Clinical Practice GUIDELINE for the Management of Obesity in Adults in Ireland

Pharmacotherapy in Obesity Management

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Cite this Chapter

ASOI Adult Obesity Clinical Practice Guideline adaptation (ASOI version 1, 2022) by: Le Roux C W1, Fitzgerald I2, Neff K3. Chapter adapted from: Pedersen SD, Manjoo P, Wharton S. Available from: https://asoi.info/guidelines/pharmacotherapy/ Accessed [date].

KEY MESSAGES FOR HEALTHCARE PROFESSIONALS

- **There are four medications indicated for chronic obesity management in Ireland in addition to health-behaviour supports: liraglutide 3 mg (Saxenda®), semaglutide 2.4 mg (Wegovy®), naltrexone/bupropion (Mysimba®) in a combination tablet and orlistat (Xenical®).** All four 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.** In choosing the most appropriate obesity pharmacotherapy, consider mechanism of action, safety, potential side effects/tolerability, contraindications, drug interactions, mode of administration and cost (see Table 1 and Table 2 of this chapter). There is a significant cost differential between products licensed for obesity management. Initial cost should be discussed with patients when choosing from available medications and ongoing affordability should be regularly reassessed.

RECOMMENDATIONS

1. Pharmacotherapy for obesity management can be used for individuals with body mass index (BMI) ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 (BMI ≥ 28 kg/m^2 in the case of orlistat) 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 mg [Level 2a, Grade B][2-4], naltrexone/bupropion 16 mg/180 mg BD [Level 2a, Grade B][5], orlistat 120mg TDS [Level 2a, Grade B])[6].

2. Pharmacotherapy may be used to maintain weight loss that has been achieved by health-behaviour changes, and to prevent weight regain (liraglutide 3 mg or orlistat 120 mg TDS) (Level 2a, Grade B)[4,7].

3. For people living with type 2 diabetes (T2DM) and a BMI ≥ 27 kg/m^2, pharmacotherapy can be used in conjunction with health-behaviour changes for weight loss and improvement in glycaemia: semaglutide 2.4 mg weekly (Level 1a, Grade A)[8], liraglutide 3 mg (Level 1b, Grade A)[9], naltrexone/bupropion combination (Level 2a, Grade B)[10], orlistat (Level 2a, Grade B)[11].

4. We recommend pharmacotherapy in conjunction with health-behaviour changes for people living with pre-diabetes and overweight or obesity (BMI > 27 kg/m^2) to delay or prevent T2DM: liraglutide 3 mg (Level 2a, Grade B) 3, orlistat (Level 2a, Grade B)[12].

5. We do not suggest the use of prescription or over-the-counter 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 where potential differences in efficacy, tolerability and affordability allow (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 modifications alone have not been effective or sustainable.**

- **There are four medications approved for long-term obesity management in Ireland: liraglutide 3 mg (Saxenda®), semaglutide 2.4 mg (Wegovy®), naltrexone/bupropion in a combination tablet (Mysimba ®) and orlistat (Xenical®).** These medications can help to improve health complications linked to excess weight, reduce weight by 5% – 10% and assist in maintaining this loss. These medications are approved by the European Medicines Agency (EMA) for use in Ireland 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.**

Table 1: **Executive Summary of Approved Obesity Management Products for Use in Ireland**

Medication	Maximum dose	Indications	Contraindications	Expected effects	Common side effects	Cost*†
Orlistat	120 mg TDS	BMI) ≥ 30 kg/m^2 Or BMI ≥ 28 kg/m^2 with obesity-related disease	Hypersensitivity to orlistat or any of the excipients Breastfeeding Chronic gastrointestinal malabsorption Cholestasis	Average weight loss of > 7% > 5% weight loss in 54% of users > 10% weight loss in 26% of users	Oily stool** Faecal urgency** Flatus** Faecal incontinence**	€
Naltrexone/ Bupropion	16 mg/1 80 mg BD	BMI ≥ 30 kg/m^2 Or BMI ≥ 27 kg/m^2 with obesity-related disease	Hypersensitivity to Naltrexone/ Bupropion or any of the excipients Uncontrolled blood pressure Opiate use Seizure disorder Severe renal impairment Severe hepatic impairment Bipolar affective disorder Anorexia nervosa Bulimia Acute alcohol or benzodiazepine withdrawal Central nervous system tumour	Average weight loss of > 6% > 5% weight loss in 48% of users > 10% weight loss in 25% of users	Nausea and vomiting Constipation Diarrhoea Dry mouth Headache Insomnia Dizziness Anxiety Increased blood pressure	€€
Liraglutide	3 mg OD	BMI ≥ 30 kg/m^2 Or BMI ≥ 27 kg/m^2 with obesity-related disease	Hypersensitivity to liraglutide or any of the excipients Caution in: Those with high risk of pancreatitis Heart failure at stage NYHA 3 or 4 Severe renal impairment Severe hepatic impairment Personal or family history of medullary thyroid cancer People with severe inflammatory bowel disease or gastroparesis	Average weight loss of > 8% Improvement in HbA1c in people with type 2 diabetes >5% weight loss in 63% of users >10% weight loss in 33% of users	Nausea*** Constipation*** Loose stool*** Acid reflux***	€€€
Semaglutide	2.4 mg once weekly	BMI ≥ 30 kg/m^2 Or BMI ≥ 27 kg/m^2 with obesity-related disease	Hypersensitivity to semaglutide or any of the excipients Caution in: Those with high risk of pancreatitis Severe renal impairment People with diabetes and retinopathy who are using insulin People with severe inflammatory bowel disease or gastroparesis	Average weight loss of > 14% Improvement in HbA1c in people with type 2 diabetes > 5% weight loss in 86% of users > 10% weight loss in 69% of users	Nausea*** Constipation*** Loose stool*** Acid reflux***	€€€

TDS: Three times daily; BD: Twice daily; OD: Once daily; BMI: Body mass index; HbA1c: Glycated haemoglobin ; NYHA: New York Heart Association;
*Number of € symbols indicates relative cost (i.e., € is least costly and €€€ is most costly) at time of writing;
only expected if fat content of diet exceeds recommended limits; * side effects can be mitigated by slowing dose escalation;
†Note that at the time of guideline writing, no product listed in this table is reimbursed under government drug schemes. Cost to patient may be significant.

