 kg/m^2 and moderate-to-severe OSA, including participants using positive airway pressure (PAP) and participants unable or unwilling to use PAP. Amongst participants not using PAP, the change in apnea-hypopnea index (AHI) with tirzepatide was -25.3 events/hour at 52 weeks versus -5.3 with placebo. Amongst participants using PAP, the change in AHI was -29.3 events/hour with tirzepatide compared to -5.5 with placebo.[30]

In the SCALE Sleep Apnea trial, among 359 patients with BMI ≥30 kg/m^2 and moderate or severe OSA who were unable or unwilling to use a continuous positive airway pressure (CPAP) machine, liraglutide 3 mg combined with health behaviour changes for 32 weeks demonstrated a change in apnea-hypopnea index (AHI) events of -12.2 events/hour, compared to -6.1 events/hour with placebo.[31]

No studies evaluating naltrexone/bupropion, orlistat, or semaglutide in people with OSA were identified.

Osteoarthritis

Obesity-related knee osteoarthritis is caused not only by increased weight stress on the joints, but also by the chronic inflammatory state that is seen in obesity. Managing weight effectively can significantly reduce knee pain, enhance physical function, and may slow osteoarthritis progression.[140]

Semaglutide 2.4 mg was evaluated with health behavior changes in 407 people with BMI ≥30 kg/m^2 and moderate knee osteoarthritis in the STEP 9 study.[32] The mean baseline BMI was 40.3 kg/m^2, with 41% of participants having a BMI of ≥40 kg/m^2. Participants in the semaglutide group reported an improvement in the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain score by -41.7 points versus -27.5 points in the placebo group, which was statistically significant across all BMI subgroups. At 68 weeks, weight change with semaglutide was -13.7% vs -3.2% with placebo. Improvements in physical function were significantly greater in the semaglutide 2.4 mg group (increase of 12 points vs 6.5 points with placebo) as measured by the Short Form-36 (SF-36) score.

Liraglutide 3 mg was evaluated in 156 adults with a BMI ≥27 kg/m^2 and knee osteoarthritis who successfully lost at least 5% weight with an 8-week run-in dietary intervention. At 1 year post randomization, there was a significant difference in body weight between the liraglutide and placebo group (-2.8kg vs +1.2kg respectively), but no difference in knee osteoarthritis pain as assessed by the Knee injury and Osteoarthritis Outcome Score (KOOS).[141] The lack of benefit in this trial may be due to insufficient magnitude of weight loss; weight loss goals of ≥10% of body weight are advised for symptomatic and functional improvement amongst people with obesity and OA of weight-bearing joints.[142]

No studies evaluating orlistat, naltrexone/bupropion, or tirzepatide in people with OA were identified.

Polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome is a common reproductive-endocrine disorder characterized by menstrual irregularities, elevated androgen levels and ovarian cysts affecting reproductive, metabolic and overall health. The prevalence of obesity is 3.8 times higher amongst individuals with PCOS than in those without PCOS.[143] Weight loss is recommended for individuals with PCOS and obesity to improve cardiometabolic and reproductive health.

Few, small studies have examined pharmacotherapy for weight management in individuals with PCOS.

Liraglutide 3 mg daily was compared to placebo, in addition to lifestyle intervention, in a 32-week trial in 82 women with PCOS and BMI ≥30 kg/m^2. Weight change was -5.7% with liraglutide vs -1.4% with placebo. The free androgen Index (FAI) decreased in the liraglutide 3 mg arm whereas the FAI increased with placebo. Menstrual cycles increased from 4.5 to 8.7 cycles/year with liraglutide 3 mg vs no change with placebo.[144]

A meta-analysis of six studies (randomized and non-randomized) evaluated the effect of liraglutide in 401 women with a diagnosis of PCOS and BMI ≥25 kg/m^2.

Weight was reduced by -4.33 kg vs placebo. [145] These studies did not evaluate menstrual frequency, fertility, or hirsutism.

Metformin with health behaviour changes may be associated with a small reduction in BMI (-0.73 kg/m2) and improved menstruation in women with polycystic ovary syndrome over six months, compared with health behaviour alone, [146] according to one systematic review and meta-analysis. However, another systematic review and meta-analysis showed no effect of metformin on weight in this population. [147]

No studies of sufficient quality evaluating orlistat, naltrexone/bupropion, semaglutide, or tirzepatide for patients with PCOS were identified.

Chronic kidney disease

Elevated BMI is associated with an increased risk of chronic kidney disease and kidney failure. [148,149] Obesity has been recognized as an independent cause of CKD, termed obesity-related glomerulopathy. [150]

The effect of semaglutide 2.4 mg weekly on renal outcomes was explored on a prespecified analysis of the SELECT trial. At baseline, just over 20% of the population had either an eGFR <60, or urine albumin-to-creatinine ratio (UACR) ≥ 3.39 mg/mmol. At 182 weeks, the incidence of the prespecified main composite kidney endpoint (death from kidney disease, initiation of chronic kidney replacement therapy, onset of persistent estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73m^2 , persistent ≥50% reduction in eGFR or onset of persistent macroalbuminuria) was reduced by 22% with semaglutide versus placebo. [151]

A small placebo-controlled trial investigated the effects of semaglutide 2.4 mg weekly in 125 adults with BMI >=27 kg/m^2 and CKD without diabetes over a 24-week period. Urinary albumin-to-creatinine ratio (UACR) was significantly reduced by 52.1% with semaglutide 2.4 mg compared to placebo. The total placebo subtracted weight change with semaglutide 2.4 mg at 24 weeks was -9.1 kg. There was no observed difference in eGFR between the two groups. [152]

Dose adjustment is not required for liraglutide 3 mg amongst people with mild/moderate renal insufficiency. Liraglutide 3 mg is not recommended in people with severe renal insufficiency, including end stage renal disease, due to very limited or no clinical experience in this population. [153]

Naltrexone-Bupropion has not been studied in patients with renal impairment. Based on data available for the individual constituents, systemic exposure is significantly higher for bupropion, naltrexone, and metabolites in subjects with moderate-to-severe renal impairment. [63] The maximum recommended daily maintenance dose for Naltrexone/Bupropion is one tablet (8mg/90mg) BID in patients with moderate or severe renal impairment. Naltrexone/Bupropion is contraindicated in patients with end-stage renal disease.

Orlistat has not been studied in patients with renal impairment as the medication is minimally absorbed from the gastrointestinal tract. There are no dosage adjustments provided in the manufacturer's labeling. [68]

No dose adjustment is required for semaglutide in patients with renal insufficiency. Semaglutide 2.4 mg is not recommended in people with end stage renal disease. [76]

No dose adjustments are recommended for tirzepatide in patients with renal insufficiency. [154] Tirzepatide is not recommended in people with end stage renal disease. [85]

Patients with severe renal impairment have higher systemic exposure of setmelanotide relative to patients with normal kidney function. [90] Setmelanotide should be commenced at a lower starting dose of 0.5 mg daily in patients with severe renal impairment with close monitoring for gastrointestinal side effects. If tolerated, the dose can be increased by 0.5 mg every 2 weeks to a maximum of 1.5 mg daily. Setmelanotide is not recommended for patients with advanced kidney disease (eGFR < 15 mL/min/1.73 m2). [90]

Gastroesophageal reflux disease (GERD)

GERD is common in people with obesity, [155] and can improve with weight loss. [156] Onset of GERD, or exacerbation of pre-existing GERD, can occur with obesity management pharmacotherapy, in particular with the GLP1 receptor agonists liraglutide, semaglutide, and GIP/GLP1 receptor agonist tirzepatide. This is typically transient, and mild to moderate in severity. [5,6,18]

No studies of pharmacotherapy for obesity management in patients with GERD were identified.

Mental health

The bidirectional relationship between obesity and mental health is complex. A mental health evaluation is an important component in the assessment of obesity and in developing a treatment plan (see the Role of Mental Health and Assessment chapter Obesity Clinical Practice Guideline). In prescribing obesity pharmacotherapy, it is important to review their safety and efficacy in individuals with mental health disorders, as well as their overall safety from a mental health perspective.

