Canadian Adult Obesity Clinical Practice GUIDELINES

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Pharmacotherapy in Obesity Management

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Update History

Version 1, August 4, 2020. Adult Obesity Clinical Practice Guidelines are a living document, with only the latest chapters posted at obesitycanada.ca/guidelines.

KEY MESSAGES FOR HEALTHCARE PROVIDERS

- There are three medications indicated for chronic obesity management in Canada in addition to health behaviour changes: liraglutide (Saxenda®) 3.0 mg, naltrexone/bupropion (Contrave®) in a combination tablet, and orlistat (Xenical®). All three medications have been shown to be effective in producing weight loss greater than placebo for a duration of at least one year.
- Medications that are not approved as pharmacotherapy for obesity management should not be used for this purpose.
- The individual response to obesity management pharmacotherapy is heterogeneous; the response to medications can differ from patient to patient. In choosing the most appropriate obesity pharmacotherapy, consider mechanism of action, safety, potential side effects/tolerability, contraindications, drug interactions, mode of administration and cost.

RECOMMENDATIONS

1. Pharmacotherapy for weight loss 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 psychological interventions (liraglutide 3.0 mg [Level 2a, Grade B)],[1–3] naltrexone/bupropion combination [Level 2a, Grade B],[4] orlistat [Level 2a, Grade B]).[5]

2. Pharmacotherapy may be used to maintain weight loss that has been achieved by health behaviour changes, and to prevent weight regain (liraglutide 3.0 mg or orlistat) (Level 2a, Grade B).[6]

3. For people living with type 2 diabetes and a BMI ≥ 27 kg/m^2, pharmacotherapy can be used in conjunction with health behaviour changes for weight loss and improvement in glycemic control: liraglutide 3.0 mg (Level 1a, Grade A);[7] naltrexone/bupropion combination (Level 2a; Grade B),[8] orlistat (Level 2a, Grade B).[9]

4. We recommend pharmacotherapy in conjunction with health behaviour changes for people living with prediabetes and overweight or obesity (BMI > 27kg/m^2) to delay or prevent type 2 diabetes. (Liraglutide 3.0 mg (Level 2a, Grade B);[2], orlistat (Level 2a, Grade B).[10]

5. We do not suggest the use of prescription or over-the-counter (OTC) medications other than those approved for weight management (Level 4, Grade D, Consensus).

6. For people living with overweight or obesity who require pharmacotherapy for other health conditions, we suggest choosing drugs that are not associated with weight gain (Level 4, Grade D, Consensus).

KEY MESSAGES FOR PEOPLE LIVING WITH OBESITY

- Obesity medication can help you in your obesity management journey when health behaviour changes alone have not been effective or sustainable.
- There are three medications approved for long-term obesity management in Canada: liraglutide 3.0 mg (Saxenda®), naltrexone/bupropion in a combination tablet (Contrave®) and orlistat (Xenical®). These medications can help you to achieve and maintain a 5%–10% weight loss and improve health complications associated with excess weight. These medications are approved by Health Canada and have been proven in robust clinical trials to be 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

Modest and sustained weight loss (5%–10%) is associated with improvements in comorbidities associated with obesity.[11–13] Health behaviour modifications are the cornerstone of obesity management; however, health behaviour changes alone are often not sufficient for achieving obesity management goals. Health behaviour modification generally achieves only a 3%–5% weight loss, which is most often not sustained over the long term (see the chapter Effective Psychological and Behavioural Interventions in Obesity Management). Pharmacotherapy for obesity should be considered to decrease weight and improve metabolic and/or health parameters when health behaviour change alone has been ineffective, insufficient or without sustained benefit.

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 chronic obesity management:

1. The agent must be studied in clinical trials of at least one year in duration.
2. The agent must induce a placebo-adjusted mean weight loss of ≥5% or must 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 chronic obesity management in Canada for individuals with a body mass index (BMI) ≥ 30 kg/m^2, or ≥ 27 kg/m^2 with comorbidities associated with excess body fat (e.g. type 2 diabetes [T2DM], hypertension, dyslipidemia).