Introduction

Modest and sustained weight loss (5% – 10%) is associated with improvements in health complications associated with obesity[13-15]. 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 change generally achieves a 3% to 5% weight loss, which may not be sustained over the long term (see Chapter 10 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 the European Medicines Agency (EMA) for use in Ireland. It is intended to inform healthcare professionals (HCPs) on the appropriate use of obesity pharmacotherapy. The EMA has produced guidance for pharmaceutical companies wishing to obtain a regulatory license within Europe for a medicinal product for use in weight management amongst adults with overweight or obesity. The guidance outlines the requirements for clinical documentation needed to support a marketing authorisation for a weight-management medication. Their criteria highlight the need for the medication to have demonstrated the following:

1. Statistically significant, placebo-corrected weight loss of at least 5% of baseline weight after 12 months treatment.

2. Proportion of patients with at least 5% and 10% weight loss after 12 months treatment.

3. Predictive value of weight loss after short-term treatment on longer-term outcomes (e.g., 12 weeks treatment on target treatment dose).

4. Effect of medication on central adiposity.

5. Neutral or beneficial effect on parameters associated with cardiovascular risk (e.g., blood glucose, blood pressure, heart rate, lipid levels).

6. Treatment impact on the risk of type 2 diabetes (T2DM) development[16].

Pharmacotherapy is indicated for chronic obesity management in Ireland for individuals with a body mass index (BMI) ≥ 30 kg/m^2, or ≥ 27 kg/m^2 (BMI ≥ 28 kg/m^2 in the case of orlistat) with comorbidities associated with excess adiposity (e.g., T2DM, pre-diabetes, hypertension, dyslipidaemia).

There are four medications approved for obesity management in Ireland: liraglutide 3 mg, semaglutide 2.4 mg, naltrexone/bupropion and orlistat (see Table 2). It is recognised that there are other medications available in Ireland that are not approved for obesity management and are used off-label in such cases. As a result, the literature search employed here applied an open strategy to capture all pharmacotherapy agents that have been studied for obesity management. With the exception of metformin for prevention of anti-psychotic-induced weight gain (see Chapter 7 The Role of Mental Health in Obesity Management for recommendations relating to metformin), we discourage HCPs 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 Chapter 16 Commercial Products and Programmes in Obesity Management.

This chapter will address clinical questions pertaining to the efficacy of pharmacotherapy in people with overweight or obesity. It will also summarise evidence for pharmacotherapy for obesity among persons with selected health complications, including T2DM, pre-diabetes, hepatic steatosis, polycystic ovary syndrome, obstructive sleep apnoea and osteoarthritis. Randomised controlled trials or meta-analyses of at least six months duration were included in the original 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 aetiology 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 msedications as well as the mode (oral versus subcutaneous) and frequency of administration can be a barrier to patient adherence and should be discussed with patients initially when prescribing pharmacotherapy, and at frequent intervals thereafter. 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 adherence, barriers to health-behaviour change and psychosocial or medical issues. It should also be recognised 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 effects have not been achieved after three months on full/maximum-tolerated dose. 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 (four months in the case of naltrexone/bupropion combination treatment). However, liraglutide and orlistat can also be used to maintain weight loss achieved with a prior health-behaviour change or a very low-energy diet[4,7]. In Ireland, no weight-management products are specifically licensed for this indication and hence, use in this way is considered off-label.

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[3,17].

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[18].

Mechanism and efficacy of approved pharmacotherapy for obesity management

Orlistat

Orlistat, a semi-synthetic derivative of lipstatin, was approved as pharmacotherapy for obesity management throughout the European Union (EU) in 1998 (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 faeces, creating a caloric deficit[19]. 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 the EMA in conjunction with a mildly hypocaloric diet for the treatment of patients with a BMI of ≥ 30 kg/m^2, and patients with a BMI of ≥ 28 kg/m^2 with associated risk factors (e.g., hypertension, T2DM, dyslipidaemia, excess visceral fat)[18].

A systematic review and meta-analysis of randomised controlled trials of orlistat 120 mg three times a day reported a mean placebo subtracted weight loss of -2.9% at one year[20]. Additionally, 54% and 26% of patients achieved ≥ 5% and ≥ 10% weight loss, respectively, compared to 33% and 14% for placebo[20]. 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 significant adverse gastrointestinal effects, including oily spotting and stool, flatus with discharge, faecal urgency and increased defecation[20]. These adverse effects may cause patients who do not lower their dietary fat intake to discontinue therapy. A long-term analysis of obesity medications demonstrated six-month, one-year and two-year persistence rates of 18%, 6% and 2% with orlistat, respectively[21]. 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 multi-vitamin at least two hours before or after taking orlistat, or before bed[18,20].

