Canadian Adult Obesity Clinical Practice GUIDELINES

obesity canada / obésité canada

Pharmacotherapy for obesity management

Sue D. Pedersen MD[i], Priya Manjoo MD[ii], Sean Wharton MD Pharm D[iii]

i) C-ENDO Diabetes & Endocrinology Clinic Calgary
ii) Department of Endocrinology, University of British Columbia
iii) Department of Medicine, McMaster University

Cite this Chapter

Pedersen SD, Manjoo P, Wharton S. Canadian Adult Obesity Clinical Practice Guidelines: Pharmacotherapy for Obesity Management. Available from: https://obesitycanada.ca/guidelines/pharmacotherapy. Accessed [date].

Update History

Version 2, October 21, 2022. Adult Obesity Clinical Practice Guidelines are a living document, with only the latest chapters posted at obesitycanada.ca/guidelines.

KEY MESSAGES FOR HEALTHCARE PROVIDERS

- Pharmacological treatments are an effective and scalable approach to treating obesity. As with any chronic disease, such as type 2 diabetes (T2DM) 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 [QoL]), not solely weight reduction, and should include outcomes that the patient identifies as important. Obesity is defined by body mass index (BMI) in clinical trials, which itself does not adequately reflect the burden of adiposity-related disease.
- There are four medications indicated for long-term obesity management in Canada as adjuncts to health-behaviour changes: liraglutide (Saxenda®), naltrexone/bupropion (Contrave®) in a combination tablet, orlistat (Xenical®) and semaglutide (Wegovy®). All four medications are effective in producing clinically significant weight loss and health benefits greater than placebo over a duration of at least one year.
- The individual response to pharmacotherapy for obesity management is heterogeneous. Efficacy (both for weight and management of obesity-related health issues), mechanism of action, safety, potential side effects/tolerability, contraindications, medication interactions, mode of administration and cost are important considerations in choosing the most appropriate obesity pharmacotherapy.
- Obesity medications are intended as part of a long-term treatment strategy. Clinical trials of pharmacotherapy for obesity management consistently demonstrate regain of weight when treatment is stopped.
- Medications that are not approved as pharmacotherapy for obesity management should not be used for this purpose.

RECOMMENDATIONS

1. Pharmacotherapy for obesity management can be used for individuals with BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 with adiposity-related complications, in conjunction with medical nutrition therapy, physical activity and/or psychological interventions (semaglutide 2.4 mg weekly [Level 1a Grade A],[1] liraglutide 3.0 mg daily [Level 2a, grade B],[2-4] naltrexone/bupropion 16 mg/180 mg BID [Level 2a, Grade B],[5] orlistat 120 mg TID [Level 2a, Grade B]).[6]
2. Pharmacotherapy may be used to maintain weight loss and to prevent weight regain (liraglutide 3.0 mg daily [Level 2a, Grade B],[4] orlistat 120 mg TID [Level 2a, Grade B]).[7]
3. Pharmacotherapy for obesity management in conjunction with health-behaviour changes for people living with prediabetes and overweight or obesity (BMI ≥ 27 kg/m^2) can be used to delay or prevent type 2 diabetes (T2DM) (liraglutide 3.0 mg daily [Level 2a, Grade B],[3] orlistat 120 mg TID [Level 2a, Grade B]).[8]

4. Obesity pharmacotherapy can be used in conjunction with health-behaviour changes in people living with T2DM and a BMI ≥ 27 kg/m^2, for weight loss and improvement in glycemic control (semaglutide 2.4 mg weekly [Level 1a, Grade A],[9] liraglutide 3.0 mg daily [Level 1b, Grade A],[10] naltrexone/bupropion 16 mg/180 mg BID [Level 2a, Grade B],[11] orlistat 120 mg TID [Level 2a, Grade B]).[12]

5. Pharmacotherapy can be considered in conjunction with health-behaviour changes in treating people with obstructive sleep apnea and BMI ≥ 30 kg/m^2, for weight loss and associated improvement in apnea-hypopnea index (liraglutide 3.0 mg daily [Level 2a, Grade B]).[13]

6. Pharmacotherapy can be considered in conjunction with health-behaviour changes in treating people living with non-alcoholic steatohepatitis (NASH) and overweight or obesity, for weight loss and improvement of NASH parameters (liraglutide 1.8 mg daily [Level 3; Grade C],[14] semaglutide [Level 4 Grade D]).[15]

7. Metformin and psychological treatment (such as cognitive behavioural therapy) should be considered for prevention of weight gain in people with severe mental illness who are treated with anti-psychotic medications associated with weight gain [Level 1a, Grade A].[16]*
   * Please see Taylor VH, Sockalingam S, Hawa R, Hahn M. Canadian Adult Obesity Clinical Practice Guidelines: The Role of Mental Health in Obesity Management. Available from: https://obesitycanada.ca/guidelines/mentalhealth.

8. For people living with overweight or obesity who require pharmacotherapy for other health conditions, we suggest choosing medications that are not associated with weight gain [Level 4, Grade D, Consensus].

9. We do not suggest the use of prescription or over-the-counter medications other than those approved in Canada for obesity management [Level 4, Grade D, Consensus].

KEY MESSAGES FOR PEOPLE LIVING WITH OBESITY

- Obesity medications are effective for managing weight and weight-related health issues, often in combination with healthy behaviour changes and/or psychological interventions.
- The goals in obesity management should include improvement in health and should include outcomes that are important to you.
- There are four medications approved by Health Canada for long-term obesity management in Canada: liraglutide 3.0 mg (Saxenda®), naltrexone/bupropion in a combination tablet (Contrave®), orlistat (Xenical®) and semaglutide 2.4 mg (Wegovy®). 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 safe and effective for obesity management.
- 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 comorbidities associated with obesity.[17-19] Healthy eating and physical activity are fundamental to successful weight management; however, these changes alone are often not sufficient for achieving sustained weight loss. Healthy behaviour changes alone generally achieve only a 3%–5% weight loss, which is most often not sustained over the long term.[20] Pharmacotherapy for obesity management should be considered to decrease weight and optimize health when healthy eating and physical activity alone have been ineffective, insufficient or without sustained benefit.

Despite the high prevalence of obesity,[21] obesity medications are prescribed far less frequently than medications for other chronic medical conditions, such as type 2 diabetes.[22] The adoption of novel diabetes medications is much greater and much more rapid than the adoption rate of new pharmacotherapies for weight management.[22] This may be due to the reluctance of public health and medical organizations to recognize obesity as a chronic disease, which in turn affects reimbursement. Provider inexperience, and/or misperceptions about the efficacy and safety of available treatments, may also contribute to this gap.

This chapter provides a review of the literature pertaining to the efficacy of the obesity medications currently approved by Health Canada. It is intended to inform primary care practitioners and specialists on the appropriate use of obesity pharmacotherapy.

Health Canada has established the following criteria that must be satisfied for a pharmacotherapeutic agent to receive regulatory approval for long-term weight management:

1. The agent must be studied in clinical trials of at least one year in duration.

2. The agent must produce a placebo-adjusted mean weight loss of ≥ 5% or demonstrate a ≥ 5% weight loss in at least 35% of patients, with this proportion being more than double that in placebo.

3. The agent should demonstrate an improvement in obesity-related comorbidities.

Pharmacotherapy is indicated for long-term weight management in Canada for individuals with a BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with comorbidities associated with excess body fat (e.g., T2DM, hypertension, dyslipidemia, obstructive sleep apnea).

There are four medications approved for obesity management in Canada: orlistat 120 mg TID, liraglutide 3.0 mg subcutaneously daily, naltrexone/bupropion 16 mg/180 mg BID, and semaglutide 2.4 mg subcutaneously weekly. It is recognized that other medications, available in Canada but not approved for obesity management, are used off-label for this purpose. As a result, our literature search employed an open strategy to capture all pharmacotherapy agents that have been studied for obesity management. However, except for metformin for prevention of anti-psychotic-medication-induced weight gain, we discourage healthcare providers from using agents solely for obesity management if they do not have regulatory approval for this indication, or do not have evidence-based recommendations for their use. We have recommended the use of metformin for prevention of anti-psychotic-medication-induced weight gain given the high quality data supporting this intervention (see the discussion and recommendation for the use of metformin in The Role of Mental Health in Obesity Management chapter of the 2020 CPGs).[16] Non-prescription treatments/supplements are reviewed separately in the Commercial Products and Programs in Obesity Management chapter.[23]

This chapter addresses clinical questions pertaining to the efficacy of pharmacotherapy in people with overweight or obesity, and summarizes existing evidence for use of pharmacotherapy for obesity among persons with obesity-related comorbidities, including prediabetes, T2DM, non-alcoholic fatty liver disease (NAFLD) and NASH, dyslipidemia, hypertension, polycystic ovary syndrome (PCOS), obstructive sleep apnea, osteoarthritis (OA), gastroesophageal reflux disease, depression, heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, chronic kidney disease and atherosclerotic vascular disease. 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 disease-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 can facilitate successful obesity management; as such, our search strategy included studies of approved pharmacotherapies for obesity management on cravings and quality of life. The 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, until January 2022.