Obesity is common in individuals with bipolar disorder. [157] Liraglutide 3 mg daily was assessed in 60 individuals with bipolar disorder and BMI>30 kg/m^2 or BMI ≥27 kg/m^2 with at least one weight-related complication. Participants were randomized to receive liraglutide 3 mg or placebo for 40 weeks, alongside health behaviour changes. A weight change of -3.3% was seen with liraglutide vs +0.2% with placebo. Improvement was seen in binge eating with liraglutide vs placebo, as assessed with the Binge Eating Scale. [158]

Weight gain is a common side effect of some antipsychotic medication. Metformin has demonstrated efficacy to prevent antipsychotic medication-induced weight gain and is particularly impactful early in the course of antipsychotic treatment. [159,160] (see the Role of Mental Health Clinical Practice Guideline Chapter)

Naltrexone/bupropion contains the antidepressant bupropion. There has been long-standing concern that antidepressants can rarely, paradoxically, worsen depression and/or cause worsening or emergence of suicidal ideation or behaviour during the early phases of

treatment. In the placebo-controlled clinical trials with naltrexone/bupropion for the treatment of obesity in adult patients, no suicides or suicide attempts were reported in studies up to 56 weeks duration. In these studies, suicidal ideation was reported by one (0.03%) of 3,239 treated with naltrexone/bupropion compared to three (0.20%) of 1,515 patients treated with placebo. [63]

Although rare post marketing case reports of suicidality have emerged amongst people taking GLP-1 or GIP/GLP1 receptor agonists, adverse neuropsychiatric effects have not been demonstrated in clinical trials of liraglutide, semaglutide or tirzepatide. [5,6,161] Regulatory agencies globally continue their evaluation of postmarketing reports of suicidal ideation with GLP1 or GIP/GLP1 receptor agonist therapy. In Canada, help for suicide crisis and prevention can be found here or by calling the Canadian Suicide Crisis Helpline at 9-8-8.

While three serious mental health adverse effects were reported in clinical trials with setmelanotide, none were considered to be related to the medication. [33,34] No treatment-related worsening of depression was observed. Nonetheless, given the small numbers of participants in these trials and increased burden of mental health conditions amongst patients with rare monogenic causes of obesity, patients should be closely monitored for worsening mental health, and treatment discontinuation should be considered in that event. [90]

No studies of obesity pharmacotherapy conducted specifically amongst patients with depression were identified.

Craving and Control of Eating

Cravings are intense desires to consume specific foods, often driven by hedonic rather than homeostatic needs. [162] Food craving has been shown to contribute to poor adherence to health behaviour interventions. Reducing and managing food cravings is a key component in the management of obesity and successful weight loss maintenance for many individuals. [163]

In the COR-I study, results from the Control of Eating Questionnaire (CoEQ) demonstrated reductions in desire for starchy foods, eating in response to food cravings, and an increased ability to resist food cravings and control eating with naltrexone/bupropion at 56 weeks. [8] An analysis of four RCTs with naltrexone/bupropion demonstrated that early improvements in craving control, and reductions in craving for sweet throughout the 56-week trial period were predictive of greater weight loss at the end of the trial. [60]

In the STEP 5 clinical trial, the CoEQ administered to a subset of 174 participants found an improvement in craving control and craving for savory domains with semaglutide vs placebo that persisted through week 104. Sweet craving was improved with semaglutide vs placebo through week 52, but was not significant at week 104. Improvements in craving domain scores were positively correlated with reductions in body weight from baseline to week 104 with semaglutide. [75]

There are no published data on the effect of tirzepatide on cravings. Orlistat and liraglutide have not been evaluated in regard to control of eating nor cravings. Orlistat would not be expected to have a benefit in this regard, as it does not have a central nervous system mechanism of action.

Quality of Life and Physical Function

Quality of life (QoL) broadly refers to how an individual measures the overall 'goodness' of various aspects of their life. [164] Obesity negatively affects many dimensions of health-related quality of life (HRQoL). [163] Most studies associate weight loss with improved QoL, and impact on QoL is a key component in the FDA submission for approval of obesity pharmacotherapy. [165] Physical function (such as walking, climbing stairs, lifting, and self-care) is an important component of QoL assessment. [166]
The SF-36 is a traditional tool used to assess QoL and physical function that is not specific to people living with obesity. [167] The Impact of Weight on Quality of Life-Lite general questionnaire (IWQOL-Lite) and the Impact of Weight on Quality of Life-Lite specifically for Clinical Trials (IWQOL-Lite CT), which are more tailored to the experiences of people living with obesity, are commonly used in obesity clinical trials. [168] The IWQoL-Lite also provides an evaluation on the impact of elevated weight on physical activities, such as walking, climbing stairs, and overall mobility. [169]

The SCALE obesity and prediabetes three-year extension study evaluated the effect of liraglutide 3 mg daily on HRQoL vs placebo in participants with prediabetes. The IWQOL-Lite questionnaire and SF-36 health survey were used. Both tools demonstrated long term improvements in HRQoL and physical function with liraglutide vs placebo. [170]

Patients in the COR clinical trials program with naltrexone/bupropion demonstrated significant improvements in QoL scores. These improvements, measured using the IWQOL-Lite questionnaire, were greater compared to placebo and were observed across subscales, including physical function, self-esteem, sexual life, public distress, and work. Improvements in both total IWQOL-Lite scores and subscale scores occurred as early as week 8. [8]

Semaglutide 2.4 mg has been shown to improve quality of life and physical functioning. [5,22,80] The STEP 1 trial assessed QoL changes from baseline to week 68 using the IWQOL-Lite-CT questionnaire. Greater improvements were reported with semaglutide vs placebo for all composite and total scores. Semaglutide-treated participants were more likely to achieve clinically meaningful improvements from baseline to week 68 in physical function, physical, psychosocial and total scores vs placebo.

Patient reported outcomes (PROs) of health-related quality of life, physical and psychosocial function were assessed in the SURMOUNT-1 tirzepatide study using the SF-36 version 2 (SF-36v2), IWQOL-Lite-CT, and EuroQol 5-Dimension 5-Level (ED-5D-5L) questionnaires. [171] There was improvement in all PROs measured using these instruments in the tirzepatide groups vs placebo, with incremental improvements among those with greater degrees of weight reduction.

In adults with Bardet Biedl syndrome, setmelanotide was associated with a clinically significant improvement in IWQOL-Lite score compared to baseline, and was correlated with degree of weight loss. [172] In patients with POMC and LEPR deficiency, setmelanotide treatment was associated with an improvement in IWQOL-Lite scores. [173]

Medications with insufficient data for obesity management

A variety of unapproved pharmacotherapeutic approaches are sometimes being utilized in the clinical setting in an attempt to assist with obesity management. Based on our review of the literature, there is insufficient evidence to support the use of pharmacotherapies or hormonal treatment strategies (e.g., testosterone, female hormone replacement therapy, thyroid hormone) that are not discussed in this document.

Non-Health Canada approved compounded GLP1 and GIP/GLP1 receptor agonists have emerged in the marketplace, as a result of shortages and cost associated with brand name medications. Given concerns and unknowns about content, safety, quality, efficacy, and lack of regulation of non-Health-Canada approved products, we recommend against their use.

Limitations

There are other medications (e.g., phentermine, phentermine/topiramate) which are approved for the management of obesity in some countries. In these guidelines, we have included only those medications that are currently approved in Canada. As there are over 200 health complications associated with obesity, it was not feasible to search literature for each subpopulation. [174] Thirteen subpopulations were selected by unanimous consensus of the author group, with selection considerations including the prevalence and clinical relevance of these conditions in clinical practice, their burden on the healthcare system, and their importance to patients as identified through lived experience and clinical engagement.