Orlistat is contraindicated in patients with chronic malabsorption syndrome, or cholestasis and in breastfeeding women. Some patients may develop increased levels of urinary oxalate on orlistat; cases of oxalate nephropathy with renal failure have been reported[22]. There have also been rare cases of severe liver injury or acute liver failure[23].

As orlistat may interfere with vitamin K absorption, international normalised ratio (INR) 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 ciclosporine levels has been observed when orlistat is co-administered; thus, it is recommended to monitor ciclosporine levels more frequently.

Orlistat may affect absorption of anti-convulsants, so patients on anti-convulsants should be monitored for possible changes in the frequency and/or severity of seizure[18]. Additional anti-epileptic plasma monitoring (where available) should be used to guide need for dosing changes during concomitant treatment. Amongst those prescribed oral contraceptives, the use of an additional contraceptive method is recommended to prevent possible contraceptive failure that could occur in the case of severe diarrhoea. A slight decrease in plasma levels of amiodarone, when given as a single dose, has been observed in a limited number of healthy volunteers who received orlistat concomitantly. The clinical relevance of this effect remains unknown but may become clinically relevant in some cases. In patients receiving concomitant amiodarone treatment, reinforcement of clinical and electrocardiogram monitoring is warranted. There are case reports of reduced efficacy of anti-retroviral HIV medicines, anti-depressants, anti-psychotics, lithium and benzodiazepines coincidental to the initiation of orlistat treatment in previously well-controlled patients. Given the frequent co-administration of psychotropic and weight-management medications, efforts should be made to separate their dosing from orlistat by two hours, where possible (e.g., night-time dosing of lithium, anti-psychotics, benzodiazepines). Additional precautionary clinical monitoring may be necessary to sustain or achieve therapeutic response when orlistat treatment is co-prescribed. This should include additional plasma monitoring, where available (e.g., lithium).

A pharmacist's advice should be sought on managing drug interactions, particularly where several concomitant medications are prescribed with orlistat[18]. The degree of 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) analogue 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[18,24,25].

Liraglutide increases insulin release and suppresses glucagon during times of glucose elevation. Liraglutide is approved in Ireland for the management of T2DM at a dose of 1.2 mg or 1.8 mg daily, with near maximal therapeutic efficacy for HbA1c lowering at the 1.8 mg dose. Liraglutide was approved by the EMA for use in Ireland in 2015 for chronic obesity management at a dose of 3 mg daily, in people with or without T2DM. The recommended starting dose of liraglutide is 0.6 mg daily, with up-titration by 0.6 mg each week until the 3 mg target dose is achieved.

Among people with normoglycemia or pre-diabetes, liraglutide 3 mg with health-behaviour modification resulted in an 8.0% weight loss at one year, compared to 2.6% on 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 mg and placebo, respectively. Patients with pre-diabetes were followed to three years, with sustained weight loss of -6.1% in the liraglutide group vs. -1.9% in placebo[3].

Following a -6.0% weight loss with a low-calorie diet, liraglutide 3 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 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 mg regained ≥ 5% body weight (1.9%) compared to placebo (17.5%)[4].

The most common side effect of liraglutide is nausea due to a transient decrease in gastric emptying, occurring in ≥ 1/10 users. Patients may also experience constipation, diarrhoea, heartburn and/or vomiting. More gradual titration can help mitigate largely mild, self-limiting gastrointestinal side effects, should these occur. Liraglutide use is associated with a 1.4% higher risk of gallstones compared to placebo, corresponding to a number needed to harm (NNH) of approximately 71%[32] higher than placebo, corresponding to a NNH of 250[32]. Liraglutide has also been associated with an increased 0.2% increased risk of pancreatitis, when compared to placebo, corresponding to a NNH of 500. The majority of cases have been associated with gallbladder disease. Patients should be informed on starting liraglutide of the signs and symptoms characteristic of gallbladder inflammation, gallstones and pancreatitis prior to starting liraglutide. Caution should be exercised amongst those with a history of pancreatitis[32].

Treatment with liraglutide is cautioned in certain groups[3]. This includes those with congestive heart failure New York Heart Associated (NYHA) class IV, those with severe renal or hepatic impairment and those with pre-existing thyroid disease. Liraglutide should not be used in those with inflammatory bowel disease and gastroparesis. Signs and symptoms of dehydration, including renal impairment and acute renal failure, have been reported in patients treated with GLP-1 receptor agonists. Patients treated with liraglutide should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion. Monitoring of blood glucose amongst those without pre-diabetes or diabetes is not required where the use of GLP-1 agonists is being used solely for weight-management purposes[33].

Liraglutide delays gastric emptying, which may impact absorption of concomitantly administered oral medications[34]. Interaction studies did not show any clinically relevant delay in absorption of concomitantly administered medications and, therefore, no dose adjustments in other medications are recommended. If severe diarrhoea occurs during treatment, this may also affect the absorption of concomitant medications. This may become clinically relevant in the case of medications with a narrow therapeutic index (e.g., lithium or warfarin) or where serial missed doses may cause significant short-term effects (e.g., loss in efficacy of oral contraceptives). Additional measures may be required to protect concomitant medication efficacy and safety should severe gastrointestinal side effects occur. Amongst those on concomitant warfarin, additional monitoring of INR is recommended[34].