Considerations in the use of pharmacotherapy for obesity management

The patient and healthcare practitioner should identify the goals of therapy prior to initiating obesity pharmacotherapy. The targets of treatment should be determined by the patient's specific values and preferences as it relates to obesity management, as well as a discussion around reasonable expectations of pharmacotherapy. It is also recognized that there is cultural heterogeneity in what is considered acceptable or desirable in terms of body size and shape. In addition to weight loss, additional or alternate treatment targets may include improvement, remission or resolution of adiposity-related comorbidities, weight maintenance, control of cravings and improvement in quality of life.

The mechanism of action, efficacy, adverse side effects, safety and tolerability of each agent must be considered in the context of each patient's comorbidities and existing medications. The cost of medications as well as the mode (oral versus subcutaneous) and frequency of administration should be discussed. It is important to assess concomitant medications as possible contributors to weight gain, and to consider alternatives where appropriate.

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 adequacy of dosing, challenges in adherence, barriers to health-behaviour change, as well as psychosocial and medical issues, should be reassessed. There is considerable heterogeneity in the response to any pharmacotherapeutic agent, and consideration should be given to adding or substituting another obesity medication or intervention if treatment goals have not been achieved after three to six months on the maximum tolerated dose.

Currently, we do not have the ability to predict which medication will be most effective for a patient, though preliminary data suggest that phenotypes of obesity may be helpful in guiding the choice of pharmacotherapy in the future,[24] especially with the evolution of hormonal and genetic profiling.

Pharmacotherapy for obesity management can be used not only to facilitate weight loss, but also for weight loss maintenance and to improve health. Regulatory agencies have traditionally recommended discontinuing pharmacotherapy for weight management if weight loss of ≥ 5% has not been achieved after three months on therapeutic dose. However, substantial health improvements may be realized without a weight loss of ≥ 5%. Pharmacotherapy can also assist in the maintenance of weight loss achieved with a prior health-behaviour change or a very low energy diet.[4,7]

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).[25] Obesity medications are intended as part of a long-term treatment strategy. Clinical trials of pharmacotherapy for obesity management consistently demonstrate regain of weight when treatment is stopped.[6]

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

BMI and waist circumferences that correlate with comorbidities vary by ethnicity.[25] The BMI criteria for inclusion in pharmacotherapy studies is in accordance with the BMI criteria for overweight and obesity in the Caucasian, Europid and North American ethnicity, which are higher than the BMI criteria in South-, Southeast- or East Asian ethnicity. The prescribing physician may elect to interpret the recommendations in this chapter with ethnicity-specific BMI criteria in mind. Ethnic minorities are underrepresented in clinical trials of pharmacotherapy for weight management; having balanced ethnic representation is important for future pharmacotherapy trials.

Approved pharmacotherapy for obesity management

Orlistat 120 mg TID

Orlistat, a semisynthetic derivative of lipstatin, was approved as pharmacotherapy for obesity management in Canada in 1999. It is a potent and selective inhibitor of pancreatic lipase, thereby inhibiting 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.[26] Orlistat does not target appetite or satiety mechanisms.

Orlistat at a dose of 120 mg three times daily (taken during or up to one hour after meals) is approved by Health Canada for weight reduction or reducing the risk of weight regain after prior weight loss in patients with a BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 in the presence of comorbidities (e.g., hypertension, T2DM, dyslipidemia, excess visceral fat).[27]

A systematic review and meta-analysis of randomized controlled trials of orlistat 120 mg three times daily reported a mean placebo subtracted weight loss of -2.9% at one year.[28] Additionally, 54% and 26% of patients achieved ≥ 5% and ≥ 10% weight loss, respectively, compared to 33% and 14% for placebo.[28] 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).[7]

Orlistat therapy is associated with gastrointestinal side effects, including oily spotting and loose stools, flatus with discharge, fecal urgency and increased defecation.[28] 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.[29] 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.[28,30] Orlistat is contraindicated in patients with chronic malabsorption syndrome or cholestasis. Some patients may develop increased levels of urinary oxalate on orlistat; cases of oxalate nephropathy with renal failure have been reported.[31] There have also been rare cases of severe liver injury or acute liver failure.[32]

As orlistat may interfere with vitamin K absorption, the international normalized ratio should be monitored closely when oral anti-coagulants are co-administered. Orlistat may affect absorption of levothyroxine and/or iodine salts; patients on levothyroxine should be monitored for changes in thyroid function. 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 anti-convulsant medications, therefore patients on anti-convulsants and orlistat should be monitored for possible changes in the frequency and/or severity of seizure.[30]

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

Liraglutide 3.0 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)/CART neurons to improve satiation and satiety and reduce hunger, with a transient effect to decrease gastric emptying.[33,34]

Liraglutide increases insulin release and suppresses glucagon during times of glucose elevation. Liraglutide is approved in Canada for the management of T2DM at a dose of 1.2 mg or 1.8 mg daily, with near-maximal therapeutic efficacy for A1C lowering at the 1.8 mg dose. Liraglutide was approved in Canada in 2015 for long-term obesity management at a dose of 3.0 mg daily, in people with or without type 2 diabetes. The recommended starting dose of liraglutide is 0.6 mg daily, with up-titration by 0.6 mg each week until the 3.0 mg target dose is achieved.

Among people with normoglycemia or prediabetes, liraglutide 3.0 mg with health-behaviour modification resulted in -8.0% weight loss at one year, compared to -2.6% with placebo (health-behaviour modification alone).[2] In terms of categorical weight loss, 63.2% of patients on liraglutide lost ≥ 5% body weight at one year, compared with 27.1% of patients in the placebo group;[2] 33.1% and 10.6% of participants lost more than 10% of their body weight on liraglutide 3.0 mg and placebo, respectively.

Table 1. Pharmacotherapy for Obesity

	Orlistat	Liraglutide	Naltrexone/Bupropion	Semaglutide
Mode of administration	Oral	Subcutaneous	Oral	Subcutaneous
Dose/frequency	120 mg TID	3.0 mg daily	16/180 mg BID	2.4 mg weekly
Effect on % weight loss at 1 year, placebo subtracted	-2.9%[28]	-5.4%[2]	-4.8%[5]	-12.5%[1]
Effect on weight over longer term, placebo subtracted	-2.8 kg at 4 years[8]	-4.2% at 3 years[3]	Not studied	Not available
% of patients achieving ≥ 5% weight loss at 1 year	54% (vs. 33% in placebo)[28]	63.2% (vs. 27.1% in placebo)[2]	48% (vs. 16% in placebo)[5]	86.4% (vs. 31.5% in placebo)[1]
% of patients achieving ≥ 10% weight loss at 1 year	26% (vs. 14% in placebo)[28]	33.1% (vs. 10.6% in placebo)[2]	25% (vs. 7% in placebo)[5]	69.1% (vs. 12% in placebo)[1]
% of patients achieving ≥ 15% weight loss at 1 year	Not studied	14.4% (vs. 3.5% with placebo)[3]	13.5% (vs. 2.4% with placebo)[36]	50.5% (vs. 4.9% with placebo)[1]
% of patients achieving ≥ 20% weight loss at 1 year	Not studied	Not studied	Not studied	32% (vs. 1.7% in placebo)[1]
Effect on maintenance of previous lifestyle-induced weight loss	2.4 kg less weight regain vs. placebo over 3 years[7]	-6.0% additional placebo-subtracted weight loss at 1 year[4]	Not studied	Not studied
Cost	$$	$$$$	$$$	Unknown
Contraindications	• Cholestasis • Chronic malabsorption syndrome • Pregnancy, attempting conception, breastfeeding	• Personal or family history of medullary thyroid cancer • Personal history of MEN2 syndrome • Pregnancy, 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 • Severe hepatic impairment • End-stage renal failure • Pregnancy, attempting conception, breastfeeding	• Personal or family history of medullary thyroid cancer • Personal history of MEN2 syndrome • Pregnancy, attempting conception, breastfeeding
Common side effects	Loose, oily stools, flatus	Nausea, constipation, diarrhea, vomiting	Nausea, constipation, headache, dry mouth, dizziness, diarrhea	Nausea, diarrhea, constipation, vomiting
Rare side effects	• Liver failure • Nephrolithiasis • Acute kidney injury	• Cholelithiasis • Pancreatitis	• Seizure • Worsening of depression	• Cholelithiasis • Pancreatitis
Medication interactions	• Fat-soluble vitamins • Levothyroxine • Cyclosporine • Oral anti-coagulants • Anti-convulsants	May affect absorption of medications due to slowing of gastric emptying	Yes: See chapter text	May affect absorption of medications due to possible slowing of gastric emptying