There are three medications approved for obesity management in Canada: orlistat, liraglutide 3.0 mg and naltrexone/bupropion. It is recognized that other medications, available in Canada but not approved for obesity management, are used off-label for obesity management. As a result, our literature search employed an open strategy to capture all pharmacotherapy agents that have been studied for obesity management. However, with the exception of metformin for prevention of antipsychotic-induced weight gain (see: The Role of Mental Health in Obesity Management for the metformin recommendation), we discourage healthcare providers from using agents solely for chronic obesity management if they do not have regulatory approval for this indication. Non-prescription treatments/supplements are reviewed separately in the Commercial Products and Programs for Obesity Management chapter.

This chapter will address clinical questions pertaining to the efficacy of pharmacotherapy in people with overweight or obesity. It will also summarize evidence for pharmacotherapy for obesity among persons with selected comorbidities, including T2DM, prediabetes, hepatic steatosis, polycystic ovary syndrome, obstructive sleep apnea and osteoarthritis. Randomized controlled trials or meta-analyses of at least six months duration were included in the literature review.

Considerations in the use of pharmacotherapy for obesity management

There are several factors to be taken into consideration in determining the appropriate choice of pharmacotherapy for patients with overweight or obesity. The etiology of obesity is complex and heterogeneous. Psychosocial, emotional and hedonic contributors of obesity should be diagnosed and managed where possible. The mechanism of action, 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 can be a barrier to patient adherence and should be discussed. It is important to assess concomitant medications that a patient is taking as possible contributors to weight gain and to consider alternatives where appropriate.

If clinically significant weight loss is not achieved with pharmacotherapy, other factors contributing to perceived pharmacotherapy failure should be assessed, including inappropriate dosing or ad-

herence, barriers to health behaviour change, and psychosocial or medical issues. It should also be recognized that there is considerable heterogeneity in the response to pharmacotherapy with any pharmacotherapeutic agent. Consideration should be given to trying another obesity medication or obesity management therapy if clinically significant obesity management success has not been achieved after three months on full/maximum tolerated dose and no other evident etiologies of the lack of success are apparent. Currently, we have no ability to predict which medication will benefit a patient most. With the evolution of precision medicine, including hormonal and genetic profiling, it may in the future become possible to predict which pharmacotherapy may benefit an individual patient the most.

Regulatory agencies recommend discontinuing pharmacotherapy for obesity if weight loss of ≥ 5% has not been achieved after three months on therapeutic dose. However, pharmacotherapy can also be used to maintain weight loss achieved with a prior health behaviour change or a very low energy diet.[3,6]

Obesity medications are intended as part of a long-term treatment strategy. Clinical trials for obesity pharmacotherapy consistently demonstrate regain of weight when active treatment is stopped.[2,14]

The use of obesity pharmacotherapy is not recommended in pregnant or breastfeeding women, or in women who are trying to conceive. There is no data available to inform on the timing of the discontinuation of obesity pharmacotherapy prior to conception.

Mechanism and efficacy of approved pharmacotherapy for obesity management

Orlistat

Orlistat, a semisynthetic derivative of lipstatin, was approved as pharmacotherapy for obesity management in Canada in 1999 (see Table 1). 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 of this, approximately 30% of ingested triglycerides are excreted, primarily in the feces, creating a caloric deficit.[15]

To date, orlistat is the only available obesity medication that does not specifically 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 ≥ 30kg/m^2, or BMI ≥ 27 kg/m^2 in the presence of comorbidities (e.g. hypertension, T2DM, dyslipidemia, excess visceral fat).[16]

A systematic review and meta-analysis of randomized controlled trials of orlistat 120 mg three times a day reported a mean placebo subtracted weight loss of -2.9% at one year.[5] Additionally, 54% and 26% of patients achieved ≥ 5% and ≥ 10% weight loss, respectively, compared to 33% and 14% for placebo.[5] 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).[6]