Semaglutide

Semaglutide is a once weekly, subcutaneously administered, human GLP-1 analogue that acts centrally on the POMC/CART neurons to improve satiation and satiety and reduce hunger, with a transient effect to decrease gastric emptying[35,36]. It increases insulin release and suppresses glucagon during times of glucose elevation. Semaglutide is approved for the management of T2DM at a dose of 1 mg weekly. The near-maximal therapeutic efficacy for HbA1c lowering is at the 1 mg weekly dose[37]. In the Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN) clinical trial programme, 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[38]. 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[39]. 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[39]. A cardiovascular outcome trial of semaglutide in people with obesity without diabetes but with a prior history of cardiovascular events is currently underway.

Semaglutide was approved in the US, UK and EU in 2021 for chronic obesity management at a dose of 2.4 mg weekly in people with or without T2DM. The recommended starting dose of semaglutide is 0.25 mg weekly, with titration of the dose until the 2.4 mg target dose is achieved. Among people with normoglyceamia or pre-diabetes, semaglutide 2.4 mg with health-behaviour modification resulted in a 14.9% weight loss at one year, compared to 2.4% on placebo (health-behaviour modification alone)[1]. In terms of categorical weight loss, 86.4% of patients on semaglutide lost ≥ 5% body weight at one year, compared with 31.5% of patients in the placebo group; 69.1% and 12% of participants lost more than 10% of their body weight on semaglutide 2.4 mg and placebo, respectively; 50.5% and 4.9% of participants lost more than 15% of their body weight on semaglutide 2.4 mg and placebo, respectively; 32.5% and 1.7% of participants lost more than 20% of their body weight on semaglutide 2.4 mg and placebo, respectively. Patients with diabetes were followed for 68 weeks, with a mean sustained weight loss of -9.6% in the semaglutide group vs. -3.4% in placebo[8].

Semaglutide 2.4 mg plus health-behaviour counselling and meal replacement reduced weight by -16.0% at one year compared with -5.7% in the placebo group (intensive behavioural therapy and meal replacements)[40]. More patients on semaglutide 2.4 mg were able to lose and maintain the ≥ 10 % run-in weight loss (79%) compared with those receiving placebo (20%). Furthermore, 64% of those who took semaglutide for 68 weeks lost at least 15% of their week zero body weight[41].The most common side effect of semaglutide is nausea due to a transient decrease in gastric emptying, occurring in ≥ 1/10 users. Patients may also experience constipation, diarrhoea, heartburn and/or vomiting. More gradual titration can help mitigate largely mild, self-limiting gastrointestinal side effects, should these occur. Where semaglutide is being used to manage overweight or obesity amongst those without T2DM, its use has been associated with a 1.2% higher risk of gallstones compared to placebo, corresponding to a NNH of approximately 83. Semaglutide 2.4 mg has been also associated with a 0.2% increased risk of pancreatitis when compared to placebo, corresponding to a NNH of 500. Patients starting on semaglutide should be informed of the signs and symptoms characteristic of gallbladder inflammation, gallstones and pancreatitis. Caution should be exercised amongst those with a history of pancreatitis. Semaglutide should also be used with caution amongst those with congestive heart failure NYHA Class IV[1,32].

New onset or worsening of diabetic retinopathy has been observed amongst those treated with semaglutide with T2DM and overweight or obesity. Although the overall number of retinopathy events was low, there was an unexpected higher rate of retinopathy complications (vitreous haemorrhage, blindness or the need for treatment with an intravitreal agent or photocoagulation) in patients with diabetes[39]; however, there is no clear, direct link and ongoing study looking for that[42]. Patients with diabetic retinopathy using semaglutide should be monitored closely and treated according to clinical guidelines. As with other GLP-1 agonists, semaglutide delays gastric emptying, which may impact absorption of concomitantly administered oral medications. There are no standard dose adjustments recommended for any other medications taken concurrently with semaglutide upon its initiation. If severe diarrhoea occurs during treatment, this may affect the absorption of concomitant medications. This may become clinically relevant in the case of medications with a narrow therapeutic index (e.g., lithium or warfarin) or where serial missed doses may cause significant short-term effects (e.g., loss in efficacy of oral contraceptives). Additional measures may be required to protect concomitant medication efficacy and safety should severe gastrointestinal side effects occur[43].

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 anti-depressant that inhibits the reuptake of dopamine and norepinephrine. The naltrexone/bupropion sustained release formulation was approved for chronic obesity management in Ireland in 2015, 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[44]. This synergistic mode of action is supported by the evidence that the use of bupropion or naltrexone alone does 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. The second dose should be taken in the early evening so as to reduce the likelihood of insomnia — a common side effect of bupropion[46].

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[5]. 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[5]. A combined analysis of three naltrexone/bupropion trials found that early improvements in cravings were predictive of greater weight-loss success[47].

The most common side effects of naltrexone/bupropion include nausea, constipation, headache, vomiting, insomnia, dry mouth, dizziness, anxiety, increased blood pressure and diarrhoea. Most nausea events occur during the dose-escalation period and are transient[46]. Naltrexone/bupropion is contraindicated in patients with uncontrolled hypertension and cautioned amongst those

with a history of active coronary artery disease or cerebrovascular disease (see "Other cardiovascular risk factors" section 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[48]. Bupropion is associated with a slightly increased risk of seizure — seizure incidence in subjects receiving naltrexone/bupropion in clinical trials was approximately 0.06% vs. 0% on placebo — naltrexone/bupropion is contraindicated in seizure disorders or amongst those with a history of seizures, anorexia nervosa, bulimia or patients undergoing abrupt discontinuation of alcohol or benzodiazepines. Naltrexone/bupropion is also contraindicated amongst those with a history of known central nervous system tumour, a history of bipolar disorder, those with severe hepatic impairment or those with end-stage renal disease[46]. The section "Mental health and quality of life" of this chapter should be consulted for advice on the potential impact of naltrexone/bupropion on mental health outcomes.