Table 2. Pharmacotherapy for Obesity: Effects on Adiposity-Related Comorbidities

	Orlistat	Liraglutide 3.0mg	Naltrexone/Bupropion	Semaglutide 2.4mg
Effect on prediabetes	37.3% reduction in risk of developing T2DM over 4 years[8]	79% reduction in risk of developing T2DM over 3 years[3]	Not studied	Not available
Effect on BP at 1 year, placebo subtracted	-1.7 mm Hg SBP -0.71 mmHg DBP[37]	-2.87 mm Hg SBP -0.73 mmHg DBP[38]	Not significantly different [37]	-5.1mm Hg SBP -2.4mm Hg DBP[1]
Effect on lipids at 1 year, placebo subtracted (only statistically significant changes in lipid parameters listed)	LDL -0.22 mmol/L HDL +0.03 mmol/L[37]	LDL -0.08 mmol/L[38]	HDL +0.06 mmol/L[37]	Total chol -0.22mmol/L LDL -0.1mmol/L HDL +0.1mmol/L Triglycerides -0.22 mmol/L[1, 39]
Effect on HR at 1 year, placebo subtracted	No change	+2.4 BPM[2]	+1.1 BPM[5]	+4.2BPM[1]
Effect on A1C in patients with diabetes at 1 year, placebo subtracted	-0.4%[12]	-1.0%[10]	-0.5%[11]	-1.2%[9]
Effect on MACE	Not studied	Cardiovascular safety demonstrated[40]	Not studied	Not available
Effect on NASH	No change	Resolution of NASH and improvement in steatosis (39% with lira 3mg vs. 9% with placebo)[14]	Not studied	Resolution of NASH (59% with semaglutide 0.4 mg daily vs. 17% with placebo)[15]
Effect on PCOS	Not studied	Not sufficiently studied	Not studied	Not studied
Effect on OA	Not studied	No benefit	Not studied	Not available
Effect on OSA (placebo subtracted)	Not studied	Reduces AHI by 6/hour[13]	Not studied	Not studied
Effect on physical function	Not studied	SF-36 – Improvement[41] IWQOL – Improvement[41]	IWQOL – Improvement[5]	SF36 – Improvement[1] IWQOL – Improvement[1]
Effect on QoL	Not studied	SF36 – Improvement[41] IWQOL – Improvement[41]	IWQOL – Improvement[5]	SF36 – Improvement[1] IWQOL – Improvement[1]
Effect on CoEQ (cravings)	Not studied	Not studied	Improvements in craving control, positive mood, craving for sweet and savoury food[42]	Improvements in craving control, positive mood, craving for sweet and savoury food[43]

Patients with prediabetes were followed for three years, with sustained weight loss of -6.1% in the liraglutide group vs. -1.9% in placebo.[3] In addition to intensive behavioural therapy, liraglutide 3.0 mg resulted in -7.5% weight loss at one year, vs. -4.0% with placebo.[35]

Following a 6.0% weight loss with a low-calorie diet, liraglutide 3.0 mg plus health-behaviour counselling reduced weight by a further 6.2% at one year compared with 0.2% in the placebo group (ongoing health-behaviour counselling alone). More patients on liraglutide 3.0 mg were able to maintain the ≥ 5% run-in weight loss (81.4%) compared with those receiving placebo (48.9%). Fewer patients on liraglutide 3.0 mg regained ≥ 5% body weight (1.9%) compared to placebo (17.5%).[4]

The most common side effect of liraglutide is nausea.[2,3,4,35] There are likely many causes for the nausea, both central and peripheral, which may include a transient delay in gastric emptying.[34] Patients may also experience constipation, diarrhea, heartburn and/or vomiting. More gradual titration can help mitigate gastrointestinal side effects, should these occur. Liraglutide use is associated with a 1.4% higher risk of gallstones compared to placebo.[10]

There is a small increased risk of pancreatitis compared to placebo, with about half of cases seen in association with gallstones.[3] 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 because of an increased risk of medullary thyroid cancer in rodent studies. There have been no cases of medullary thyroid cancer in human studies of liraglutide. Liraglutide delays gastric emptying, which may impact absorption of concomitantly administered oral medications.

Naltrexone/Bupropion 16 mg/180 mg BID

Naltrexone hydrochloride/bupropion hydrochloride is a combination of two medications. Naltrexone is an opioid receptor antagonist that has been used for decades for the treatment of alcohol and opioid dependence. Bupropion is a widely used anti-depressant that inhibits the reuptake of dopamine and norepinephrine. The naltrexone/bupropion sustained release formulation was approved for long-term obesity management in Canada in 2018, at a dose of 16 mg naltrexone and 180 mg bupropion given twice daily. Bupropion induces satiety centrally by enhancing production and release of α-melanocyte stimulating hormone (α-MSH) and β-endorphin from the pro-opiomelanocortin cells in the arcuate nucleus of the hypothalamus. Naltrexone disrupts the auto-inhibitory effect of β-endorphin on the pro-opiomelanocortin cells by blocking the μ-opioid receptors. Naltrexone/bupropion also influences the mesolimbic reward system, resulting in a reduction in cravings.[44] This synergistic mode of action is supported by the evidence that the use of bupropion or naltrexone alone do not lead to clinically meaningful weight loss.[45]

Each tablet of the naltrexone/bupropion combination contains 8 mg of naltrexone and 90 mg of bupropion. The recommended titration schedule is one tablet daily for the first week, with an increase by one tablet each week until the maintenance dose of two tablets twice daily (total daily dose 32 mg/360 mg) is reached.

Among patients with overweight or obesity without diabetes, naltrexone/bupropion 16 mg/180 mg BID with a hypocaloric diet (500 kcal/day deficit) and exercise was associated with weight loss of -6.1% versus -1.3% in placebo. Weight loss of ≥ 5% was seen in 48% of patients, and ≥ 10% weight loss was seen in 25% of patients with naltrexone/bupropion, compared with 16% and 7% in the placebo group, respectively.[5]

Naltrexone/bupropion has demonstrated a reduction in cravings.[5,36] Results from the Control Of Eating Questionnaire (COEQ) demonstrated reductions in eating in response to food cravings, and increased ability to resist food cravings and control eating.[5] A combined analysis of three naltrexone/bupropion trials found that early improvements in cravings were predictive of greater weight loss.[45]

The most common side effects of naltrexone/bupropion include nausea, constipation, headache, vomiting, insomnia, dry mouth, dizziness and diarrhea. Most nausea 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 for seven to 10 days prior to initiation of naltrexone/bupropion to prevent the precipitation of opioid withdrawal.[46] 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 anti-epileptic medications. Naltrexone/bupropion should be dosed with caution with any medications that lower seizure threshold. Monoamine inhibitors can increase the risk of hypertensive reactions, and naltrexone/bupropion should therefore not be used within 14 days of taking monoamine inhibitors. Naltrexone/bupropion should not be taken with a high fat meal, as this significantly increases systemic exposure to the medication.[47]

There are multiple potential medication 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 medication 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, anti-psychotic agents, type 1C anti-arrhythmic agents and many tricyclic anti-depressants, such as citalopram, metoprolol, risperidone, propafenone and desipramine).[48] 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).[49] 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).[48] Central nervous system toxicity can occur when naltrexone/bupropion is used concomitantly with dopaminergic medications (e.g., levodopa, amantadine).

Semaglutide 2.4 mg SC weekly

Semaglutide is a once-weekly, subcutaneously administered, human GLP-1 analog that acts centrally on the POMC/CART neurons to improve satiation and satiety, reduce hunger and reduce cravings.[43]

Semaglutide increases insulin release and suppresses glucagon during times of glucose elevation. Semaglutide was approved in Canada in 2018 for the management of T2DM at a dose of 0.5 mg or 1.0 mg weekly, with near maximal therapeutic efficacy for A1C lowering at the 1.0 mg dose. Semaglutide was approved in Canada in 2021 for long-term obesity management at a dose of 2.4 mg weekly in people with or without type 2 diabetes. The recommended starting dose of semaglutide is 0.25 mg weekly, with up-titration every four weeks to 0.5 mg weekly, 1 mg weekly, 1.7 mg weekly and then to the maximum dose of 2.4 mg weekly.

Amongst 1,961 people with overweight or obesity and normoglycemia or prediabetes, semaglutide 2.4 mg with health-behaviour modification resulted in -14.9% weight loss at 68 weeks, compared to -2.4% with placebo (health-behaviour modification alone). In terms of categorical weight loss, 86.4% of patients lost ≥ 5% body weight with semaglutide vs. 31.5% with placebo; 69.1% of patients lost ≥ 10% body weight with semaglutide, compared with 12.0% of patients with placebo; 50.5% of patients lost ≥ 15% body weight with semaglutide vs. 4.9% with placebo, respectively.[1]

In addition to a low-calorie diet for eight weeks followed by intensive behavioural therapy for 68 weeks, semaglutide 2.4 mg resulted in -16.0% weight loss vs. -5.7% with placebo.[50] Among 803 adults with overweight or obesity who completed a 20-week run-in period with semaglutide 2.4 mg weekly (with a mean weight loss of 10.6%), maintaining treatment with semaglutide resulted in continued weight loss of -7.9% over the following 48 weeks vs. +6.9% weight gain with switch to placebo.[51]

In a study of semaglutide 2.4 mg weekly vs. liraglutide 3 mg daily amongst 338 people with overweight or obesity without diabetes, mean weight loss at 68 weeks was -15.8% with semaglutide vs. -6.4% with liraglutide. Gastrointestinal adverse events (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 and 27.6% with liraglutide.[52]

The most common side effects of semaglutide are gastrointestinal, including nausea, vomiting, diarrhea, constipation and heartburn. More gradual titration can help mitigate gastrointestinal side effects, should these occur. Semaglutide use is associated with a 1.2% higher risk of gallstones compared to placebo.[1]

There is a small increased risk of pancreatitis compared to placebo.[53] Semaglutide is contraindicated in patients with a personal or family history of medullary thyroid cancer or a personal history of multiple endocrine neoplasia type 2 because of an increased risk of medullary thyroid cancer in rodent studies.[53] There have been no cases of medullary thyroid cancer in human studies of semaglutide 1.0 mg nor semaglutide 2.4 mg.[53]