Areas of uncertainty

There is limited evidence in some areas upon which to guide decision making with obesity pharmacotherapy. Studies to evaluate the potential benefit of obesity pharmacotherapy are lacking in several important subpopulations, including polycystic ovary syndrome, chronic kidney disease, and gastroesophageal reflux disease. There is a need for more evidence to inform on the use of combination therapy for weight management, especially given the complex multifactorial etiology of obesity and the potential benefits of targeting multiple mechanisms of action. Evaluation of quality of weight loss with pharmacotherapy (including quantity of lean muscle lost compared to fat and change in muscle strength and function) is in need of further exploration. Fertility, conception planning, and ensuring nutritional adequacy while taking obesity pharmacotherapy are also areas requiring more focused evidence. Studies are needed to inform on management of patients taking GLP1-based medication in the context of preoperative planning for surgery and procedures requiring conscious sedation.

Funding

This guideline update was funded by public donations and revenue generated by Obesity Canada's educational programs.

Acknowledgements

The authors would like to acknowledge the McMaster Evidence Review and Synthesis Team (MERST) who provided their expertise in conducting an independent methods review, with special thanks to Dr. Diana Sherafali and Dr. Megan Racey. The authors sincerely thank the lived experience experts who reviewed this manuscript for their valuable insights and perspectives. Their contributions have strengthened the relevance and clarity of this work. We appreciate the constructive feedback provided by peer reviewers Dr. Joseph Roshan Abraham, Dr. Helena Piccinini-Vallis, Dr. Sanjeev Sockalingam, Dr. Arya Sharma, Dr. Shahebina Walji, Dr. Sean Wharton and to the anonymous reviewers who contributed to the refinement of this guideline.

Contributor Statement

Author contributions based on the Contributor Role Taxonomy (CRediT), a 14-role taxonomy used to describe the key types of contributions typically made to the production and publication of research output.

All the authors contributed to the conception and design of the work; the five physician authors contributed to acquisition, analysis, and interpretation of data. All the authors drafted the manuscript, revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Author Disclosure

Sue D. Pedersen reported she is/has been an investigator in clinical trials funded by Novo Nordisk, AstraZeneca, Sanofi, Eli Lilly, Boehringer Ingelheim, Prometic, and Pfizer. She reports receiving funding from AstraZeneca, Bausch Health, Eli Lilly, Novo Nordisk, Janssen, Boehringer Ingelheim, Sanofi, Merck, Abbott, Dexcom, HLS, Bayer and Pfizer. She reports she has participated in advisory boards for AstraZeneca, Abbvie, Amgen, Bausch, Eli Lilly, Novo Nordisk, Janssen, Boehringer Ingelheim, Sanofi, Merck, Abbott, Dexcom, HLS, Bayer, and Pfizer. In addition, she reports participating on a data safety monitoring board for Regeneron. Priya Manjoo reports she has participated in advisory board meetings for Eli Lilly, Rhythm Pharmaceuticals, Amgen, Merck, and Bausch Health. Satya Dash reports he has received research grants from CIHR, Diabetes Canada, Banting and Best Diabetes Centre, Mclaughlin Foundation and the Heart & Stroke Foundation. He reports he has received funding from Novo Nordisk, Eli Lilly, Medison, and Rhythm Pharmaceuticals. Akshay Jain reports he is/has been an investigator in clinical trials funded by Abbott, Amgen, Astra Zeneca, Eli Lilly, Novo Nordisk and Sanofi. He reports receiving funding from Abbott, Abbvie, Antibody, Amgen, AstraZeneca, Eli Lilly, Novo Nordisk, Bausch Health, Bayer, Boehringer Ingelheim, Care to Know, CCRN, Connected in Motion, CPD Network, Diabetes Canada, Eisai, Dexcom, Embecta, EOCI, GSK, HLS Therapeutics, Insulet, Janssen, Master Clinician Alliance, MDBriefCase, Medtronic, Merck, Novartis, Partners in Progressive Medical Education, PocketPills, Pfizer, Roche, Sandoz, Six Degrees, Timed Right, Unik, WebMD, and Sanofi. He reports he has participated in advisory boards for Abbott, Amgen, AstraZeneca, Eli Lilly, Novo Nordisk, Bausch Health, Bayer, Boehringer Ingelheim, Eisai, Dexcom, Embecta, Gilead Sciences, GSK, HLS Therapeutics, Insulet, Medtronic, Novartis, Roche, Sandoz, Takeda, Ypsomed, and Sanofi. He reports holding personal stocks in Amgen, Eli Lilly, and Novo Nordisk, with a total value of less than $10,000 Canadian dollars. Nicole Pearce reports she is a full-time employee with Obesity Canada and owns the Global Obesity Learning Centre, Go Learn. Megha Poddar reports receiving royalties or licences from the Medical Weight Management Center of Canada. She also reports receiving funding from Bausch Health, Novo Nordisk, Eli Lilly, EOCI, CCRN, Janssen, Merck, Antibody Solutions, CPD Network, Johnson & Johnson, Boehringer Ingelheim, Rhythm Pharmaceuticals, and the College of Physicians and Surgeons of Ontario. She also reports participation in a data and safety monitoring board for the OK-TRANSPLANT-2 clinical trial. Megha Poddar reports being the medical advisor for Nymble Health and Shoppers Drug Mart.