Naltrexone/bupropion should be dosed with caution with any drugs that lower seizure threshold[46]. Monoamine inhibitors (MOAIs) can increase the risk of hypertensive reactions, and use of naltrexone/bupropion within 14 days of stopping an MAOI is contraindicated[46]. Naltrexone/bupropion should not be taken with any other products containing naltrexone or bupropion. Naltrexone/bupropion should not be taken with a high-fat meal (≥ 55% fat), as this significantly increases systemic exposure to the medication[49]. There have been post-marketing reports of serotonin syndrome, a potentially life-threatening condition when naltrexone/bupropion was co-administered with a serotonergic agent, such as a selective serotonergic reuptake inhibitor or a serotonergic norepinephrine reuptake inhibitor. Monitoring for signs and symptoms consistent with the syndrome should be undertaken when these medications are co-prescribed[46].

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 metabolised 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 antiarrhythmic agents and many tricyclic anti-depressants, such as citalopram, metoprolol, risperidone, propafenone and desipramine, respectively)[50]. 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 metabolised 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)[51]. 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)[50]. Central nervous system toxicity can occur when naltrexone/bupropion is used concomitantly with dopaminergic drugs (e.g., levodopa, amantadine).

Table 2: **Effects of Pharmacotherapy for Obesity on Comorbidities**

	Orlistat	Liraglutide	Naltrexone/ Bupropion	Semaglutide
Mode of administration	Oral	Subcutaneous	Oral	Subcutaneous
Dose/frequency	120 mg TDS	3.0 mg daily	16 mg /180 mg BD	2.4 mg weekly
Effect on % weight loss at 1 year, placebo subtracted	-2.9%[20]	-5.4%[2]	-4.8%[5]	-12.5%[1]
Effect on weight over longer term, placebo subtracted	-2.8 kg at 4 years[12]	-4.2% at 3 years[3]	Not studied	Not available
% of patients achieving ≥ 5% weight loss at 1 year	54% (vs. 33% in placebo)[20]	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)[20]	33.1% (vs. 10.6% in placebo)[2]	25% (vs. 7% in placebo)[5]	69.1% (vs.12% in placebo)
% of patients achieving ≥ 15% weight loss at 1 year	Not studied	14.4% (vs. 3.5% in placebo)[3]	13.5% (vs. 2.4% in placebo)[26]	50.5% (vs. 4.9% in 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 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
Effect on pre-diabetes	37.3% reduction in risk of developing T2DM over 4 years[12]	79% reduction in risk of developing T2DM over 3 years[3]	Not studied	Not available

	Orlistat	Liraglutide	Naltrexone/ Bupropion	Semaglutide
Effect on BP at 1 year, placebo subtracted	-1.9 mmHg SBP -1.5 mmHg DBP[27]	-2.8mmHg SBP -0.9mmHg DBP[2]	+1.8mmHg SBP 0.9mmHg DBP[5]	-5.1mmHg SBP -2.4mmHg DBP[1]
Effect on lipids at 1 year, placebo subtracted	-0.27 mmol/L TC -0.21 mmol/L LDL -0.02 mmol/L HDL -0.00 mmol/L TG [27]	-2.3% TC -2.4% LDL +1.9% HDL -3.9% non-HDL -9.3% TG[2]	-1.5 % LDL +7.2% HDL - 9.6 % TG 5	TC +0.22mmol/L HDL +0.1mmol/L LDL -0.1mmol/L TG -0.22 mmol/L[1,28]
Effect on HR at 1 year, placebo subtracted	No change	+2.4 BPM[2]	+1.1 BPM[5]	+4.2BPM[1]
Effect on HbA1c in patients with T2DM at 1 year, placebo subtracted	-0.4%[11]	-1.0%[9]	-0.5%[10]	-1.2% [8]
Effect on NASH	No improvement	Improvement[29]	Not studied	Resolution of NASH (59% with 0.4 mg OD vs. 17% with placebo)
Effect on PCOS	Not studied	-5.2 kg placebo subtracted weight loss at 6 mo; no data on menstrual cyclicity[30]	Not studied	Not studied
Effect on OA	Not studied	Not studied	Not studied	Not available
Effect on OSA	Not studied	Reduces AHI by 6 / hr[31]	Not studied	Not studied
Cost for 1 month supply of maintenance dose^	€74.22	€257.53	€97.64	Unavailable
Contraindications	• Hypersensitivity to the active substance or excipients • Cholestasis • Chronic malabsorption syndrome • Breastfeeding[18]	• Hypersensitivity to the active substance or excipients	• Uncontrolled hypertension • Any opioid use • History of seizures or diagnosis of seizure disorder • Abrupt discontinuation of alcohol or benzodiazepine • Concomitant administration of MAOI or MAOI cessation within the last 14 days • Severe hepatic impairment • End-stage renal failure • Known central nervous tumour • History of bipolar disorder • History of bulimia or anorexia nervosa • Concomitant administration of other products containing naltrexone or bupropion.	• Personal or family history of medullary thyroid cancer • Personal history of MEN2 syndrome • Pregnancy, attempting conception, breastfeeding
Common side effects	Loose, oily stools, flatus, influenza like symptoms	Nausea, constipation, diarrhoea, vomiting	Nausea, constipation, headache, dry mouth, dizziness, diarrhoea, anxiety, insomnia	Nausea, diarrhoea, constipation, vomiting
Rare side effects	• Liver failure • Nephrolithiasis • Acute kidney injury	• Pancreatitis • Cholelithiasis	• Seizure • Worsening of mood disorders	Cholelithiasis Pancreatitis
Drug interactions	• Fat-soluble vitamins • Levothyroxine • Oral contraceptives • Anti-retrovirals • Some psychotropic medications • Ciclosporine • Oral anti-coagulants, anti-convulsants[18]	May affect absorption of medications due to slowing of gastric emptying. See chapter text	See chapter text	May affect absorption of medications due to possible slowing of gastric emptying
Deprescribing advice where weight loss is the treatment goal	Treatment should be discontinued after 12 weeks if patients have not lost at least 5% of body weight as measured at the start of therapy	Treatment should be discontinued after 12 weeks on the 3.0 mg/d dose if patients have not lost at least 5% of their initial body weight	Treatment with naltrexone/bupropion should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight at the maximum tolerated dose	No deprescribing advice specified