Semaglutide may delay gastric emptying, which could potentially influence absorption of concomitantly administered oral medications. However, in a pharmacodynamic study, no clinically relevant effect on the rate of gastric emptying was observed with semaglutide 2.4 mg at 20 weeks.[43]

Efficacy of pharmacotherapy on health parameters

Prevention of T2DM

T2DM is a common complication of obesity and prevention of diabetes is an important goal in long-term obesity management. People with prediabetes are at high risk of developing T2DM, with about 25% of individuals with either impaired fasting glucose or impaired glucose tolerance progressing to T2DM over three to five years.[54] Amongst individuals with prediabetes, one kilogram of weight loss is associated with a 16% relative risk reduction in the development of T2DM.[54]

Pharmacotherapy for obesity can prevent or delay the development of T2DM. Orlistat was evaluated for diabetes prevention in a trial of 3,305 patients with obesity and either normal (79%) or impaired (21%) glucose tolerance. Patients were randomized to health-behaviour changes plus either orlistat or placebo.[8] After four years of treatment, the cumulative incidence of diabetes was 6.2% in the orlistat group compared with 9.0% in placebo, with a corresponding 37.3% decrease in risk of progression to T2DM. People with impaired glucose tolerance derived the greatest benefit in terms of decreased rate of progression to T2DM, compared to participants with normoglycemia. A secondary analysis demonstrated greater weight loss to be the primary reason for diabetes prevention.[8]

Liraglutide 3.0 mg has demonstrated efficacy to prevent and delay T2DM amongst people with prediabetes. The SCALE Obesity and Prediabetes trial randomized 2,254 patients to receive liraglutide 3.0 mg (n = 1,505) or placebo (n = 749), in addition to health-behaviour change. The time to onset of T2DM over a three-year treatment period in this study was 2.7 times longer with liraglutide 3.0 mg vs. health behaviour alone, and the risk of developing T2DM was reduced by 79%.[3] These improvements are likely due

to a combined effect of the glucose lowering effects of liraglutide as well as liraglutide-mediated weight loss.

An analysis of 3,375 adults with overweight/obesity across the STEP 1, 3 and 4 trials evaluated whether more participants with prediabetes had normoglycemia after 68 weeks' treatment with semaglutide 2.4 mg weekly. Significantly more participants with baseline prediabetes had normoglycemia at week 68 vs. placebo (STEP 1: 84.1% vs. 47.8%; STEP 3: 89.5% vs. 55.0%; STEP 4: 89.8% vs. 70.4%; all $p < 0.0001$).[50,51,55] An ongoing study is currently evaluating the effect of semaglutide 2.4 mg on regression to normoglycemia among patients with obesity and prediabetes.[56]

There are no published studies evaluating the efficacy of naltrexone/bupropion on diabetes prevention.

Our systematic review identified one randomized control trial evaluating the efficacy of exenatide (a short-acting GLP-1 analog) versus placebo on body weight and glucose tolerance among people with obesity with normoglycemia, impaired glucose tolerance or impaired fasting glucose, on a background of health-behaviour intervention over a 24-week period.[57] The exenatide group demonstrated a -5.1 kg weight loss compared with -1.6 kg with placebo. Impaired glucose tolerance or impaired fasting glucose normalized in 77% of exenatide-treated patients compared with 56% in the placebo group. Exenatide is not indicated for obesity management, nor for the prevention of T2DM.

Type 2 diabetes mellitus

Obesity in T2DM is associated with poorer glycemic control, blood pressure and lipid profiles, and increased use of lipid lowering and anti-hypertensive medications, compared with people with diabetes who do not have obesity.[58]

The effect of glucose-lowering pharmacotherapy on weight should be considered in choosing the most appropriate medication(s) for glycemic control. GLP-1 receptor agonists and sodium/glucose cotransporter 2 inhibitors are associated with weight loss in addition to improving glycemic control. Metformin, dipeptidyl peptidase-4 inhibitors and acarbose are typically weight neutral. Insulin, insulin secretagogues and thiazolidinediones are associated with weight gain.[59] Pharmacotherapy for obesity can be of benefit for weight management, improved diabetes control and reduction in need for other glucose-lowering medication.

Orlistat has been demonstrated to improve glycemic control in patients with T2DM. A meta-analysis comprising 2,550 patients with T2DM and obesity randomized to orlistat 120 mg TID or placebo found that patients treated with orlistat had significantly greater mean decreases in fasting plasma glucose and HbA1c compared with placebo (1.39 mmol/l vs. 0.47 mmol/l and 0.74% vs. 0.31%, respectively).[12] Weight loss in the orlistat group was -3.8 kg compared to -1.4 kg on placebo. The primary reason for improvement in glycemic control with orlistat is weight loss, although orlistat may provide beneficial metabolic effects independent of weight loss.

In the SCALE diabetes trial, liraglutide 3.0 mg SC daily was compared to liraglutide 1.8 mg SC daily and placebo, in addition to health-behaviour changes, in people with obesity and T2DM managed with oral agents or health behaviours alone. At one year, liraglutide 3.0 mg reduced weight by -6.0% (n = 423) compared to -4.7% among those receiving liraglutide 1.8 mg (n = 211) and -2.0% with placebo (n = 212). A clinically significant weight loss of ≥ 5% was achieved by 54.3% of patients on liraglutide 3.0 mg, versus 40.4% with liraglutide 1.8 mg and 21.4% with placebo. Weight loss of ≥ 10% occurred in 25.2% of patients on liraglutide 3.0 mg, 15.9% of people with liraglutide 1.8 mg and 6.7% of people with placebo. A1C was reduced by -1.3% in the liraglutide 3.0 mg group, -1.1% in the liraglutide 1.8 mg group and -0.3% in those receiving placebo. In addition, more participants treated with liraglutide 3.0 mg and 1.8 mg reduced their net use of oral glucose-lowering agents compared with placebo.[10] In the SCALE insulin trial, 396 participants with T2DM and obesity treated with basal insulin and ≤ two oral glucose-lowering agents were randomized to receive liraglutide 3 mg daily vs. placebo, combined with intensive behavioural therapy. At 56 weeks, mean weight change was -5.8% with liraglutide 3 mg, versus -1.5% with placebo. Liraglutide 3 mg was associated with significantly greater reductions in A1C and less need for insulin compared with placebo.[60]

The Contrave Obesity Research Diabetes trial evaluated the safety and efficacy of naltrexone/bupropion 16 mg/180 mg BID in addition to health-behaviour changes amongst adults with a BMI of 27–45 kg/m2 and T2DM managed with oral agents or diet.[11] Naltrexone/bupropion treated patients achieved a -5.0% weight reduction compared with -1.8% in the placebo group. Additionally, 44.5% of patients achieved ≥ 5% weight loss compared with 18.9% in the placebo arm, and 18.5% of patients lost ≥ 10% weight loss compared with 5.7% of patients with placebo. Patients treated with naltrexone/bupropion demonstrated a -0.5% greater improvement in A1C compared to placebo, and were more likely to achieve an A1C < 7% (44.1% in the naltrexone/bupropion group vs. 26.3% in placebo). The change in A1C was correlated with the change in body weight in both study arms. However, fewer patients receiving naltrexone/bupropion required an increase in dose or the addition of glucose-lowering agents compared with placebo (22.3% vs. 35.2%, respectively).

In the STEP 2 study,[9] 1,210 people with overweight or obesity and T2DM managed with oral agents or health behaviours alone were randomized to semaglutide 2.4 mg weekly, semaglutide 1.0 mg weekly or placebo, in addition to health-behaviour modification. Semaglutide 2.4 mg resulted in a superior weight loss of -9.6% at 68 weeks, compared to -7.0% with semaglutide 1.0 mg, and -3.4% with placebo. More participants achieved weight reductions of at least 5% with semaglutide 2.4 mg (68.8%) than with semaglutide 1.0 mg (57.1%) or placebo (28.5%). Weight loss ≥ 10% occurred in 45.6% of patients in the semaglutide 2.4 mg group, 28.7% in the semaglutide 1.0 mg group and 8.2% in the placebo group. Weight loss ≥ 15% occurred in 25.8% of participants in the semaglutide 2.4 mg group, 13.7% in the semaglutide 1.0 mg group and 3.2% in the placebo group. Reduction in

hemoglobin A1C was similar at both doses of semaglutide, with a reduction of -1.6% with semaglutide 2.4 mg, -1.5% with semaglutide 1.0 mg and -0.4% with placebo. A decrease in use of concomitant glucose-lowering medication was reported in 28·6% of patients with semaglutide 2.4 mg, 25.1% with semaglutide 1.0 mg and 7.1% with placebo.

Other cardiovascular risk factors: Hypertension and lipids

Pharmacotherapy-induced weight loss can be of benefit to improve cardiovascular risk factors.