Orlistat therapy is associated with significant adverse gastrointestinal effects, including oily spotting and stool, flatus with discharge, fecal urgency and increased defecation.[5] 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 of 18%, 6% and 2% with orlistat, respectively.[17] 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.[5,16] 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.[18] There have also been rare cases of severe liver injury or acute liver failure.[19]

As orlistat may interfere with vitamin K absorption, international normalized ratio should be monitored closely when oral anticoagulants are co-administered. Orlistat may affect absorption of levothyroxine and/or iodine salts; patients on levothyroxine should be monitored for changes in thyroid 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 anticonvulsants, so patients on anticonvulsants should be monitored for possible changes in the frequency and/or severity of seizure.[16]

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

Liraglutide

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.[24,25]

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 chronic 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 an 8.0% weight loss at one year, compared to 2.6% on placebo (health behaviour

Table 1. Pharmacotherapy for Obesity*

	Orlistat	Liraglutide	Naltrexone/Bupropion
Mode of administration	Oral	Subcutaneous	Oral
Dose/frequency	120 mg TID	3.0 mg daily	16/180 mg BID
Effect on % weight loss at 1 year, placebo subtracted	-2.9%[5]	-5.4%1	-4.8%[4]
Effect on weight over longer term, placebo subtracted	-2.8kg at 4 years[10]	-4.2% at 3 years[2]	Not studied
% of patients achieving ≥ 5% weight loss at 1 year	54% (vs 33% in placebo)[5]	63.2% (vs 27.1% in placebo)[1]	48% (vs 16% in placebo)[4]
% of patients achieving ≥ 10% weight loss at 1 year	26% (vs 14% in placebo)[5]	33.1% (vs 10.6% in placebo)[1]	25% (vs 7% in placebo)[4]
Effect on maintenance of previous weight loss	2.4kg less weight regain vs placebo over 3 years[6]	-6.0% additional placebo-subtracted weight loss at 1 year[3]	Not studied
Effect on prediabetes	37.3% reduction in risk of developing T2DM over 4 years[10]	79% reduction in risk of developing T2DM over 3 years[2]	Not studied
Effect on BP at 1 year, placebo subtracted	-1.9 mmHg SBP -1.5 mmHg DBP[20]	-2.8mmHg SBP -0.9mmHg DBP[1]	+1.8mmHg sBP +0.9mm Hg dBP[4]
Effect on lipids at 1 year, placebo subtracted	- 0.27 mmol/L total chol - 0.21 mmol/L LDL - 0.02 mmol/L HDL - 0.00 mmol/L TG[20]	-2.3% total chol -2.4% LDL +1.9% HDL -3.9% nonHDL -9.3% TG[1]	-1.5 % LDL +7.2% HDL - 9.6 % TG[4]
Effect on HR at 1 year, placebo subtracted	No change	+2.4 BPM[1]	+1.1 BPM[4]
Effect on A1C in patients with diabetes at 1 year, placebo subtracted	-0.4%[9]	-1.0%[7]	-0.5%8
Effect on NASH	No improvement	Improvement[21]	Not studied
Effect on PCOS	Not studied	-5.2 kg placebo subtracted weight loss at 6mo; no data on menstrual cyclicity[22]	Not studied
Effect on OA	Not studied	Not studied	Not studied
Effect on OSA	Not studied	Reduces AHI by 6/hr[23]	Not studied
Cost	$$	$$$$	$$$
Contraindications	• Cholestasis • Chronic malabsorption syndrome[16] • Pregnancy	• Past history of pancreatitis • Personal or family history of medullary thyroid cancer • Personal history of MEN2 syndrome • Pregnancy	• Uncontrolled hypertension • Any opioid use • History of, or risk factors for, seizure • Abrupt discontinuation of alcohol • Concomitant administration of monoamine oxidase inhibitors (MAOI) • Severe hepatic impairment • End-stage renal failure • Pregnancy
Common side effects	Loose, oily stools, flatus	Nausea, constipation, diarrhea, vomiting	Nausea, constipation, headache, dry mouth, dizziness, diarrhea
Rare side effects	• Liver failure • Nephrolithiasis • Acute kidney injury	Pancreatitis Cholelithiasis	• Seizure • Worsening of depression
Drug interactions	• Fat-soluble vitamins • Levothyroxine • Cyclosporine • Oral anticoagulants anticonvulsants[16]	May affect absorption of medications due to slowing of gastric emptying	Yes: See chapter text