Kg: kilogram; HbA1c: glycated haemoglobin; mo: month; hr: hour; d: day; T2DM: type 2 diabetes; mmHg: millimetres of mercury; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; LDL: low density lipoprotein; HDL: high density lipoprotein; TG: triglyceride; HR: heart rate; BPM: beats per minute; NASH: non-alcoholic steatohepatitis; OA: osteoarthritis; OSA: obstructive sleep apnoea; PCOS: polycystic ovarian syndrome; MEN2: multiple endocrine neoplasia type 2; MAOI: monoamine oxidase inhibitors; ^Cost in Ireland as of November 2021. This represents product cost. Cost to patient may be greater. Non-oral products will also be charged VAT at 23%.

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 pre-diabetes 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[52]. Among individuals with pre-diabetes, one kilogram of weight loss is associated with a 16% relative risk reduction in the development of T2DM [53].

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 3,305 patients with obesity and either normal (79%) or impaired (21%) glucose tolerance. Patients were randomised to health-behaviour support plus either orlistat or placebo[12]. 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 normoglyceamia. A secondary analysis demonstrated greater weight loss to be the primary reason for diabetes prevention[12].

Liraglutide 3 mg has demonstrated efficacy to prevent and delay T2DM amongst people with pre-diabetes. The SCALE Obesity and Prediabetes trial randomised 2,254 patients to receive liraglutide 3 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 mg vs. health behaviour support alone, and the risk of developing T2DM was reduced by 79%[3]. These improvements are likely due to a combined effect of the anti-hyperglycaemic effects of liraglutide as well as liraglutide-mediated weight loss. Semaglutide 2.4 mg did not have a specific trial focused on patients with pre-diabetes, but in the STEP 1 trial 44% of the 1,961 participants had pre-diabetes, with an average glycated haemoglobin of 5.9% (41 mmol/mol). During the 68-week trial, those taking semaglutide lost, on average, 13.7% of their baseline body weight, which was in line with the 14.9% reduction in the cohort overall, while 84.1% of the participants with pre-diabetes who were taking semaglutide reverted to normoglyceamia, compared with 47.8% of those taking placebo[1].

Currently, there are no published studies evaluating the efficacy of naltrexone/bupropion on diabetes prevention.

The systematic review that underpins these guidelines identified one randomised control trial evaluating the efficacy of exenatide (a short-acting GLP-1 analogue) versus placebo on body weight and glucose tolerance among people with obesity with normoglyceamia, impaired glucose tolerance or impaired fasting glucose, on a background of health-behaviour intervention over a 24-week period[47]. The exenatide group demonstrated a -5.1 kg weight loss compared with -1.6 kg on placebo. Impaired fasting tolerance normalised 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

People with T2DM and obesity are less likely to achieve their glycaemia, blood pressure and lipid profile treatment targets than people with T2DM who do not have obesity[54]. Therefore, people with T2DM and obesity have a higher rate of use of lipid lowering and anti-hypertensive drugs, compared with people with diabetes who do not have obesity[54].

The effect of hypoglycaemic pharmacotherapy on weight should be considered in choosing the most appropriate medication(s) for glycaemia. GLP1 receptor agonists and sodium/glucose cotransporter 2 inhibitors are associated with weight loss in addition to improving glycaemia. Metformin, dipeptidyl peptidase-4 inhibitors and acarbose are typically weight neutral. Insulin, insulin secretagogues and thiazolidinediones are associated with weight gain[55]. Pharmacotherapy for obesity can be of benefit for weight loss and improved glycaemia.

Orlistat has been demonstrated to improve glycaemia in patients with T2DM. A meta-analysis comprising 2,550 patients with T2DM and obesity randomised to orlistat 120 mg TDS 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)[11]. Weight loss in the orlistat group was -3.8 kg compared to -1.4 kg on placebo. The primary reason for improvement in glycaemia 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%)[11].

In the SCALE diabetes trial, liraglutide 3 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 activity and nutrition 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 anti-hyperglycaemic agents compared with placebo[9].