A systematic review assessed the effect of long-term obesity pharmacotherapy (at least one-year duration) on various aspects of cardiometabolic risk, including blood glucose, cholesterol profile, blood pressure and visceral adiposity.[37] Studies from inception of databases until 2017 were included. Randomized controlled trials were included that evaluated adults with a BMI of ≥ 30 kg/m^2 or BMI 25–29.9 kg/m^2 with and without obesity-associated comorbidities (hypertension, hyperlipidemia, diabetes mellitus, impaired glucose tolerance or obstructive sleep apnea); treated with obesity-management pharmacotherapy for at least one year; compared to another active agent or placebo; and reporting at least one prespecified cardiometabolic outcome in addition to a primary weight-loss outcome (5% of baseline weight loss or mean weight loss). There were 17 trials of orlistat vs. placebo (n = 10,702), three trials of liraglutide vs. placebo (n = 4,557) and four trials of naltrexone/bupropion vs. placebo (n = 3,953).

In this systematic review, orlistat, liraglutide and naltrexone/bupropion demonstrated modest effects on cholesterol profiles (Table 2). Though the effects of some of these medications on the lipid profile were statistically significant, they were of doubtful clinical significance. Orlistat, liraglutide and naltrexone/bupropion had minimal effects on blood pressure (BP), with very small decline in systolic and diastolic BP (Table 2). As naltrexone/bupropion can increase BP on initiation, it is contraindicated in patients with uncontrolled hypertension.[61]

Among patients with obesity and prediabetes, liraglutide reduced systolic blood pressure by -2.8 mmHg compared with placebo over three years, with modest improvements in lipid parameters. A heart rate increase of two beats per minute (BPM) was observed, in keeping with what is seen in the GLP-1 class.[3]

Semaglutide reduced systolic blood pressure by -6.1 mmHg vs. -1.1 mmHg with placebo at 68 weeks, with modest improvement in lipid parameters, in a study of people with obesity without type 2 diabetes (see Table 2). A heart rate increase of +3.5 BPM was noted vs. -0.7 BPM with placebo, in keeping with what is seen in the GLP-1 class.[1]

Atherosclerotic cardiovascular disease

Regulatory requirements for obesity pharmacotherapy do not include a standard requirement for cardiovascular outcome trials to assess the cardiovascular safety of these medications. However, cardiovascular outcome studies may be required by regulatory agencies, particularly if there is any concern for potential adverse effects on any cardiovascular risk factor. Sibutramine, which is no longer available in Canada, was studied in a cardiovascular outcome trial because of reported increases in blood pressure and heart rate. This study found an increased risk of cardiovascular events in people with pre-existing cardiovascular disease.[62]

In patients with type 2 diabetes, liraglutide 1.2 mg – 1.8 mg has been shown to reduce cardiovascular events and mortality in people with T2DM.[63] 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 T2DM, at the therapeutic dose of 3.0 mg. The cardiovascular safety of liraglutide 3.0mg was evaluated post-hoc using data from five randomized, double-blind, placebo-controlled clinical trials comprising 5,908 patients, the majority (97%) of whom did not have diabetes. Liraglutide 3.0 mg was not associated with excess cardiovascular risk, with a hazard ratio of 0.42 (95% CI: 0.17–1.08) vs. pooled comparators (1,941 receiving placebo, 95 receiving orlistat).[40]

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 number of major adverse cardiovascular events (MACE) 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 demonstrated a hazard ratio for the time to the first MACE of 0.88 (95% CI: 0.57–1.34).[64] These results could not be used to establish non-inferiority due to the compromise of the trial.

A subsequent meta-analysis including 12 RCTs comprising 19,176 patients was conducted to evaluate the relationship of bupropion, naltrexone or naltrexone/bupropion in combination with MACE. The additive network meta-analysis model for random effects showed no significant effect of bupropion (odds ratio [OR] = 0.90; 95% CI: 0.65–1.25), naltrexone (OR = 1.08; 95% CI: 0.71–1.63) or naltrexone/bupropion (OR = 0.97; 95% CI: 0.75–1.24) on MACE.[65]

Semaglutide 0.5 mg–1 mg has been shown to decrease cardiovascular events among patients with T2DM with established cardiovascular disease or at high risk of cardiovascular disease compared with placebo.[53] A long-term cardiovascular outcome study of semaglutide 2.4 mg is currently underway in people with obesity and cardiovascular disease (without diabetes).[66]

There are no cardiovascular outcome trials for orlistat.

Heart failure with preserved ejection fraction (HFpEF)

Over 80% of people with HFpEF have overweight or obesity.[67] As weight loss has been shown to improve HFpEF,[68] it is of interest

whether pharmacotherapy for obesity management may be of benefit in people with HFpEF.

Currently there are no obesity medications that have been studied in people with HFpEF. Semaglutide 2.4 mg is currently under investigation in people with HFpEF and obesity.[69]

Heart failure with reduced ejection fraction (HFrEF)

No studies of weight loss pharmacotherapy in this subpopulation were identified.

Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)

NAFLD is currently recognized as the most prevalent chronic liver disease, and globally affects approximately 25% of the adult population. Metabolic comorbidities associated with NAFLD included obesity (51.3%), type 2 diabetes (22.5%), hyperlipidemia (69.1%), hypertension (39.3%) and metabolic syndrome (42.5%).[70] Weight loss is recognized as the cornerstone of treatment of people with NASH and overweight or obesity.[71]

Fifty participants with overweight (BMI ≥ 27) with biopsy-proven non-alcoholic steatohepatitis 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. The primary study endpoint was improvement in steatosis, NAFLD activity score and fibrosis score on follow-up liver biopsy obtained at 36 weeks. Twenty-three participants in the orlistat/diet/vitamin E group and 18 in the diet/vitamin E group completed the study. Orlistat did not enhance weight loss or improve liver enzymes, measures of insulin resistance or histopathology compared to placebo. However, participants in either group who lost ≥ 5% body weight improved insulin resistance and steatosis, and those subjects who lost ≥ 9% also achieved improved hepatic histologic changes.[72]

A 48-week, multicentre, randomized, double-blind, placebo-controlled study assessed the efficacy of liraglutide 1.8 mg subcutaneously daily in 52 adults with NASH and BMI ≥ 25 kg/m^2.[14] Patients treated with liraglutide achieved a mean weight loss of -5.5% vs. -0.7% with placebo. The study demonstrated that 39% of patients in the liraglutide group met the primary endpoint of histological resolution of NASH without worsening of fibrosis vs. 9% in the placebo group. Additionally, 36% of those in the placebo group had progression of fibrosis compared to only 9% with liraglutide. Steatosis improved in 83% of those receiving liraglutide vs. 45% of those with placebo. The changes in body weight were not different between those who had resolution of NASH and those who did not with liraglutide, suggesting that the hepatic effects of liraglutide may be independent of weight loss.

The effect of semaglutide in patients with NASH was evaluated in a 72-week, phase 2, double-blind trial involving 320 patients with BMI > 25 and biopsy-confirmed NASH and liver fibrosis of stage F1, F2 or F3.[15] Patients received subcutaneous semaglutide at a dose of 0.1 mg, 0.2 mg or 0.4 mg once daily, or placebo. The percentage of patients who experienced NASH resolution with no worsening of fibrosis was 40% in the 0.1 mg group, 36% in the 0.2 mg group, 59% in the 0.4 mg group and 17% in the placebo group ($p < 0.001$ for semaglutide 0.4 mg daily vs. placebo). Weight loss was -5%, -9%, -13% and -1% in the semaglutide 0.1 mg, 0.2 mg, 0.4 mg and placebo groups, respectively. Semaglutide 2.4 mg weekly is currently under ongoing study in people with NASH.[73]

No studies of naltrexone/bupropion in patients with NASH or NAFLD were identified.

Though data is conflicting, some small studies have suggested that metformin may cause a small decrease in BMI of -0.5 kg/m^2 to -1.3 kg/m^2 with an improvement in aminotransferases and/or liver histology in patients with non-alcoholic fatty liver disease.[74,75]

Current literature suggests that GLP-1 agonists are likely the optimal choice for obesity management in a person with NAFLD/NASH. Medications in this class have consistently demonstrated reductions in liver fat, and have frequently also shown benefits to reduce serum markers of liver injury.

Polycystic ovary syndrome

Among women with polycystic ovary syndrome, liraglutide 1.8 mg daily has been shown in a small study to induce placebo subtracted weight loss of -5.2 kg and reduced liver fat content, visceral fat and the presence of non-alcoholic fatty liver disease over 26 weeks.[76] A meta-analysis of six studies (randomized and non-randomized) with 401 women evaluated the effect of liraglutide monotherapy and add-on pharmacotherapy on weight, BMI, waist circumference and homeostatic model assessment for insulin resistance (HOMA-IR) among women with a diagnosis of PCOS. Weight, BMI and waist circumference were significantly reduced vs. placebo by -4.33 kg (95% CI: -6.05, -2.61), -2.53 kg/m^2 (95%CI: -2.79, -2.27), and -6.28 cm (95%CI: -7.89, -4.67). FSH and LH showed a decline in the liraglutide group, and there was a moderate decline in HOMA-IR.[77] These studies did not evaluate menstrual frequency, fertility or hirsutism.

There are no studies of sufficient quality evaluating orlistat, naltrexone/bupropion nor semaglutide in patients with polycystic ovary syndrome.