modification alone).[1] 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;[1] 33.1% and 10.6% of participants lost more than 10% of their body weight on liraglutide 3.0 mg and placebo, respectively. Patients with prediabetes were followed to three years, with sustained weight loss of -6.1% in the liraglutide group vs. -1.9% in placebo.[2]

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%).[3]

The most common side effect of liraglutide is nausea due to a transient decrease in gastric emptying. 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.[26]

There is a small increased risk of pancreatitis compared to placebo, with the majority of these cases seen in association with gallbladder disease.[2] 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 seen 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

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 antidepressant that inhibits the reuptake of dopamine and norepinephrine. The naltrexone/bupropion sustained release formulation was approved for chronic obesity management in Canada in 2018, at a total daily dose of 32 mg naltrexone and 360 mg bupropion. 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 to reduce cravings.[27] 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.[28]

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 32 mg/360 mg with a hypocaloric diet (500 kcal/day deficit) and exercise was associated with weight loss of -6.1% versus -1.3% in placebo.[4] A ≥ 5% weight loss was seen in 48% of patients, and ≥ 10% weight loss was seen in 25% of patients, compared with 16% and 7% in the placebo groups, respectively.[4] A combined analysis of three naltrexone/bupropion trials found that early improvements in cravings were predictive of greater weight loss success.[29]

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 (see other cardiovascular risk factors, below). 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.[30] As bupropion is associated with a slightly increased risk of seizure, naltrexone/bupropion is contraindicated in seizure disorders, anorexia nervosa, bulimia or patients undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates or antiepileptic drugs. Naltrexone/bupropion should be dosed with caution with any drugs that lower seizure threshold. Monoamine inhibitors (MOAIs) 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 (≥ 55% fat), as this significantly increases systemic exposure to the medication.[31]

There are multiple potential drug interactions with naltrexone/bupropion, which stem from the effect of bupropion and its metabolites to inhibit the hepatic CYP2D6 enzyme system. Physicians and pharmacists must be aware of the importance of evaluating potential drug interactions prior to initiating naltrexone/bupropion. Among patients already receiving naltrexone/bupropion, medications metabolized by CYP2D6 should be started at the lower end of their recommended dosage range with cautious titration (e.g. selective serotonin reuptake inhibitors, beta blockers, antipsychotic agents, type 1C antiarrhythmic agents and many tricyclic antidepressants, e.g. citalopram, metoprolol, risperidone, propafenone and desipramine, respectively).[32] 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).[33] 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).[32] Central nervous system toxicity can occur when naltrexone/bupropion is used concomitantly with dopaminergic drugs (e.g. levodopa, amantadine).

Efficacy of pharmacotherapy on health parameters

Type 2 diabetes mellitus prevention

T2DM is a common complication of obesity, and prevention of diabetes is an important goal in chronic 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.[34] Among individuals with prediabetes, one kilogram of weight loss is associated with a 16% relative risk reduction in the development of T2DM.[35]

Pharmacotherapy for obesity can be of benefit to prevent or delay the development of T2DM. Orlistat was evaluated for diabetes prevention in a trial of 3305 patients with obesity and either normal (79%) or impaired (21%) glucose tolerance. Patients were randomized to health behaviour changes plus either orlistat or placebo.[10] 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 study participants with normoglycemia. A secondary analysis demonstrated greater weight loss to be the primary reason for diabetes prevention.[10]

Liraglutide 3.0 mg has demonstrated efficacy to prevent and delay T2DM amongst people with prediabetes. The SCALE Obesity and Prediabetes trial randomized 2254 patients to receive liraglutide 3.0 mg (n=1505) 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%.[2] These improvements are likely due to a combined effect of the antihyperglycemic effects of liraglutide as well as liraglutide-mediated weight loss.