References

1. Wildman RP, Muntner P, Reynolds K, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). *Arch Intern Med.* Aug 11 2008;168(15):1617-24. doi:10.1001/archinte.168.15.1617
2. Browning LM, Hsieh SD, Ashwell M. A systematic review of waist-to-height ratio as a screening tool for the prediction of cardiovascular disease and diabetes: 0·5 could be a suitable global boundary value. *Nutrition Research Reviews.* 2010;23(2):247-269. doi:10.1017/S0954422410000144
3. Yusuf S, Hawken S, Ounpuu S, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet.* Nov 5 2005;366(9497):1640-9. doi:10.1016/s0140-6736(05)67663-5
4. Caleyachetty R, Barber TM, Mohammed NI, et al. Ethnicity-specific BMI cutoffs for obesity based on type 2 diabetes risk in England: a population-based cohort study. *Lancet Diabetes Endocrinol.* Jul 2021;9(7):419-426. doi:10.1016/s2213-8587(21)00088-7
5. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med.* Mar 18 2021;384(11):989-1002. doi:10.1056/NEJMoa2032183
6. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide Once Weekly for the Treatment of Obesity. *N Engl J Med.* Jul 21 2022;387(3):205-216. doi:10.1056/NEJMoa2206038
7. Pi-Sunyer X, Astrup A, Fujioka K, et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *N Engl J Med.* Jul 2 2015;373(1):11-22. doi:10.1056/NEJMoa1411892
8. Greenway FL, Fujioka K, Plodkowski RA, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* Aug 21 2010;376(9741):595-605. doi:10.1016/S0140-6736(10)60888-4
9. Sjöström L, Rissanen A, Andersen T, et al. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. *The Lancet.* 1998;352(9123):167-172. doi:10.1016/s0140-6736(97)11509-4
10. Rubino D, Abrahamsson N, Davies M, et al. Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial. *Jama.* 2021;325(14):1414-1425. doi:https://dx.doi.org/10.1001/jama.2021.3224
11. Aronne LJ, Sattar N, Horn DB, et al. Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity: The SURMOUNT-4 Randomized Clinical Trial. *Jama.* 2024;331(1):38-48. doi:https://dx.doi.org/10.1001/jama.2023.24945
12. Wadden TA, Hollander P, Klein S, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes (Lond).* Nov 2013;37(11):1443-51. doi:10.1038/ijo.2013.120
13. Richelsen B, Tonstad S, Rossner S, et al. Effect of orlistat on weight regain and cardiovascular risk factors following a very-low-energy diet in abdominally obese patients: a 3-year randomized, placebo-controlled study. *Diabetes Care.* Jan 2007;30(1):27-32. doi:10.2337/dc06-0210
14. Wadden TA, Chao AM, Machineni S, et al. Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. *Nature Medicine.* 2023;29(11):2909-2918. doi:https://dx.doi.org/10.1038/s41591-023-02597-w
15. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. *The New England journal of medicine.* Dec 14 2023;389(24):2221-2232. doi:https://dx.doi.org/10.1056/NEJMoa2307563
16. Packer M, Zile MR, Kramer CM, et al. Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med.* Jan 30 2025;392(5):427-437. doi:doi:10.1056/NEJMoa2410027
17. Kosiborod MN, Abildstrom SZ, Borlaug BA, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med.* 2023;389(12):1069-1084. doi:https://dx.doi.org/10.1056/NEJMoa2306963
18. le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet.* Apr 8 2017;389(10077):1399-1409. doi:10.1016/S0140-6736(17)30069-7
19. Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care.* Jan 2004;27(1):155-61. doi:10.2337/diacare.27.1.155
20. Jastreboff AM, le Roux CW, Stefanski A, et al. Tirzepatide for Obesity Treatment and Diabetes Prevention. *N Engl J Med.* Mar 6 2025;392(10):958-971. doi:10.1056/NEJMoa2410819
21. McGowan BM, Bruun JM, Capehorn M, et al. Efficacy and safety of once-weekly semaglutide 2· 4 mg versus placebo in people with obesity and prediabetes (STEP 10): a randomised, double-blind, placebo-controlled, multicentre phase 3 trial. *Lancet Diabetes Endocrinol.* 2024;12(9):631-642. doi:10.1016/S2213-8587(24)00182-7
22. Davies M, Faerch L, Jeppesen OK, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet (London, England).* 2021;397(10278):971-984. doi:https://dx.doi.org/10.1016/S0140-6736(21)00213-0
23. Garvey WT, Frias JP, Jastreboff AM, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet.* Aug 19 2023;402(10402):613-626. doi:10.1016/S0140-6736(23)01200-X
24. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes: The SCALE Diabetes Randomized Clinical Trial. *Jama.* Aug 18 2015;314(7):687-99. doi:10.1001/jama.2015.9676
25. Hollander P, Gupta AK, Plodkowski R, et al. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. *Diabetes Care.* Dec 2013;36(12):4022-9. doi:10.2337/dc13-0234
26. Jacob S, Rabbia M, Meier MK, Hauptman J. Orlistat 120 mg improves glycaemic control in type 2 diabetic patients with or without concurrent weight loss. *Diabetes Obes Metab.* Apr 2009;11(4):361-71. doi:10.1111/j.1463-1326.2008.00970.x
27. Sanyal AJ, Newsome PN, Kliers I, et al. Phase 3 Trial of Semaglutide in Metabolic Dysfunction–Associated Steatohepatitis. *N Engl J Med.* 2025;doi:doi:10.1056/NEJMoa2413258
28. Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet.* Feb 13 2016;387(10019):679-90. doi:10.1016/S0140-6736(15)00803-X
29. Loomba R, Hartman ML, Lawitz EJ, et al. Tirzepatide for Metabolic Dysfunction-Associated Steatohepatitis with Liver Fibrosis. *The New England journal of medicine.* 2024;doi:https://dx.doi.org/10.1056/NEJMoa2401943
30. Malhotra A, Grunstein RR, Fietze I, et al. Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity. *The New England journal of medicine.*

Oct 3 2024;391(13):1193-1205. doi:https://dx.doi.org/10.1056/NEJMoa2404881

31. Blackman A, Foster GD, Zammit G, et al. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. *Int J Obes (Lond).* Aug 2016;40(8):1310-9. doi:10.1038/ijo.2016.52
32. Bliddal H, Bays H, Czernichow S, et al. Once-Weekly Semaglutide in Persons with Obesity and Knee Osteoarthritis. *N Engl J Med.* Oct 31 2024;391(17):1573-1583. doi:10.1056/NEJMoa2403664
33. Haqq AM, Chung WK, Dollfus H, et al. Efficacy and safety of setmelanotide, a melanocortin-4 receptor agonist, in patients with Bardet-Biedl syndrome and Alstrom syndrome: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial with an open-label period. *The Lancet Diabetes and Endocrinology.* 2022;10(12):859-868. doi:https://dx.doi.org/10.1016/S2213-8587%2822%2900277-7
34. Clement K, van den Akker E, Argente J, et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. *The Lancet Diabetes and Endocrinology.* 2020;8(12):960-970. doi:https://dx.doi.org/10.1016/S2213-8587%2820%2930364-8
35. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* Feb 7 2002;346(6):393-403. doi:10.1056/NEJMoa012512
36. Promrat K, Kleiner DE, Niemeier HM, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. *Hepatology.* Jan 2010;51(1):121-9. doi:10.1002/hep.23276
37. Stevens VJ, Corrigan SA, Obarzanek E, al. e. Weight Loss Intervention in Phase 1 of the Trials of Hypertension Prevention. *Arch Intern Med.* 1993;153(7):849-858.
38. Ryan DH, Yockey SR. Weight Loss and Improvement in Comorbidity: Differences at 5%, 10%, 15%, and Over. *Curr Obes Rep.* Jun 2017;6(2):187-194. doi:10.1007/s13679-017-0262-y
39. Ryan DH. Lifestyle-Based Obesity Care. *Gastroenterol Clin North Am.* Dec 2023;52(4):645-660. doi:10.1016/j.gtc.2023.08.001
40. Mann T, Tomiyama AJ, Westling E, Lew AM, Samuels B, Chatman J. Medicare's search for effective obesity treatments: diets are not the answer. *Am Psychol.* Apr 2007;62(3):220-33. doi:10.1037/0003-066X.62.3.220
41. Gasoyan H, Pfoh ER, Schulte R, Sullivan E, Le P, Rothberg MB. Association of patient characteristics and insurance type with anti-obesity medications prescribing and fills. *Diabetes Obes Metab.* May 2024;26(5):1687-1696. doi:10.1111/dom.15473
42. Thomas CE, Mauer EA, Shukla AP, Rathi S, Aronne LJ. Low adoption of weight loss medications: A comparison of prescribing patterns of antiobesity pharmacotherapies and SGLT2s. *Obesity (Silver Spring).* Sep 2016;24(9):1955-61. doi:10.1002/oby.21533
43. Lau DCW, Patton I, Lavji R, Belloum A, Ng G, Modi R. Therapeutic inertia in obesity management among people living with obesity from the perspective of general/family practitioners in Canada: A mixed-methods study. *Clin Obes.* Feb 2025;15(1):e12701. doi:10.1111/cob.12701
44. Brouwers M, Kho ME, Browman GP, et al. *AGREE II: User's Manual and 23-item Instrument.* 2009. https://www.agreetrust.org/wp-content/uploads/2013/10/AGREE-II-Users-Manual-and-23-item-Instrument_2009_UPDATE_2013.pdf
45. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. *Bmj.* Feb 27 1999;318(7183):593-6. doi:10.1136/bmj.318.7183.593
46. Carter J, Husain F, Papasavas P, et al. American Society for Metabolic and Bariatric Surgery review of the body mass index. *Surgery for Obesity and Related Diseases.* 2025;21(3):199-206. doi:10.1016/j.soard.2024.10.038
47. Ashwell M, Gibson S. A proposal for a primary screening tool: `Keep your waist circumference to less than half your height'. *BMC Medicine.* 2014/11/07 2014;12(1):207. doi:10.1186/s12916-014-0207-1
48. Sweatt K, Garvey WT, Martins C. Strengths and Limitations of BMI in the Diagnosis of Obesity: What is the Path Forward? *Current Obesity Reports.* 2024/09/01 2024;13(3):584-595. doi:10.1007/s13679-024-00580-1
49. Off-Label Use of Drugs (CADTH) (2017).
50. Acosta A, Camilleri M, Abu Dayyeh B, et al. Selection of Antiobesity Medications Based on Phenotypes Enhances Weight Loss: A Pragmatic Trial in an Obesity Clinic. *Obesity (Silver Spring).* 2021;29(4):662-671. doi:http://dx.doi.org/10.1002/oby.23120
51. Hocking S, Sumithran P. Individualised prescription of medications for treatment of obesity in adults. *Rev Endocr Metab Disord.* Oct 2023;24(5):951-960. doi:10.1007/s11154-023-09808-2
52. Bays HE, Burridge K, Richards J, Fitch A. Obesity Pillars roundtable: Excessive weight reduction with highly effective anti-obesity medications (heAOMs). *Obesity Pillars.* 2022/12/01/ 2022;4:100039. doi:https://doi.org/10.1016/j.obpill.2022.100039
53. Secher A, Jelsing J, Baquero AF, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. *J Clin Invest.* Oct 2014;124(10):4473-88. doi:10.1172/JCI75276
54. Jelsing J, Vrang N, Hansen G, Raun K, Tang-Christensen M, Knudsen LB. Liraglutide: short-lived effect on gastric emptying -- long lasting effects on body weight. *Diabetes Obes Metab.* Jun 2012;14(6):531-8. doi:10.1111/j.1463-1326.2012.01557.x
55. Novo Nordisk Canada I. Saxenda® (liraglutide) product monograph. Updated 2024/04/24. https://www.novonordisk.ca/content/dam/nncorp/ca/en/products/saxenda-product-monograph-24-april-2024.pdf
56. Ball GDC, Merdad R, Birken CS, et al. Managing obesity in children: a clinical practice guideline. *Canadian Medical Association Journal.* 2025;197(14):E372. doi:10.1503/cmaj.241456
57. Wadden TA, Tronieri JS, Sugimoto D, et al. Liraglutide 3.0 mg and Intensive Behavioral Therapy (IBT) for Obesity in Primary Care: The SCALE IBT Randomized Controlled Trial. *Obesity (Silver Spring).* 2020;28(3):529-536. doi:http://dx.doi.org/10.1002/oby.22726
58. Greenway FL, Whitehouse MJ, Guttadauria M, et al. Rational design of a combination medication for the treatment of obesity. *Obesity (Silver Spring).* Jan 2009;17(1):30-9. doi:10.1038/oby.2008.461
59. Apovian CM, Aronne L, Rubino D, et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity (Silver Spring).* May 2013;21(5):935-43. doi:10.1002/oby.20309
60. Dalton M, Finlayson G, Walsh B, Halseth AE, Duarte C, Blundell JE. Early improvement in food cravings are associated with long-term weight loss success in a large clinical sample. *International Journal of Obesity (2005).* 2017;41(8):1232-1236. doi:10.1038/ijo.2017.89
61. Wadden TA, Foreyt JP, Foster GD, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity (Silver Spring).* Jan 2011;19(1):110-20. doi:10.1038/oby.2010.147
62. le Roux CW, Fils-Aime N, Camacho F, Gould E, Barakat M. The relationship between early weight loss and weight loss maintenance with naltrexone-bupropion therapy. *EClinicalMedicine.* 2022;49:101436. doi:https://dx.doi.org/10.1016/j.eclinm.2022.101436
63. Bausch H. Contrave® product monograph. Updated 2023/08/21. https://bauschhealth.ca/wp-content/uploads/2023/08/Contrave-PM-E-2023-08-21.pdf
64. Booth K, Clements JN. Role of Bupropion Plus Naltrexone for the Management of Obesity. *J Pharm Technol.* Jun 2016;32(3):125-132. doi:10.1177/8755122515624220