Metformin with health-behaviour changes may be associated with a small reduction in BMI (-0.73 kg/m^2) and improved menstruation in women with polycystic ovary syndrome over six months, compared with health behaviour alone,[78] 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.[79]

In a small study comparing exenatide, metformin and the combination of exenatide and metformin in women with polycystic ovary syndrome and overweight, weight loss in both exenatide arms was superior to metformin with weight loss of -6.0 kg on

the combination of exenatide and metformin, -3.2 kg with exenatide alone and -1.6 kg on metformin alone. The combination of exenatide and metformin was superior to either medication as monotherapy to improve menstrual cyclicity and ovulation rate.[80]

A small open-label study (n = 119) compared the effect of once-weekly exenatide,[81] exenatide and dapagliflozin in combination, dapagliflozin and metformin in combination and phentermine/topiramate (a weight-management pharmacotherapy not available in Canada) on weight and metabolic health parameters in women with PCOS and obesity without diabetes. Phentermine/topiramate and the combination of exenatide and dapagliflozin resulted in the greatest weight loss of -9.0 kg and -6.0 kg, respectively. Testosterone and free androgen index were significantly improved in all treatment groups. Exenatide/dapagliflozin and exenatide resulted in significant improvements in mean blood glucose and insulin sensitivity. Improvements in menstrual cyclicity was not assessed.

Obstructive sleep apnea

The only obesity pharmacotherapy available in Canada which has been specifically studied amongst patients with obstructive sleep apnea is liraglutide. Among patients with moderate or severe obstructive sleep apnea who were unable or unwilling to use a continuous positive airway pressure machine, liraglutide 3.0 mg combined with health-behaviour modification significantly reduced the number of apnea-hypopnea index events by -12.2 events per hour, compared with a reduction of -6.1 events per hour with health-behaviour modification alone.[13]

Osteoarthritis

In a trial of 156 adults with BMI ≥ 27 and knee osteoarthritis, participants were randomized to receive liraglutide 3.0 mg or placebo, following 5% weight loss with an eight-week dietary intervention. At week 52, there was a significant difference in body weight between the liraglutide and placebo group (-2.8 kg vs. +1.2 kg, respectively), but no difference in knee osteoarthritis pain as assessed by the Knee injury and Osteoarthritis Outcome Score.[82] The lack of benefit in this trial is likely due to insufficient magnitude of weight loss; weight loss goals of ≥ 10% of body weight are advised for symptomatic and functional improvement among people with overweight or obesity and OA of weight-bearing joints.[83]

A study of semaglutide in patients with knee osteoarthritis is currently underway.[84]

Chronic kidney disease

Elevated BMI has consistently been associated with increased risk of chronic kidney disease and kidney failure.[85,86] None of the pharmacotherapies for obesity management available in Canada have been evaluated for renal benefit among patients with obesity and chronic kidney disease. Consideration for efficacy and safety of any medication is important among people with chronic kidney disease.

Liraglutide and semaglutide are endogenously metabolized without a specific organ as a major route of elimination. The efficacy and safety of liraglutide and semaglutide at T2DM treatment doses have been established in patients with T2DM and chronic kidney disease.[53,63] Liraglutide and semaglutide resulted in lower rates of development and progression of albuminuria compared with placebo. Semaglutide 1.0 mg weekly is currently being investigated in a renal outcome trial amongst people with T2DM and chronic kidney disease.[87]

Dose adjustment is not required for liraglutide 3 mg amongst people with mild/moderate renal insufficiency. Liraglutide 3.0 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.[88]

For semaglutide 2.4 mg weekly, no dosage adjustment is required for patients with renal insufficiency. Semaglutide 2.4 mg is not recommended in people with end-stage renal disease.[89]

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.[61] The maximum recommended daily maintenance dose for naltrexone/bupropion is one tablet (8 mg/90 mg) BID in patients with moderate or severe renal impairment. Naltrexone/bupropion is contraindicated in patients with end-stage renal disease. There is a lack of adequate information to guide naltrexone/bupropion dosing in patients with mild renal impairment. All patients with renal impairment should be closely monitored for possible adverse effects.

Orlistat has not been studied in patients with renal impairment. There are no dosage adjustments provided in the manufacturer's labelling. However, the need for dosage adjustment in renal insufficiency is unlikely due to low systemic absorption. The major route of excretion is in feces with < 2% excretion in the urine. [90]

Gastroesophageal reflux disease (GERD)

GERD is common in people with overweight and obesity,[91] and can improve with weight loss.[92] Onset of GERD, or exacerbation of pre-existing GERD, can occur with obesity pharmacotherapy, in particular with the GLP-1 receptor agonists liraglutide and semaglutide. This is typically transient and mild to moderate in severity.[1,3]

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

Mental health

Clinicians should consider the impact on weight when prescribing medication for treatment of mental health concerns (e.g., depres-

sion, psychosis; see the Role of Mental Health in Obesity Management chapter of the 2020 CPG).[25] Pharmacotherapy for binge eating disorder and attention deficit hyperactivity disorder may also impact weight.

While the relationship between mental health and obesity is complex, most studies show that successful weight management is associated with an improvement in mental health parameters. As most obesity medications are active in the brain, it is important to ascertain their effect and safety on mental health parameters.

There has been a long-standing concern that anti-depressants 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 three (0.20%) of 1,515 patients treated with placebo compared with one (0.03%) of 3,239 treated with naltrexone/bupropion. The same precautions pertaining to anti-depressants should be considered when treating patients with naltrexone/bupropion, including screening patients for suicidal behaviours and ideation.[93]

Liraglutide 3.0 mg has demonstrated neuropsychiatric safety.[94]

Neuropsychiatric concerns have not been identified with semaglutide.[95]

Weight gain is a common side effect of some anti-psychotic medications. A systematic review and meta-analysis were conducted to assess the effect of metformin on preventing weight gain associated with mental health medications. Twelve double-blind, randomized, placebo-controlled trials of 12 weeks to 24 weeks duration, including a total of 743 patients with schizophrenia or schizoaffective disorder were included in the study. The study found that metformin was effective for the management of anti-psychotic-induced weight gain in this population, with a mean weight loss in adults of -3.2 kg compared with placebo. Metformin is most impactful earlier in the course of anti-psychotic treatment or with initiation of anti-psychotic medication, with a mean difference in weight of -5.9 kg compared with placebo, versus -2.1 kg in patients who had been on anti-psychotic medication longer term before starting metformin.[96]

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

Craving and Control of Eating

Food craving is the intense desire to eat a particular food, and can be distinguished from hunger, as cravings occur spontaneously, whereas hunger increases in intensity over the time spent without food. Food craving has been shown to contribute to adherence difficulties with health-behaviour interventions; reducing and managing food cravings is a key component in the management of obesity and successful weight-loss maintenance.[7,97]

An integrated analysis of four RCTs with naltrexone/bupropion assessed food craving using the COEQ. The study demonstrated that early improvements in craving control and reductions in craving for sweet throughout the 56-week trial period were greater in the subjects treated with naltrexone/bupropion, and these scores were predictive of greater reductions in BMI at the end of the trial.[42]

In a study of 72 subjects over 20 weeks, semaglutide 2.4 mg weekly improved control of eating and reduced cravings, based on the results from the COEQ. The study found overall better control of eating, fewer food cravings, less hunger and, subsequently, less energy intake with semaglutide 2.4 mg vs. placebo.[43]

Orlistat and liraglutide 3.0 mg 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

QoL broadly encompasses how an individual measures the "goodness" of multiple aspects of their life.[98] Obesity has a negative impact on many aspects of health-related QoL (HRQoL).[99] Measuring QoL for weight-loss interventions has been challenging, as the SF-36 is the traditional tool used for assessment, but it is not specific to people living with obesity. The recently developed IWQOL-Lite CT, which is more specific to people living with obesity, is now being utilized in many clinical trials.[100]

Weight loss is associated with improved quality of life in most studies, and is a component of the FDA submission for approval.[101]

The SCALE three-year extension study evaluated the effect of liraglutide 3.0 mg daily on HRQoL vs. placebo in participants with overweight or obesity and prediabetes. The IWQOL-Lite questionnaire and SF-36 health survey were used. Both tools demonstrated long-term, statistically significant improvement in HRQoL and physical function with liraglutide vs. placebo.[41]

Patients in the COR trials program with naltrexone/bupropion also demonstrated significant improvements in quality of life. Scores on the IWQOL-Lite assessment tool were improved compared to placebo in the following subscales: physical function, self-esteem, sexual life, public distress and work. This improvement in IWQOL-Lite total and subscale scores occurred as early as week eight.[5]

Semaglutide 2.4 mg has been shown to improve quality of life and physical functioning.[1,9,50] The STEP 1 trial assessed QoL changes from baseline to week 68 using the IWQOL-Lite Clinical Trials version (IWQOL-Lite-CT). Significantly greater improvements in IWQOL-Lite-CT 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.

Medications with insufficient data for obesity management

We recognize that 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, thyroid hormone) that are not discussed in this document.

Two separate randomized, placebo-controlled trials evaluated the efficacy of topiramate on weight loss among patients with obesity and T2DM over 24 weeks to 40 weeks. These trials demonstrated clinically meaningful weight loss of 4.5%–6.6% and 6.5%–9.1% in the 96 mg/day group and 192 mg/day doses, respectively, compared with weight losses of 1.7%–2.5% in the placebo groups.[102,103] While topiramate is not intended as pharmacotherapy for obesity, it could be considered in patients who require topiramate for other indications (e.g., anti-seizure or migraine therapy) and for whom weight gain is a clinically relevant concern.