The STEP 2 trial comprised adults with BMI ≥ 27 kg/m^2 and HbA1c ranging from 7% to 10%; all participants had been diagnosed with T2DM ≥ 6 months prior to study screening[8]. In a 1:1:1 ratio, the trial randomised 1,210 participants to 2.4 mg semaglutide, 1.0 mg semaglutide or placebo. The 2.4 mg semaglutide with health behaviour support interventions reduced body weight more from baseline to week 68 compared with placebo and lifestyle interventions (MD = -6.2%, 95% CI: -7.3, -5.2). Moreover, the proportions of participants with ≥ 5%, ≥ 10% and ≥ 15% weight loss at week 68 were 68.8%, 45.6% and 25.8%, respectively. Semaglutide also improved systolic blood pressure, HbA1c, waist circumference and physical function scores. The rate of any reported side effect was greater in the 2.4 mg semaglutide arm contrasted with the placebo arm (87.6% vs. 76.9%). Moreover, the number of reported serious side effects was comparable between both treatment arms. Additionally, the rate of drug termination was higher in the semaglutide 2.4 mg arm (6.2% vs. 3.5%), mostly secondary to gastrointestinal-related symptoms (4.2% vs. 1.0%). Gallbladder-related symptoms occurred in only 0.2% and 0.7% of the semaglutide 2.4 mg and placebo arms, respectively. In contrast with the placebo arm, the most commonly documented side effects in ≥ 10% of the semaglutide 2.4 mg patients included nausea (33.7% vs. 9.2%), diarrhoea (21.8% vs. 2.7%), vomiting (21.3% vs. 11.9%), constipation (17.4% vs. 5.5%) and nasopharyngitis (16.9% vs. 14.7%). The rates of hypoglycaemia, acute pancreatitis and injection-site reactions were infrequent in the semaglutide 2.4 mg arm (0.2%, 0.2%, and 3.0%, respectively)[8].

The Contrave Obesity Research Diabetes 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 kg/m^2 – 45 kg/m^2 and T2DM managed with oral agents or diet[10]. 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 HbA1c compared to placebo and were more likely to achieve a HbA1c < 7% (44.1% in the naltrexone/bupropion group vs. 26.3% in placebo). The change in HbA1c 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 anti-diabetic agent compared with placebo (22.3% vs. 35.2%, respectively)[10].

Other cardiovascular risk factors

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

A meta-analysis demonstrated that orlistat produced a modest improvement in lipid profile and small reductions in blood pressure (see Table 1)[27].

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 was noted amongst people with obesity and pre-diabetes at three years[3]. Naltrexone/bupropion is associated with modest improvements in lipid parameters[5,10,56,57]. 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[46,49].

European regulatory requirements for obesity pharmacotherapy outline the need for drug companies requesting authorisation for a medical product for use in weight management to have characterised the cardiovascular safety profile of the medication as part of their drug-development programme and from both clinical and non-clinical data[16].

Sibutramine, which is no longer available in Ireland, 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.

Liraglutide has been shown to reduce cardiovascular events and mortality in people with T2DM[56] at a 1.2 mg – 1.8 mg dose. These data have been accepted as sufficient safety data by the EMA to reassure the cardiovascular safety of liraglutide in people with obesity without T2DM, at the therapeutic dose of 3 mg.

Semaglutide has previously been shown to decrease cardiovascular events in T2DM with established cardiovascular disease[39]. However, the first clinical trial exploring the superiority of weekly subcutaneous semaglutide 2.4 mg vs. placebo for preventing major adverse cardiovascular events is currently underway in patients with obesity and established cardiovascular disease without diabetes (Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight and Obesity (SELECT))[58].

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 occurred, compromising the integrity of the trial. Although the trial was terminated upon the recommendation of the lead investigator, the results of the pre-planned 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[59]. 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.

Other obesity-related comorbidities

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

Non-alcoholic steatohepatitis (NASH)

In a small study (n = 41), individuals with BMI > 27 kg/m^2 with biopsy-proven non-alcoholic steatohepatitis were randomised to receive a 1,400 Kcal/day diet plus vitamin E (800 IU) daily with or without orlistat for 36 weeks. Both groups had similarly improved liver enzymes and non-alcoholic 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[60].

In a small study of 52 patients, liraglutide treatment at a dose of 1.8 mg daily resulted in resolution of non-alcoholic 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[29].

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 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[61,62].

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 non-alcoholic fatty liver disease over 26 weeks[63]. 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[64], 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[65].

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[66].

Obstructive sleep apnoea

The only obesity pharmacotherapy available in Ireland which has been specifically studied in the obstructive sleep apnoea population is liraglutide. Among patients with moderate or severe obstructive sleep apnoea who were unable or unwilling to use a continuous positive airway pressure machine, liraglutide 3 mg combined with health-behaviour modification significantly reduced the number of apnoea-hypopnea index events by -12.2 events per hour, compared with a reduction of -6.1 events per hour with health-behaviour modification alone[31].

Osteoarthritis

The effect of obesity pharmacotherapy on osteoarthritis has not been adequately studied at the time this chapter was reviewed.

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 Chapter 7 The Role of Mental Health in Obesity Management). Pharmacotherapy for binge eating disorder and attention deficit hyperactivity disorder must also take potential effects 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 (QoL) 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 mg has been shown to improve health-related QoL in people with obesity and pre-diabetes[67] and weight-related QoL in people with T2DM 9, as well as demonstrating neuropsychiatric safety[68].

Naltrexone/bupropion has demonstrated a greater improvement in weight-related QoL compared to placebo in participants without pre-diabetes or T2DM. 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[69].

There has been a long-standing concern that anti-depressants, including bupropion, 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. Suicidality events (including suicidal ideation) have been reported in subjects of all ages treated with naltrexone/bupropion in post-marketing studies. The same precautions pertaining to anti-depressants should be considered when treating patients with naltrexone/bupropion, including screening patients for suicidal behaviours and ideation, particularly at the start of treatment and following dose increases[70].