Currently, 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.[29] The exenatide group demonstrated a -5.1 kg weight loss compared with -1.6 kg on placebo. Impaired fasting tolerance 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 antihypertensive drugs, compared with people with diabetes who do not have obesity.[36]

The effect of antidiabetic pharmacotherapy on weight should be considered in choosing the most appropriate medication(s) for glycemic control. GLP1 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.[37] Pharmacotherapy for obesity can be of benefit for weight loss and improved diabetes control.

Orlistat has been demonstrated to improve glycemic control in patients with T2DM. A meta-analysis comprising 2550 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).[9] 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. For patients with minimal weight loss (1% of baseline body weight), orlistat provided a significantly greater decrease in fasting plasma glucose (0.83 mmol/l vs. 0.02 mmol/l) and HbA1c (0.29% vs. 0.14%).[9]

In the SCALE diabetes trial, liraglutide 3.0 mg was compared to liraglutide 1.8 mg 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% on liraglutide 1.8 mg (n=211) and -2.0% on 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% on liraglutide 1.8 mg and 21.4% on placebo. Weight loss ≥ 10% occurred in 25.2% of patients on liraglutide 3.0 mg versus 15.9% with liraglutide 1.8 mg versus 6.7% of people receiving health behaviour modification alone. Liraglutide 3.0 mg reduced HbA1c by 1.3% compared with 1.1% on liraglutide 1.8 mg and 0.3% on placebo. In addition, more participants treated with liraglutide 3.0 mg and 1.8 mg reduced their net use of oral antihyperglycemic agents compared with placebo.[7]

The Contrave Obesity Research Diabetes (COR-DM) trial evaluated the safety and efficacy of naltrexone/bupropion 32 mg /360 mg in addition to health behaviour changes amongst adults with a BMI of 27–45 kg/m^2 and T2DM managed with oral agents or diet.[8]

Naltrexone/bupropion treated patients achieved a 5% 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 in the placebo arm. 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 versus 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 another oral antidiabetic agent compared with placebo (22.3% vs. 35.2%, respectively).

Other cardiovascular risk factors

Pharmacotherapy-induced weight loss can be of benefit to improve cardiovascular risk factors in addition to glycemic control.

A meta-analysis demonstrated that orlistat produced a modest improvement in lipid profile and small reductions in blood pressure (see Table 1)[20]

Liraglutide reduced systolic blood pressure by -2.8 mmHg compared with placebo, with modest improvements in lipid parameters. A heart rate increase of two beats per minute (BPM) was noted amongst people with obesity and prediabetes at three years.[2] Naltrexone/bupropion is associated with modest improvements in lipid parameters.[4,8,38,39] Naltrexone/bupropion attenuates the blood pressure reduction associated with weight loss, which may be due to its action to inhibit reuptake of norepinephrine. Naltrexone/bupropion is contraindicated in patients with uncontrolled hypertension and should be used with caution in patients with controlled hypertension.[31]

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 effect 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 preexisting cardiovascular disease.

Liraglutide has been shown to reduce cardiovascular events and mortality in people with T2DM[38] at a 1.2–1.8 mg dose. These data have been accepted as sufficient safety data by the US 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 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 major adverse cardiac event of 0.88 (95% CI: 0.57–1.34) in favour of naltrexone/bupropion.[40] These results could not be used to establish non-inferiority due to the compromise of the trial. A new cardiovascular outcome trial is in planning stages.