A systematic review and meta-analysis evaluating the metabolic effects and weight loss of fluoxetine 60 mg daily in 215 adults with overweight or obesity and T2DM demonstrated a -4.3 kg weight loss compared with placebo. These patients did not have depression. Follow-up was six months to 12 months in four studies, but only two months in the fifth study included. Fluoxetine should not be prescribed for weight loss but could be considered in patients who require it for other indications, such as depression, and for whom weight gain is a clinically relevant concern.[104]

A review summarizes medications available in Canada that cause weight gain, as well as alternative choices.[105]

Emerging obesity pharmacotherapy

Tirzepatide is a once-weekly, subcutaneously administered, dual GIP/GLP-1 agonist that is approved in United States as a treatment for T2DM. In the SURPASS clinical trial program, tirzepatide 5 mg, 10 mg and 15 mg once weekly, administered subcutaneously, were evaluated as monotherapy, with metformin in comparison to semaglutide 1 mg, in comparison to basal insulin and as an add-on to basal insulin therapy.[106-109] Superior and robust A1C reduction was seen with tirzepatide vs. comparators, with most tirzepatide arms achieving A1C reduction of greater than 2%. Weight loss with tirzepatide 15 mg weekly ranged from -9.5% to -12.9%, and was superior to comparator arms. In the SURPASS-4 trial, which evaluated tirzepatide in comparison to open-label insulin glargine, study completion was driven by the accrual of MACE. Adjudicated MACE were not increased on tirzepatide compared with glargine (hazard ratio 0.74, 95% CI: 0.51-1.08).[109]

Tirzepatide is currently under evaluation as an obesity pharmacotherapy. In the SURMOUNT-1 study, 2,539 participants with overweight or obesity, without diabetes, were randomized to receive tirzepatide 5 mg, 10 mg, 15 mg or placebo.[110] Prediabetes was present among 40.6% of participants at baseline. At 72 weeks, weight loss was -15%, -19.5% and -20.9% with tirzepatide 5 mg, 10 mg and 15 mg, respectively, vs. -3.1% with placebo. The proportion of patients achieving at least 5% weight loss were 85%, 89% and 91% for tirzepatide 5 mg, 10 mg and 15 mg, respectively, vs. 35% of participants with placebo. The proportion of persons achieving at least 20% weight loss were 30%, 50% and 57% with tirzepatide 5 mg, 10 mg and 15 mg, respectively, vs. 3% of participants with placebo. Over 95% of people with prediabetes at baseline converted to normoglycemia vs. 62% with placebo. Significant improvements were seen with systolic and diastolic blood pressure. The most common adverse events were gastrointestinal side effects of mild to moderate severity and transient, occurring primarily during dose escalation.

Tirzepatide is currently also under study as a treatment for HFpEF[111] and as a treatment of NASH.[112]

Cagrilintide is a long-acting, once-weekly, subcutaneously administered amylin analog under investigation for obesity management in combination with semaglutide 2.4 mg weekly. In the phase 2 trial of cagrilintide monotherapy, 706 participants with a BMI of $\geq$ 30 kg/m^2 or $\geq$ 27 kg/m^2 with hypertension or dyslipidemia were randomly assigned various doses of once-weekly cagrilintide, once-daily liraglutide 3.0 mg or placebo for 26 weeks. Mean percentage weight reductions were greater with all doses of cagrilintide vs. placebo, and superior for the highest dose of cagrilintide studied (4.5 mg weekly) vs. liraglutide 3.0 mg daily (-10.8% vs. -9.0%, respectively). The most frequent adverse events were gastrointestinal, predominantly nausea, constipation and diarrhea.[113]

Setmelanotide has been granted marketing authorisation in the U.S. and the EU for long-term obesity management in people with obesity due to POMC, proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency. Obesity due to POMC, PCSK1 or LEPR deficiency is extremely rare. Variants in POMC, PCSK1 or LEPR genes impair the MC4R pathway causing extreme, insatiable hunger beginning at a young age, and resulting in early-onset, severe obesity[114,115] As an MC4R agonist, setmelanotide is designed to restore impaired MC4R pathway activity arising due to genetic deficits upstream of the MC4 receptor.[116] Adults and children with POMC deficiency (homozygous or compound heterozygous variants in POMC or PCSK1) were treated with open-label setmelanotide, with adult dosing starting at 1.0 mg subcutaneously once daily, then titrated to achieve weight loss of 2 kg/week to 3 kg/week, with a maximum dose of 3 mg/day. Amongst 10 participants enrolled in the trial (including four adults), 80% of patients achieved $\geq$ 10% weight loss at approximately one year, and mean weight loss was -25.6%. Hunger scores decreased by -27.1%. In a study of 11 participants (including eight adults) with LEPR deficiency (homozygous or compound heterozygous variants in LEPR), using the same dosing protocol

described above, 45% of patients achieved ≥ 10% weight loss at one year, and mean weight loss was -12.5%. Hunger score decreased by -43.7%. The most common adverse events were injection site reactions, skin disorders (including hyperpigmentation) and nausea.[117]

Multiple treatment options are being studied, which include monotherapy, dual or tri-agonist combinations of various hormones such as GLP-1, GIP, glucagon, oxyntomodulin and PYY3-36. It is anticipated that administering combinations of these hormones will be beneficial to address the highly redundant hormonal physiology that defends body weight.

The summary of the Canadian Adult Obesity Clinical Practice Guideline is published in the Canadian Medical Association Journal, and contains information on the full methodology, management of authors' competing interests, a brief overview of all recommendations and other details. More detailed guideline chapters are published on the Obesity Canada website at www.obesitycanada.ca/guidelines.

Correspondence:
guidelines@obesitynetwork.ca

References

1. 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

2. 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

3. 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

4. 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

5. 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

6. 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

7. 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

8. 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

9. 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. Comment in: Lancet. 2021 Mar 13;397(10278):942-943; PMID: 33667415 [https://www.ncbi.nlm.nih.gov/pubmed/33667415]. doi:https://dx.doi.org/10.1016/S0140-6736(21)00213-0

10. 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

11. 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

12. 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

13. 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

14. 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

15. Newsome PN, Buchholtz K, Cusi K, et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. *N Engl J Med*. Mar 25 2021;384(12):1113-1124. doi:10.1056/NEJMoa2028395

16. Taylor VH SS, Hawa R, Hahn M. . The Role of Mental Health in Obesity Management. Accessed August 25, 2022. https://obesitycanada.ca/guidelines/mentalhealth

17. 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

18. 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

19. 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.

20. 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

21. Twells LK JI, Kuk JL. Epidemiology of Adult Obesity. Accessed August 25, 2022. https://obesitycanada.ca/guidelines/epidemiology/

22. 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

23. Langlois MF FY, Morin MP. Commercial Products and Programs in Obesity Management. Accessed August 25, 2022. https://obesitycanada.ca/guidelines/commercialproducts

24. 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

25. Rueda-Clausen CF PM, Lear SA, Poirier P, Sharma AM. Assessment of People Living with Obesity. Accessed August 25, 2022. https://obesitycanada.ca/guidelines/assessment.

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

27. Wharton S, Lee J, Christensen RA. Weight loss medications in Canada - a new frontier or a repeat of past mistakes? *Diabetes Metab Syndr Obes*. 2017;10:413-417. doi:10.2147/DMSO.S141571

28. 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

29. 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

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

31. 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

32. 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

33. 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

34. 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

35. 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

36. 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

37. 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*. 04 2018;154(5):1309-1319.e7. doi:https://dx.doi.org/10.1053/j.gastro.2017.12.024

38. Moon S, Chung HS, Kim YJ, et al. Efficacy and Safety of the New Appetite Suppressant, Liraglutide: A Meta-Analysis of Randomized Controlled Trials. *Endocrinology and Metabolism*. 2021;36(3):647-660. doi:http://dx.doi.org/10.3803/ENM.2020.934

39. Nordisk N. Effect and safety of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity. Accessed August 25, 2022. https://s3.amazonaws.com/ctr-nvo-7271/NN9536-4373/c1309fcd-9eff-4b1a-b58c-52afe3ce30bc/605bc0c8-0374-4f2f-8f34-80c4184508b2/4373_ctr_nn-trials_redacted-v1.pdf

40. 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

41. 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

42. 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). 05/02
07/25/received
03/20/revised
03/26/accepted 2017;41(8):1232-1236. doi:10.1038/ijo.2017.89

43. 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

44. 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

45. Smith SR, Fujioka K, Gupta AK, et al. Combination therapy with naltrexone and bupropion for obesity reduces total and visceral adiposity. *Diabetes Obes Metab*. Sep 2013;15(9):863-6. doi:10.1111/dom.12095

46. I TPA. Highlights of Prescribing Information. Accessed August 25, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/200063s000lbl.pdf

47. 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

48. 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.