65. Bjornsson TD, Callaghan JT, Einolf HJ, et al. The conduct of in vitro and in vivo drug-drug interaction studies: a PhRMA perspective. *J Clin Pharmacol.* May 2003;43(5):443-69.

66. Turpeinen M, Tolonen A, Uusitalo J, Jalonen J, Pelkonen O, Laine K. Effect of clopidogrel and ticlopidine on cytochrome P450 2B6 activity as measured by bupropion hydroxylation. *Clin Pharmacol Ther.* Jun 2005;77(6):553-9. doi:10.1016/j.clpt.2005.02.010

67. McNeely W, Benfield P. Orlistat. *Drugs.* Aug 1998;56(2):241-9; discussion 250. doi:10.2165/00003495-199856020-00007

68. CHEPLAPHARM Arzneimittel G. XENICAL® (orlistat) Product monograph. Updated Jun 8 2023. https://pdf.hres.ca/dpd_pm/00071194.PDF

69. Rucker D, Padwal R, Li SK, Curioni C, Lau DC. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. *Bmj.* Dec 8 2007;335(7631):1194-9. doi:10.1136/bmj.39385.413113.25

70. Padwal R, Kezouh A, Levine M, Etminan M. Long-term persistence with orlistat and sibutramine in a population-based cohort. *Int J Obes (Lond).* Oct 2007;31(10):1567-70. doi:10.1038/sj.ijo.0803631

71. McDuffie JRea. Effects of Orlistat on Fat-Soluble Vitamins in Obese Adolescents. *Pharmacotherapy.* 2002;22(7)

72. Weir MA, Beyea MM, Gomes T, et al. Orlistat and acute kidney injury: an analysis of 953 patients. *Arch Intern Med.* Apr 11 2011;171(7):703-4. doi:10.1001/archinternmed.2011.103

73. Wilson N, Shah N, Manitpisitkul W, al e. Liver Failure Requiring Transplantation After Orlistat Use. *Am Coll Clin Pharm.* 2011;31(11):1145-1145. doi:10.1592/phco.31.11.1145

74. Friedrichsen M, Breitschaft A, Tadayon S, Wizert A, Skovgaard D. The effect of semaglutide 2.4 mg once weekly on energy intake, appetite, control of eating, and gastric emptying in adults with obesity. *Diabetes Obes Metab.* Mar 2021;23(3):754-762. doi:10.1111/dom.14280

75. Wharton S, Batterham RL, Bhatta M, et al. Two-year effect of semaglutide 2.4 mg on control of eating in adults with overweight/obesity: STEP 5. *Obesity (Silver Spring, Md).* 2023;31(3):703-715. doi:https://dx.doi.org/10.1002/oby.23673

76. Novo Nordisk Canada I. Wegovy® (semaglutide) product monograph. Updated April 2025. https://www.novonordisk.ca/content/dam/nncorp/ca/en/products/Wegovy-product-monograph.pdf

77. Wilding JPH, Batterham RL, Davies M, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. *Diabetes Obes Metab.* 2022;24(8):1553-1564. doi:https://dx.doi.org/10.1111/dom.14725

78. Garvey WT, Batterham RL, Bhatta M, et al. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. *Nature medicine.* 2022;28(10):2083-2091. doi:https://dx.doi.org/10.1038/s41591-022-02026-4

79. Ryan DH, Lingvay I, Deanfield J, et al. Long-term weight loss effects of semaglutide in obesity without diabetes in the SELECT trial. *Nat Med.* Jul 2024;30(7):2049-2057. doi:10.1038/s41591-024-02996-7

80. Wadden TA, Bailey TS, Billings LK, et al. Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial. *Jama.* Apr 13 2021;325(14):1403-1413. doi:10.1001/jama.2021.1831

81. Rubino DM, Greenway FL, Khalid U, et al. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial. *Jama.* 2022;327(2):138-150. doi:https://dx.doi.org/10.1001/jama.2021.23619

82. Heise T, DeVries JH, Urva S, et al. Tirzepatide Reduces Appetite, Energy Intake, and Fat Mass in People With Type 2 Diabetes. *Diabetes Care.* 2023;46(5):998-1004. doi:https://dx.doi.org/10.2337/dc22-1710

83. Urva S, Coskun T, Loghin C, et al. The novel dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist tirzepatide transiently delays gastric emptying similarly to selective long-acting GLP-1 receptor agonists. *Diabetes, Obesity and Metabolism.* 2020;22(10):1886-1891. doi:http://dx.doi.org/10.1111/dom.14110