There are no cardiovascular outcome trials for orlistat.

To date, no randomized clinical trial of obesity pharmacotherapy has demonstrated a reduction in cardiovascular events or mortality amongst people without diabetes.

Other obesity-related comorbidities

Weight loss can improve health comorbidities associated with obesity, including hepatic steatosis, polycystic ovary syndrome, obstructive sleep apnea and osteoarthritis.

Nonalcoholic steatohepatitis (NASH)

In a small study (n=41), individuals with BMI >27 kg/m^2 with biopsy-proven nonalcoholic steatohepatitis were randomized to receive a 1400 Kcal/day diet plus vitamin E (800 IU) daily with or without orlistat for 36 weeks. Both groups had similarly improved liver enzymes and nonalcoholic fatty liver disease activity scores, and there was no significant difference in weight loss between groups (-8.3% on orlistat vs. -6.0% on placebo). Orlistat did not enhance weight loss or improve liver enzymes, measures of insulin resistance or histopathology. Subjects with greater weight loss had improved NASH scores in both the orlistat and placebo groups.[41]

In a small study of 52 patients, liraglutide treatment at a dose of 1.8 mg daily resulted in resolution of nonalcoholic steatohepatitis in 39% of patients compared with 9% of patients on placebo. These results are based on liver biopsies performed after 48 weeks of treatment and may be the result of the combination of weight loss and a direct beneficial hepatic effect.[21]

Naltrexone/bupropion has not been specifically studied in regard to hepatic steatosis.

Though data is conflicting, some small studies have suggested that metformin may cause a small decrease in BMI of -0.5 to -1.3 kg/m^2 with an improvement in aminotransferases and/or liver histology in patients with nonalcoholic fatty liver disease.[42,43]

Polycystic ovary syndrome

Among women with polycystic ovary syndrome, liraglutide 1.8 mg 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 nonalcoholic fatty liver disease over 26 weeks.[22,44] These studies did not evaluate menstrual frequency, fertility or hirsutism. There are no studies of sufficient quality evaluating orlistat or naltrexone/bupropion 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,[45] 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.[46]

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 drug as monotherapy to improve menstrual cyclicity and ovulation rate.[47]

Obstructive sleep apnea

The only obesity pharmacotherapy available in Canada which has been specifically studied in the obstructive sleep apnea population 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.[23]

Osteoarthritis

The effect of obesity pharmacotherapy on osteoarthritis has not been adequately studied.

Mental health and quality of life

The choice of agents to treat mental health concerns (e.g. depression, psychosis) must take effect on weight into consideration (see The Role of Mental Health in Obesity Management. Pharmacotherapy for binge eating disorder and attention deficit hyperactivity disorder must also take effect on weight into consideration.

While the relationship between mental health and obesity is complex, most studies show that successful obesity management is associated with an improvement in mental health parameters. Weight loss is associated with improved quality of life in some, but not all, weight loss trials. As most obesity medications are active in the brain, it is important to ascertain their effect and safety on mental health parameters.

Liraglutide 3.0 mg has been shown to improve health-related quality of life in people with obesity and prediabetes[48] and weight-related quality of life (QoL) in people with T2DM,[7] as well as demonstrating neuropsychiatric safety.[49]

Naltrexone/bupropion has demonstrated a greater improvement in weight-related QoL compared to placebo. Study participants losing the most weight experienced the greatest improvement in weight-related QoL regardless of whether the weight was lost on naltrexone/bupropion or placebo, suggesting that the improvement in QoL was related to the weight loss rather than the medication itself.[50] There has been a long-standing concern that antidepressants can rarely, paradoxically, worsen depression and/or cause worsening or emergence of suicidal ideation or behaviour during the early phases of treatment. In the placebo-controlled clinical trials with naltrexone/bupropion for the treatment of obesity in adult patients, no suicides or suicide attempts were reported in studies up to 56 weeks duration. In these studies, suicidal ideation was reported by three (0.20%) of 1515 patients treated with placebo compared with one (0.03%) of 3239 treated with naltrexone/bupropion. The same precautions pertaining to antidepressants should be considered when treating patients with naltrexone/bupropion, including screening patients for suicidal behaviours and ideation.