49. 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

50. 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*. 2021;325(14):1403-1413. Comment in: JAMA. 2021 Sep 28;326(12):1213-1214; PMID: 34581745 [https://www.ncbi.nlm.nih.gov/pubmed/34581745]. doi:https://dx.doi.org/10.1001/jama.2021.1831

51. 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. Comment in: Ann Intern Med. 2021 Aug;174(8):-JC88; PMID: 34339232 [https://www.ncbi.nlm.nih.gov/pubmed/34339232]. doi:https://dx.doi.org/10.1001/jama.2021.3224

52. 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

53. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. Nov 10 2016;375(19):1834-1844. doi:10.1056/NEJMoa1607141

54. 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

55. Le Roux CW, Davies M, Frias JP, et al. Once-weekly semaglutide 2.4 mg improved metabolic syndrome in adults with overweight or obesity: Post-hoc analysis of the STEP 1 Trial. *Obes Facts*. 2021;14(SUPPL 1):52. 28th European Congress on Obesity, ECO 2021. Online. doi:http://dx.doi.org/10.1159/000515911

56. A/S NN. Research Study Looking at How Well Semaglutide Works in People Living With Obesity and Prediabetes (STEP 10). Accessed August 25, 2022. https://clinicaltrials.gov/ct2/show/NCT05040971

57. Rosenstock J, Klaff LJ, Schwartz S, et al. Effects of exenatide and lifestyle modification on body weight and glucose tolerance in obese subjects with and without pre-diabetes. *Diabetes Care*. Jun 2010;33(6):1173-5. doi:10.2337/dc09-1203

58. 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

59. 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

60. 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

61. Valeant. Product Monograph-Contrave. Accessed August 25, 2022. https://pdf.hres.ca/dpd_pm/00043849.PDF

62. James WP, Astrup A, Finer N, et al. Effect of sibutramine on weight maintenance after weight loss: a randomised trial. STORM Study Group. Sibutramine Trial of Obesity Reduction and Maintenance. *Lancet*. Dec 23-30 2000;356(9248):2119-25. doi:10.1016/s0140-6736(00)03491-7

63. 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

64. 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

65. 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

66. A/S NN. Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity (SELECT). Accessed August 25, 2022. https://www.clinicaltrials.gov/ct2/show/NCT03574597

67. Haykowsky MJ, Nicklas BJ, Brubaker PH, et al. Regional Adipose Distribution and its Relationship to Exercise Intolerance in Older Obese Patients Who Have Heart Failure With Preserved Ejection Fraction. *JACC Heart Fail*. Aug 2018;6(8):640-649. doi:10.1016/j.jchf.2018.06.002

68. 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

69. A/S NN. Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity (STEP-HFpEF). Accessed August 25, 2022. https://clinicaltrials.gov/ct2/show/NCT04788511

70. 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

71. 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

72. 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:https://dx-.doi.org/10.1002/hep.22575

73. A/S NN. Research Study on Whether Semaglutide Works in People With Non-alcoholic Steatohepatitis (NASH) (ESSENCE). Accessed August 25, 2022. https://clinicaltrials.gov/ct2/show/NCT04822181

74. Bugianesi E, Gentilcore E, Manini R, et al. A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. *Am J Gastroenterol*. May 2005;100(5):1082-90. doi:10.1111/j.1572-0241.2005.41583.x

75. Uygun A, Kadayifci A, Isik AT, et al. Metformin in the treatment of patients with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther*. Mar 1 2004;19(5):537-44. doi:10.1111/j.1365-2036.2004.01888.x

76. Frossing S, Nylander M, Chabanova E, et al. Effect of liraglutide on ectopic fat in polycystic ovary syndrome: A randomized clinical trial. *Diabetes Obes Metab*. Jan 2018;20(1):215-218. doi:10.1111/dom.13053

77. 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

78. 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

79. 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

80. Elkind-Hirsch K, Marrioneaux O, Bhushan M, Vernor D, Bhushan R. Comparison of single and combined treatment with exenatide and metformin on menstrual cyclicity in overweight women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. Jul 2008;93(7):2670-8. doi:10.1210/jc.2008-0115

81. Elkind-Hirsch KE, Chappell N, Seidemann E, Storment J, Bellanger D. Exenatide, Dapagliflozin, or Phentermine/Topiramate Differentially Affect Metabolic Profiles in Polycystic Ovary Syndrome. *J Clin Endocrinol Metab*. Sep 27 2021;106(10):3019-3033. doi:10.1210/clinem/dgab408

82. 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

83. 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

84. A/S NN. Research Study Looking at How Well Semaglutide Works in People Suffering From Obesity and Knee Osteoarthritis. Accessed August 25, 2022. https://clinicaltrials.gov/ct2/show/NCT05064735

85. 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

86. 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

87. A/S NN. A Research Study to See How Semaglutide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease (FLOW). Accessed August 25, 2022. https://clinicaltrials.gov/ct2/show/NCT03819153

88. 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

89. Marbury TC, Flint A, Jacobsen JB, Derving Karsbøl J, Lasseter K. Pharmacokinetics and Tolerability of a Single Dose of Semaglutide, a Human Glucagon-Like Peptide-1 Analog, in Subjects With and Without Renal Impairment. *Clin Pharmacokinet*. Nov 2017;56(11):1381-1390. doi: 10.1007/s40262-017-0528-2.

90. Chintam K, Chang AR. Strategies to Treat Obesity in Patients With CKD. *Am J Kidney Dis*. Mar 2021;77(3):427-439. doi:10.1053/j.ajkd.2020.08.016

91. 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

92. 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

93. Pi-Sunyer X, Apovian CM, McElroy SL, Dunayevich E, Acevedo LM, Greenway FL. Psychiatric adverse events and effects on mood with prolonged-release naltrexone/bupropion combination therapy: a pooled analysis. *Int J Obes (Lond)*. Oct 2019;43(10):2085-2094. doi:10.1038/s41366-018-0302-z

94. 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

95. Nordisk N. Product Monograph OZEMPIC. Accessed August 25, 2022. https://www.novonordisk.ca/content/dam/Canada/AFFILIATE/www-novonordisk-ca/OurProducts/PDF/ozempic-product-monograph.pdf

96. 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

97. 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.

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

99. Ul-Haq Z, Mackay DF, Fenwick E, Pell JP. Meta-analysis of the association between body mass index and health-related quality of life among adults, assessed by the SF-36. *Obesity (Silver Spring)*. Mar 2013;21(3):E322-7. doi:10.1002/oby.20107

100. 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

101. 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

102. Toplak H, Hamann A, Moore R, et al. Efficacy and safety of topiramate in combination with metformin in the treatment of obese subjects with type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Int J Obes (Lond)*. Jan 2007;31(1):138-46. doi:10.1038/sj.ijo.0803382

103. Stenlof K, Rossner S, Vercruysse F, et al. Topiramate in the treatment of obese subjects with drug-naive type 2 diabetes. *Diabetes Obes Metab*. May 2007;9(3):360-8. doi:10.1111/j.1463-1326.2006.00618.x

104. Serralde-Zuniga AE, Gonzalez Garay AG, Rodriguez-Carmona Y, Melendez G. Fluoxetine for adults who are overweight or obese. *Cochrane Database Syst Rev*. Oct 15 2019;10:CD011688. doi:10.1002/14651858.CD011688.pub2

105. Wharton S, Raiber L, Serodio KJ, Lee J, Christensen RA. Medications that cause weight gain and alternatives in Canada: a narrative review. *Diabetes Metab Syndr Obes*. 2018;11:427-438. doi:10.2147/DMSO.S171365

106. Rosenstock J, Wysham C, Frías JP, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. *The Lancet*. 2021;398(10295):143-155. doi:10.1016/s0140-6736(21)01324-6

107. Frias JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *N Engl J Med*. Aug 5 2021;385(6):503-515. doi:10.1056/NEJMoa2107519

108. Ludvik B, Giorgino F, Jódar E, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. *The Lancet*. 2021;398(10300):583-598. doi:10.1016/s0140-6736(21)01443-4

109. Del Prato S, Kahn SE, Pavo I, et al. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *The Lancet*. 2021;398(10313):1811-1824. doi:10.1016/s0140-6736(21)02188-7

110. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide Once Weekly for the Treatment of Obesity. *N Engl J Med*. 2022;doi:10.1056/NEJMoa2206038

111. Company ELa. A Study of Tirzepatide (LY3298176) in Participants With Heart Failure With Preserved Ejection Fraction and Obesity (SUMMIT) (SUMMIT). U.S. National Library of Medicine. Accessed August 25, 2022. https://clinicaltrials.gov/ct2/show/NCT04847557

112. Company ELa. A Study of Tirzepatide (LY3298176) in Participants With Non-alcoholic Steatohepatitis (NASH) (SYNERGY-NASH). U.S. National Library of Medicine. Accessed August 25, 2022. https://clinicaltrials.gov/ct2/show/NCT04166773

113. Lau DCWea. Once-weekly cagrilintide for weight management in people with overweight and obesity: a multicentre, randomised, double-blind, placebo-controlled and active-controlled, dose-finding phase 2 trial. *The Lancet*. 2021;398(Supp 3)

114. 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

115. Ryan DH. Setmelanotide: what does it mean for clinical care of patients with obesity? *Lancet Diabetes Endocrinol*. 2020;8(12):933-935. doi:10.1016/s2213-8587(20)30366-1

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

117. 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 & endocrinology*. 2020;8(12):960-970. Comment in: Lancet Diabetes Endocrinol. 2020 Dec;8(12):933-935; PMID: 33137294 [https://www.ncbi.nlm.nih.gov/pubmed/33137294]. doi:https://dx.doi.org/10.1016/S2213-8587(20)30364-8