84. Samms RJ, Coghlan MP, Sloop KW. How May GIP Enhance the Therapeutic Efficacy of GLP-1? *Trends in Endocrinology & Metabolism.* 2020/06/01/ 2020;31(6):410-421. doi:https://doi.org/10.1016/j.tem.2020.02.006

85. Eli Lilly Canada I. ZEPBOUND™ KwikPen® tirzepatide injection product monograph. Updated 2025/05/13. https://pi.lilly.com/ca/zepbound-ca-pm.pdf

86. Aronne LJ, Horn DB, le Roux CW, et al. Tirzepatide as Compared with Semaglutide for the Treatment of Obesity. *N Engl J Med.* Jul 3 2025;393(1):26-36. doi:10.1056/NEJMoa2416394

87. Heymsfield SB, Avena NM, Baier L, et al. Hyperphagia: current concepts and future directions proceedings of the 2nd international conference on hyperphagia. *Obesity (Silver Spring).* Feb 2014;22 Suppl 1(0 1):S1-s17. doi:10.1002/oby.20646

88. Heymsfield SB, Clément K, Dubern B, et al. Defining Hyperphagia for Improved Diagnosis and Management of MC4R Pathway–Associated Disease: A Roundtable Summary. *Current Obesity Reports.* 2025/01/25 2025;14(1):13. doi:10.1007/s13679-024-00601-z

89. Markham A. Setmelanotide: First Approval. *Drugs.* Feb 2021;81(3):397-403. doi:10.1007/s40265-021-01470-9

90. Rhythm Pharmaceuticals I. IMCIVREE® product monograph. Updated 2023/05. https://rhythmtx.ca/wp-content/uploads/2023/05/IMCIVREE-Product-Monograph-EN.pdf

91. Melluso A, Secondulfo F, Capolongo G, Capasso G, Zacchia M. Bardet-Biedl Syndrome: Current Perspectives and Clinical Outlook. *Ther Clin Risk Manag.* 2023;19:115-132. doi:10.2147/tcrm.S338653

92. Forsythe E, Kenny J, Bacchelli C, Beales PL. Managing Bardet–Biedl Syndrome—Now and in the Future. Mini Review. *Frontiers in Pediatrics.* 2018-February-13 2018;6doi:10.3389/fped.2018.00023

93. Tomlinson JW. Bardet-Biedl syndrome: A focus on genetics, mechanisms and metabolic dysfunction. *Diabetes Obes Metab.* Apr 2024;26 Suppl 2:13-24. doi:10.1111/dom.15480

94. Kuhnen P, Clement K, Wiegand S, et al. Proopiomelanocortin deficiency treated with a melanocortin-4 receptor agonist. *N Engl J Med.* 21 Jul 2016;375(3):240-246. doi:http://dx.doi.org/10.1056/NEJMoa1512693

95. Saeed S, Bonnefond A, Froguel P. Obesity: exploring its connection to brain function through genetic and genomic perspectives. *Molecular Psychiatry.* 2025/02/01 2025;30(2):651-658. doi:10.1038/s41380-024-02737-9

96. Huvenne H, Dubern B, Clément K, Poitou C. Rare Genetic Forms of Obesity: Clinical Approach and Current Treatments in 2016. *Obes Facts.* 2016;9(3):158-73. doi:10.1159/000445061

97. A Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial: Multiple Independent Sub-studies of Setmelanotide in Patients With POMC/PCSK1, LEPR, NCOA1(SRC1), or SH2B1 Gene Variants in the Melanocortin-4 Receptor Pathway. *National Library of Medicine (US).* https://clinicaltrials.gov/study/NCT05093634

98. Roth CL, Scimia C, Shoemaker AH, et al. Setmelanotide for the treatment of acquired hypothalamic obesity: a phase 2, open-label, multicentre trial. *The Lancet Diabetes and Endocrinology.* 2024;12(6):380-389. doi:https://dx.doi.org/10.1016/S2213-8587%2824%2900087-1

99. A Phase 3, Double Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Setmelanotide in Patients With Acquired Hypothalamic Obesity. National Library of Medicine (US). https://clinicaltrials.gov/study/NCT05774756

100. Valenzuela PL, Carrera-Bastos P, Castillo-Garcia A, Lieberman DE, Santos-Lozano A, Lucia A. Obesity and the risk of cardiometabolic diseases. *Nature Reviews Cardiology.* 2023;20(7):475-494. doi:https://dx.doi.org/10.1038/s41569-023-00847-5

101. Powell-Wiley TM, Poirier P, Burke LE, et al. Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation.* May 25 2021;143(21):e984-e1010. doi:10.1161/cir.0000000000000973

102. World Health Organization. Cardiovascular diseases. Accessed Feb 25, 2025. https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1

103. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* Jul 28 2016;375(4):311-22. doi:10.1056/NEJMoa1603827

104. Davies MJ, Aronne LJ, Caterson ID, Thomsen AB, Jacobsen PB, Marso SP. Liraglutide and cardiovascular outcomes in adults with overweight or obesity: A post hoc analysis from SCALE randomized controlled trials. *Diabetes, Obesity and Metabolism.* March 2018;20(3):734-739. doi:http://dx.doi.org/10.1111/dom.13125

105. Nissen SE, Wolski KE, Prcela L, et al. Effect of Naltrexone-Bupropion on Major Adverse Cardiovascular Events in Overweight and Obese Patients With Cardiovascular Risk Factors: A Randomized Clinical Trial. *Jama.* Mar 8 2016;315(10):990-1004. doi:10.1001/jama.2016.1558

106. Sposito AC, Bonilha I, Luchiari B, et al. Cardiovascular safety of naltrexone and bupropion therapy: Systematic review and meta-analyses. *Obes Rev.* Jun 2021;22(6):e13224. doi:10.1111/obr.13224

107. A Phase IV Study to Assess the Effect of Naltrexone Hydrochloride Extended Release (ER) and Bupropion Hydrochloride ER Combination (Contrave®/Mysimba®) on the Occurrence of Major Adverse Cardiovascular Events. National Library of Medicine (US). https://clinicaltrials.gov/study/NCT06098079

108. A Phase 3, Randomized, Double-blind, Placebo-Controlled Study to Investigate the Effect of Tirzepatide on the Reduction of Morbidity and Mortality in Adults With Obesity. National Library of Medicine (US). https://clinicaltrials.gov/study/NCT05556512

109. The Effect of Tirzepatide Versus Dulaglutide on Major Adverse Cardiovascular Events in Patients With Type 2 Diabetes (SURPASS-CVOT). National Library of Medicine (US). https://clinicaltrials.gov/study/NCT04255433

110. Brown CD, Higgins M, Donato KA, et al. Body mass index and the prevalence of hypertension and dyslipidemia. *Obes Res.* Dec 2000;8(9):605-19. doi:10.1038/oby.2000.79

111. El Meouchy P, Wahoud M, Allam S, Chedid R, Karam W, Karam S. Hypertension Related to Obesity: Pathogenesis, Characteristics and Factors for Control. *Int J Mol Sci.* Oct 14 2022;23(20)doi:10.3390/ijms232012305

112. Patton I, Salas XR, Hussey B, et al. Patient perceptions about obesity management in the context of concomitant care for other chronic diseases. *Obesity Pillars.* 2023/12/01/ 2023;8:100089. doi:https://doi.org/10.1016/j.obpill.2023.100089

113. Klop B, Elte JWF, Cabezas MC. Dyslipidemia in Obesity: Mechanisms and Potential Targets. *Nutrients.* 2013;5(4):1218-1240.