Weight gain is a common side effect of some antipsychotic medications. A systematic review and meta-analysis was conducted of 12 double-blind, randomized, placebo-controlled trials of 12–24 weeks' duration, including a total of 743 patients with schizophrenia or schizoaffective disorder. The study found that metformin was effective for the management of antipsychotic 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 antipsychotic treatment or with initiation of antipsychotic medication, with a mean difference in weight of -5.9 kg compared with placebo, versus -2.1 kg in patients who had been on antipsychotic medication longer term before starting metformin.[51]

Medications with insufficient data for obesity management

It is recognized 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 24–40 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.[52,53]

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) for patients in 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 to twelve 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, for patients in whom weight gain is a clinically relevant concern.

A recent review summarizes medications available in Canada that cause weight gain, as well as alternative choices.[54]

Emerging treatments and future directions

There are medications approved for obesity management in other countries that are not currently available in Canada. There are also several agents under development that may prove to be beneficial for the treatment of obesity.

Lorcaserin is a 5HT2c receptor agonist that is available in some countries. It works by stimulation of the pro-opiomelanocortin (POMC)/CART neurons (see The Science of Obesity chapter) to induce satiety and provides a -3.0% placebo subtracted weight loss at a dose of 10 mg BID for one year.[55] Lorcaserin has demonstrated cardiovascular safety in the Cardiovascular Safety of Lorcaserin in Overweight or Obese Patients cardiovascular outcome trial (CAMELLIA) but did not reduce the risk of cardiovascular events.[56]