114. Khera R, Pandey A, Chandar AK, et al. Effects of Weight-Loss Medications on Cardiometabolic Risk Profiles: A Systematic Review and Network Meta-analysis. Meta-Analysis
Research Support, N.I.H., Extramural
Review. *Gastroenterology.* Apr 2018;154(5):1309-1319 e7. doi:10.1053/j.gastro.2017.12.024

115. Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension.* Nov 2003;42(5):878-84. doi:10.1161/01.Hyp.0000094221.86888.Ae

116. Haass M, Kitzman DW, Anand IS, et al. Body Mass Index and Adverse Cardiovascular Outcomes in Heart Failure Patients With Preserved Ejection Fraction. *Circulation: Heart Failure.* 2011;4(3):324-331. doi:doi:10.1161/CIRCHEARTFAILURE.110.959890

117. Borlaug BA, Jensen MD, Kitzman DW, Lam CSP, Obokata M, Rider OJ. Obesity and heart failure with preserved ejection fraction: new insights and pathophysiological targets. *Cardiovasc Res.* Feb 3 2023;118(18):3434-3450. doi:10.1093/cvr/cvac120

118. Kitzman DW, Brubaker P, Morgan T, et al. Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial. *Jama.* Jan 5 2016;315(1):36-46. doi:10.1001/jama.2015.17346

119. Kosiborod MN, Petrie MC, Borlaug BA, et al. Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes. *The New England journal of medicine.* 2024;390(15):1394-1407. doi:https://dx.doi.org/10.1056/NEJMoa2313917

120. Savji N, Meijers WC, Bartz TM, et al. The Association of Obesity and Cardiometabolic Traits With Incident HFpEF and HFrEF. *JACC: Heart Failure.* 2018/08/01/ 2018;6(8):701-709. doi:https://doi.org/10.1016/j.jchf.2018.05.018

121. Pandey A, LaMonte M, Klein L, et al. Relationship Between Physical Activity, Body Mass Index, and Risk of Heart Failure. *Journal of the American College of Cardiology.* 2017/03/07/ 2017;69(9):1129-1142. doi:https://doi.org/10.1016/j.jacc.2016.11.081

122. Vest AR, Schauer PR, Rodgers JE, et al. Obesity and Weight Loss Strategies for Patients With Heart Failure. *JACC: Heart Failure.* 2024/09/01/ 2024;12(9):1509-1527. doi:https://doi.org/10.1016/j.jchf.2024.06.006

123. Deanfield J, Verma S, Scirica BM, et al. Semaglutide and cardiovascular outcomes in patients with obesity and prevalent heart failure: a prespecified analysis of the SELECT trial. *The Lancet.* 2024;404(10454):773-786. doi:10.1016/S0140-6736(24)01498-3

124. Jorsal A, Kistorp C, Holmager P, et al. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE)-a multicentre, double-blind, randomised, placebo-controlled trial. *Eur J Heart Fail.* Jan 2017;19(1):69-77. doi:10.1002/ejhf.657

125. Neves JS, Vasques-Novoa F, Borges-Canha M, et al. Risk of adverse events with liraglutide in heart failure with reduced ejection fraction: A post hoc analysis of the FIGHT trial. *Diabetes, Obesity and Metabolism.* 2023;25(1):189-197. doi:https://dx.doi.org/10.1111/dom.14862

126. Hauguel-Moreau M, Hergault H, Cazabat L, et al. Prevalence of prediabetes and undiagnosed diabetes in a large urban middle-aged population: the CARVAR 92 cohort. *Cardiovascular Diabetology.* 2023/02/13 2023;22(1):31. doi:10.1186/s12933-023-01761-3

127. Andes LJ, Cheng YJ, Rolka DB, Gregg EW, Imperatore G. Prevalence of Prediabetes Among Adolescents and Young Adults in the United States, 2005-2016. *JAMA Pediatr.* Feb 1 2020;174(2):e194498. doi:10.1001/jamapediatrics.2019.4498

128. Diabetes Prevention Program Research G, Knowler WC, Fowler SE, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet.* Nov 14 2009;374(9702):1677-86. doi:10.1016/S0140-6736(09)61457-4

129. Daousi C, Casson IF, Gill GV, MacFarlane IA, Wilding JP, Pinkney JH. Prevalence of obesity in type 2 diabetes in secondary care: association with cardiovascular risk factors. *Postgrad Med J.* Apr 2006;82(966):280-4. doi:10.1136/pmj.2005.039032

130. Diabetes Canada Clinical Practice Guidelines Expert C, Lipscombe L, Booth G, et al. Pharmacologic Glycemic Management of Type 2 Diabetes in Adults. *Can J Diabetes.* Apr 2018;42 Suppl 1:S88-S103. doi:10.1016/j.jcjd.2017.10.034

131. Garvey WT, Birkenfeld AL, Dicker D, et al. Efficacy and Safety of Liraglutide 3.0 mg in Individuals With Overweight or Obesity and Type 2 Diabetes Treated With Basal Insulin: The SCALE Insulin Randomized Controlled Trial. *Diabetes Care.* 2020;43(5):1085-1093. doi:https://dx.doi.org/10.2337/dc19-1745

132. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology.* Jul 2016;64(1):73-84. doi:10.1002/hep.28431

133. European Association for the Study of the L, European Association for the Study of D, European Association for the Study of O. EASL-EASD-EASO Clinical Practice Guidelines on the Management of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). *Obes Facts.* 2024:1-70. doi: https://dx.doi.org/10.1159/000539371

134. Loomba R, Friedman SL, Shulman GI. Mechanisms and disease consequences of nonalcoholic fatty liver disease. *Cell.* May 13 2021;184(10):2537-2564. doi:10.1016/j.cell.2021.04.015

135. Quek J, Chan KE, Wong ZY, et al. Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol.* Jan 2023;8(1):20-30. doi:10.1016/s2468-1253(22)00317-x

136. Musso G, Cassader M, Rosina F, Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. *Diabetologia.* Apr 2012;55(4):885-904. doi:10.1007/s00125-011-2446-4

137. The Effect of Semaglutide in Subjects With Non-cirrhotic Non-alcoholic Steatohepatitis. National Library of Medicine (US). https://clinicaltrials.gov/study/NCT04822181

138. Harrison SA, Fecht W, Brunt EM, Neuschwander-Tetri BA. Orlistat for overweight subjects with nonalcoholic steatohepatitis: A randomized, prospective trial. Randomized Controlled Trial. *Hepatology.* Jan 2009;49(1):80-6. doi:10.1002/hep.22575

139. Jehan S, Zizi F, Pandi-Perumal SR, et al. Obstructive Sleep Apnea and Obesity: Implications for Public Health. *Sleep Med Disord.* 2017;1(4)

140. Salis Z, Gallego B, Nguyen TV, Sainsbury A. Association of Decrease in Body Mass Index With Reduced Incidence and Progression of the Structural Defects of Knee Osteoarthritis: A Prospective Multi-Cohort Study. *Arthritis Rheumatol.* Apr 2023;75(4):533-543. doi:10.1002/art.42307

141. Gudbergsen H, Overgaard A, Henriksen M, et al. Liraglutide after diet-induced weight loss for pain and weight control in knee osteoarthritis: a randomized controlled trial. *Am J Clin Nutr.* Feb 2 2021;113(2):314-323. doi:10.1093/ajcn/nqaa328

142. Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity. *Endocr Pract.* Jul 2016;22 Suppl 3:1-203. doi:10.4158/EP161365.GL

143. Vine D, Ghosh M, Wang T, Bakal J. Increased Prevalence of Adverse Health Outcomes Across the Lifespan in Those Affected by Polycystic Ovary Syndrome: A Canadian Population Cohort. *CJC Open.* Feb 2024;6(2Part B):314-326. doi:10.1016/j.cjco.2023.12.010

144. Elkind-Hirsch KE, Chappell N, Shaler D, Storment J, Bellanger D. Liraglutide 3 mg on weight, body composition, and hormonal and metabolic parameters in women with obesity and polycystic ovary syndrome: a randomized placebo-controlled-phase 3 study. *Fertil Steril.* Aug 2022;118(2):371-381. doi:10.1016/j.fertnstert.2022.04.027

145. Tian D, Chen W, Xu Q, Li X, Lv Q. Liraglutide monotherapy and add on therapy on obese women with polycystic ovarian syndromes: a systematic review and meta-analysis. *Minerva medica.* 2021;doi:https://dx.doi.org/10.23736/S0026-4806.21.07085-3

146. Naderpoor N, Shorakae S, de Courten B, Misso ML, Moran LJ, Teede HJ. Metformin and lifestyle modification in polycystic ovary syndrome: systematic review and meta-analysis. *Hum Reprod Update.* Sep-Oct 2015;21(5):560-74. doi:10.1093/humupd/dmv025

147. Wang FF, Wu Y, Zhu YH, et al. Pharmacologic therapy to induce weight loss in women who have obesity/overweight with polycystic ovary syndrome: a systematic review and network meta-analysis. *Obes Rev.* Oct 2018;19(10):1424-1445. doi:10.1111/obr.12720

148. Madero M, Katz R, Murphy R, et al. Comparison between Different Measures of Body Fat with Kidney Function Decline and Incident CKD. *Clin J Am Soc Nephrol.* Jun 7 2017;12(6):893-903. doi:10.2215/CJN.07010716

149. Kramer H, Shoham D, McClure LA, et al. Association of waist circumference and body mass index with all-cause mortality in CKD: The REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study. *Am J Kidney Dis.* Aug 2011;58(2):177-85. doi:10.1053/j.ajkd.2011.02.390

150. Martínez-Montoro JI, Morales E, Cornejo-Pareja I, Tinahones FJ, Fernández-García JC. Obesity-related glomerulopathy: Current approaches and future perspectives. *Obes Rev.* 2022;23(7):e13450. doi:https://doi.org/10.1111/obr.13450

151. Colhoun HM, Lingvay I, Brown PM, et al. Long-term kidney outcomes of semaglutide in obesity and cardiovascular disease in the SELECT trial. *Nature medicine.* 2024;doi:https://dx.doi.org/10.1038/s41591-024-03015-5

152. Apperloo EM, Gorriz JL, Soler MJ, et al. Semaglutide in patients with overweight or obesity and chronic kidney disease without diabetes: a randomized double-blind placebo-controlled clinical trial. *Nature Medicine.* 2025/01/01 2025;31(1):278-285. doi:10.1038/s41591-024-03327-6

153. Jacobsen LV, Hindsberger C, Robson R, Zdravkovic M. Effect of renal impairment on the pharmacokinetics of the GLP-1 analogue liraglutide. *Br J Clin Pharmacol.* Dec 2009;68(6):898-905. doi:10.1111/j.1365-2125.2009.03536.x

154. Urva S, Quinlan T, Landry J, Martin J, Loghin C. Effects of renal impairment on the pharmacokinetics of the dual GIP and GLP-1 receptor agonist tirzepatide. *Clinical Pharmacokinetics.* 2021;60:1049-1059.

155. Anand G, Katz PO. Gastroesophageal reflux disease and obesity. *Gastroenterol Clin North Am.* Mar 2010;39(1):39-46. doi:10.1016/j.gtc.2009.12.002

156. Khan A, Kim A, Sanossian C, Francois F. Impact of obesity treatment on gastroesophageal reflux disease. *World J Gastroenterol.* Jan 28 2016;22(4):1627-38. doi:10.3748/wjg.v22.i4.1627

157. Simon GE, Von Korff M, Saunders K, et al. Association between obesity and psychiatric disorders in the US adult population. *Arch Gen Psychiatry.* Jul 2006;63(7):824-30. doi:10.1001/archpsyc.63.7.824

158. McElroy SL, Guerdjikova AI, Blom TJ, Mori N, Romo-Nava F. Liraglutide in Obese or Overweight Individuals With Stable Bipolar Disorder. *J Clin Psychopharmacol.* Mar-Apr 01 2024;44(2):89-95. doi:https://dx.doi.org/10.1097/JCP.0000000000001803

159. de Silva VA, Suraweera C, Ratnatunga SS, Dayabandara M, Wanniarachchi N, Hanwella R. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. *BMC Psychiatry.* Oct 3 2016;16(1):341. doi:10.1186/s12888-016-1049-5

160. Carolan A, Hynes-Ryan C, Agarwal SM, et al. Metformin for the Prevention of Antipsychotic-Induced Weight Gain: Guideline Development and Consensus Validation. *Schizophrenia Bulletin.* 2024;doi:10.1093/schbul/sbae205

161. O'Neil PM, Aroda VR, Astrup A, et al. Neuropsychiatric safety with liraglutide 3.0 mg for weight management: Results from randomized controlled phase 2 and 3a trials. *Diabetes Obes Metab.* Nov 2017;19(11):1529-1536. doi:10.1111/dom.12963

162. Hill AJ. The psychology of food craving. *Proc Nutr Soc.* May 2007;66(2):277-85. doi:10.1017/s0029665107005502

163. Ferguson KJ, et al. Characteristics of successful dieters as measured by guided interview responses and Restraint Scale scores. *J Am Diet Assoc.* 1992:1119-1121.

164. Felce D, Perry, J. Quality of Life: Its Definition and Measurement. *Research in Developmental Disabilities.* 1995;16(1):51-74.

165. Colman E. Food and Drug Administration's Obesity Drug Guidance Document: a short history. *Circulation.* May 1 2012;125(17):2156-64. doi:10.1161/CIRCULATIONAHA.111.028381

166. Stewart AL, Greenfield S, Hays RD, et al. Functional Status and Well-being of Patients With Chronic Conditions: Results From the Medical Outcomes Study. *Jama.* 1989;262(7):907-913. doi:10.1001/jama.1989.03430070055030

167. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* Jun 1992;30(6):473-83.

168. Kolotkin RL, Williams VSL, Ervin CM, et al. Validation of a new measure of quality of life in obesity trials: Impact of Weight on Quality of Life-Lite Clinical Trials Version. *Clin Obes.* Jun 2019;9(3):e12310. doi:10.1111/cob.12310

169. Kolotkin RL, Crosby RD, Kosloski KD, Williams GR. Development of a brief measure to assess quality of life in obesity. *Obes Res.* Feb 2001;9(2):102-11. doi:10.1038/oby.2001.13

170. Kolotkin RL, Gabriel Smolarz B, Meincke HH, Fujioka K. Improvements in health-related quality of life over 3 years with liraglutide 3.0 mg compared with placebo in participants with overweight or obesity. *Clin.* 2018;8(1):1-10. doi:https://dx.doi.org/10.1111/cob.12226

171. Gudzune KA, Stefanski A, Cao D, et al. Association between weight reduction achieved with tirzepatide and quality of life in adults with obesity: Results from the SURMOUNT-1 study. *Diabetes, Obesity and Metabolism.* 2024;27(2):539-550. doi:https://doi.org/10.1111/dom.16046

172. Forsythe E, Haws RM, Argente J, et al. Quality of life improvements following one year of setmelanotide in children and adult patients with Bardet-Biedl syndrome: phase 3 trial results. *Orphanet Journal of Rare Diseases.* 2023;18(1):12. doi:https://dx.doi.org/10.1186/s13023-022-02602-4

173. Kuhnen P, Wabitsch M, von Schnurbein J, et al. Quality of life outcomes in two phase 3 trials of setmelanotide in patients with obesity due to LEPR or POMC deficiency. *Orphanet journal of rare diseases.* 2022;17(1):38. doi:https://dx.doi.org/10.1186/s13023-022-02186-z

174. Horn DB, Almandoz JP, Look M. What is clinically relevant weight loss for your patients and how can it be achieved? A narrative review. *Postgrad Med.* 2022;134(4):359-375. doi:https://dx.doi.org/10.1080/00325481.2022.2051366

175. Zhong P, Zeng H, Huang M, Fu W, Chen Z. Efficacy and safety of once-weekly semaglutide in adults with overweight or obesity: a meta-analysis. *Endocrine.* 2022;75(3):718-724. doi:https://dx.doi.org/10.1007/s12020-021-02945-1