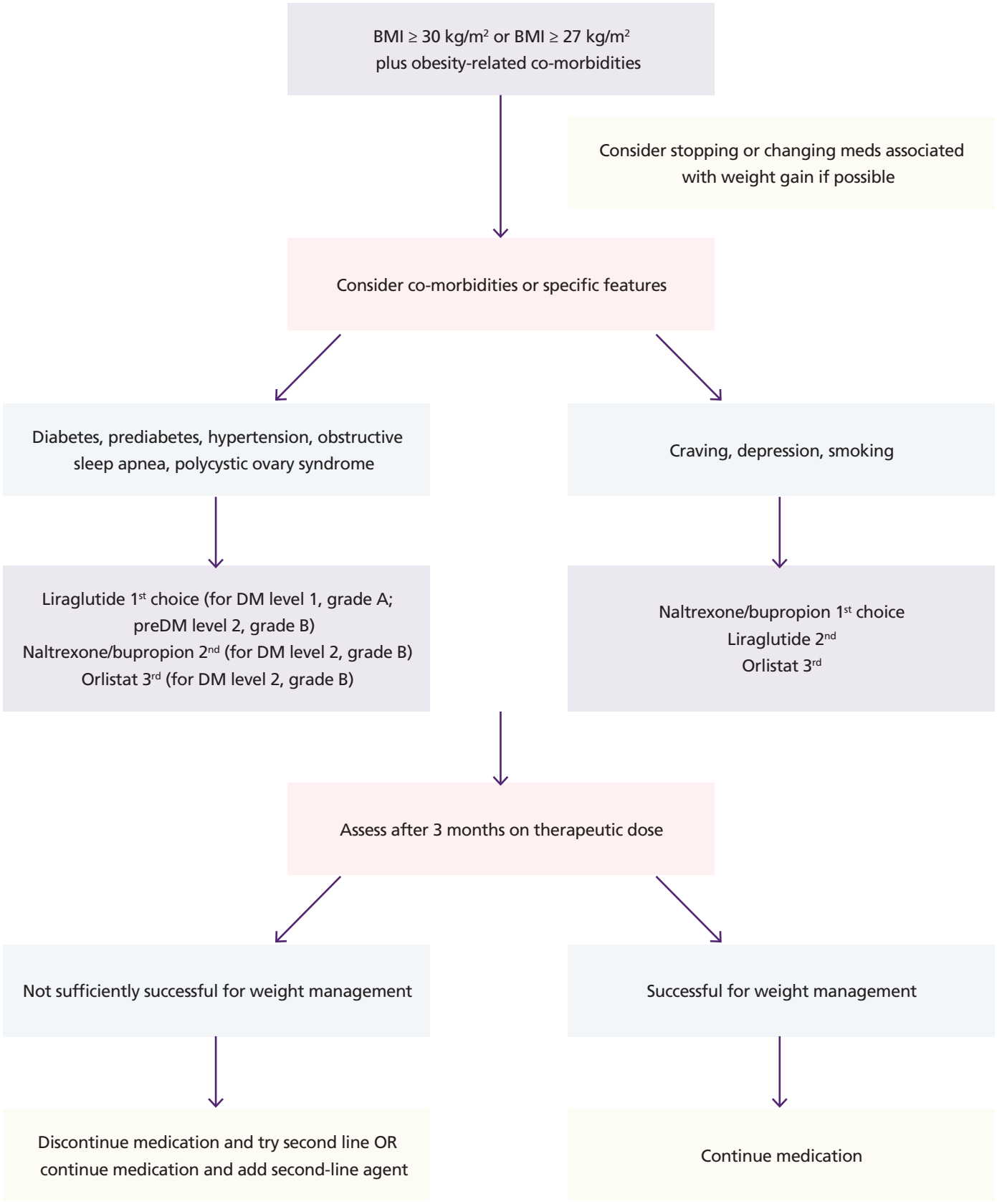
Phentermine and topiramate (controlled release) are approved as combination therapy for obesity in some countries. Phentermine is an appetite suppressant that works by inhibiting the neuropeptide Y/agouti-related peptide neurons and increasing energy expenditure. The mechanism by which topiramate induces weight loss is unclear and may involve multiple pathways. At one year, -6.6% placebo subtracted weight loss was seen on the lower dose of 7.5 mg/46 mg, and -8.6% on the higher dose of 15 mg/92 mg.[57]

Emerging obesity pharmacotherapy

Semaglutide, which is approved for treatment of T2DM in Canada, is currently under evaluation in clinical trials as a potential pharmacotherapeutic agent for chronic obesity management. In the Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN) clinical trial program, weight loss in people with T2DM on semaglutide 1.0 mg SC weekly over 30–56 weeks ranged from -4.5 to -6.5 kg, with up to -5.0 kg placebo subtracted weight loss.[58] Up to 65.7% of participants in both semaglutide dose groups (0.5 mg and 1.0 mg weekly) achieved weight loss responses of ≥ 5%, compared with up to 11.3% of patients on placebo. Among patients with T2DM with established cardiovascular disease or at high cardiovascular risk, semaglutide 0.5 mg and 1 mg weekly was associated with -2.9 kg and -4.3 kg placebo subtracted weight loss at two years, respectively.[59] Semaglutide also decreased cardiovascular events among patients with T2DM aged 50 or greater with established cardiovascular disease or at high risk of cardiovascular disease compared with placebo (heart rate, 0.74 (95% CI, 0.58–0.95) over two years.[59] Among people with obesity without diabetes, semaglutide at a dose of up to 0.4 mg subcutaneous per day demonstrated weight loss of up to -13.8% compared with -2.3% on placebo.[60] A cardiovascular outcome trial of semaglutide in people with obesity without diabetes but with a prior history of cardiovascular events is currently underway.

Multiple treatment options are being studied, which include monotherapy or combinations of various hormones (e.g. GLP-1, GIP, glucagon, oxyntomodulin, amylin, 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.

Figure 1. Algorithm: Choice of Obesity Pharmacotherapy



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.

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