Naltrexone/bupropion is contraindicated amongst those who have a history of bipolar disorder, due to concerns of switching from depressive to hypomanic or manic mood states when anti-depressant medications are initiated. Risk of switching is higher amongst anti-depressants that act on several neurotransmitter systems, including bupropion. One of bupropion's common side effect is insomnia. Patients, particularly those with a history of mental health disorders, must be counselled on this side effect and measures to alleviate the likelihood of this occurring. Administration of the second dose of bupropion eight to nine hours after the morning dose and not taking bupropion close to bedtime may help to reduce the likelihood of sleep disturbance occurring[46].

Weight gain is a common side effect of some anti-psychotic medications. A systematic review and meta-analysis were conducted of 12 double-blind, randomised, placebo-controlled trials of 12- to 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 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[71].

Medications with insufficient data for obesity management

We recognise that a variety of unapproved pharmacotherapeutic approaches are sometimes being utilised in the clinical setting in an attempt to assist with obesity management. Based on the original 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 randomised, placebo-controlled trials evaluated the efficacy of topiramate on weight loss among patients with obesity and T2DM over 24 to 40 weeks. These trials demonstrated clinically meaningful weight loss of 4.5% to 6.6% and 6.5% to 9.1% in the 96 mg/day group and 192 mg/day doses, respectively, compared with weight losses of 1.7% to 2.5% in the placebo groups[72,73].

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 whom weight gain is a clinically relevant concern. Of note, topiramate should not be used in females of child-bearing age due to concerns of teratogenicity unless a highly effective form of contraceptive is co-prescribed[74].

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 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, for patients in whom weight gain is a clinically relevant concern[75].

A 2018 review by Wharton *et al*. summarises medications that cause weight gain, as well as alternative choices[76], many of which are relevant to the Irish setting. A pharmacist should be consulted to confirm when considering appropriateness of alternatives and their availability in Ireland. Chapter 6 Clinical Assessment of People living with Obesity also has a table describing weight-promoting medications and alternative therapies.

Emerging treatments and future directions

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

Lorcaserin is a 5HT2c receptor agonist that is available in some countries. It works by stimulation of the POMC/CART neurons (see Chapter 3 The Science of Obesity) to induce satiety and provides a -3.0% placebo-subtracted weight loss at a dose of 10 mg BD for one year[77]. 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[78].

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[79,80].

Emerging obesity pharmacotherapy

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.

Tirzepatide

Tirzepatide is a dual GIP/GLP1 agonist which is administered subcutaneously once weekly. It is approved by the FDA for T2DM treatment with studies showing significant improvements in glycaemia and reductions in body weight vs. placebo and other agents[37,81,82]. The SURMOUNT-1 trial recently examined the effectiveness of tirzepatide 5 mg, 10 mg or 15 mg vs. placebo in individuals with obesity but without T2DM and found -15%, -19.5% and -20.9% weight loss, respectively, at 72 weeks. Fifty percent of participants in the 10 mg group, and 57% in the 15 mg group had a reduction in body weight of > 20%, compared with 3% in the placebo group. All pre-specified cardiometabolic measures improved, including systolic and diastolic blood pressure and glycaemia in individuals with impaired glucose tolerance. The most common adverse events were gastrointestinal, and most were mild to moderate in severity, occurring primarily during dose escalation. Adverse events caused treatment discontinuation in 4.3%, 7.1%, 6.2% and 2.6% of participants receiving 5 mg, 10 mg and 15 mg doses and placebo, respectively[83].

Cagrilintide

Cagrilintide is a long-acting amylin analogue[84]. A recent 26-week, phase 2 trial compared once weekly subcutaneous dosing (0.3 mg, 0.6 mg, 1.2 mg, 2.4 mg or 4.5 mg), to once-daily liraglutide 3 mg and placebo. Weight reductions from baseline were greater with all doses of cagrilintide (6% – 10.8%) versus placebo (3%) and for cagrilintide 4.5 mg (10.8%) versus liraglutide 3 mg (9%). The most frequent adverse events were gastrointestinal disorders (nausea, constipation and diarrhoea) and administration-site reactions. More participants receiving cagrilintide (0.3 mg – 4.5 mg) had gastrointestinal adverse events compared with placebo (41% – 63% vs. 32%), primarily nausea (20% – 47% vs. 18%)[85].

Monogenic obesity

Some forms of obesity are caused by genetic variants. For example, genetic variants in the MC4R pathway, a key neurosignalling pathway in the hypothalamus is responsible for excess hunger and hyperphagia leading to early-onset, severe obesity, irrespective of environmental and behavioural factors[86,87]. Clinical guidelines recommend genetic testing to inform diagnosis and appropriate interventions in patients with early-onset, severe obesity and hyperphagia[88,89].

Setmelanotide

Setmelanotide was granted marketing authorisation by the European Commission (EC) in the EU on 23 July 2021, for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including proprotein convertase subtilisin/kexin type 1 (PCSK1), deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children older than six years. Setmelanotide should be prescribed and supervised by a physician with expertise in obesity with underlying genetic aetiology.

Obesity due to POMC, PCSK1 or LEPR deficiency is rare. Variants in POMC, PCSK1 or LEPR genes impair the MC4R pathway[86,87] causing extreme, insatiable hunger beginning at a young age, resulting in early-onset, severe obesity[90,91]. As an MC4R agonist, setmelanotide is designed to restore impaired MC4R pathway activity arising due to genetic deficits upstream of the MC4 receptor.

The authorisation of setmelanotide is based on results from two Phase 3 clinical trials, showing that 80% of patients with obesity due to POMC or PCSK1 deficiency achieved > 10% body weight loss and 45% of patients with obesity due to LEPR deficiency achieved > 10% body weight loss after one year of treatment[92].

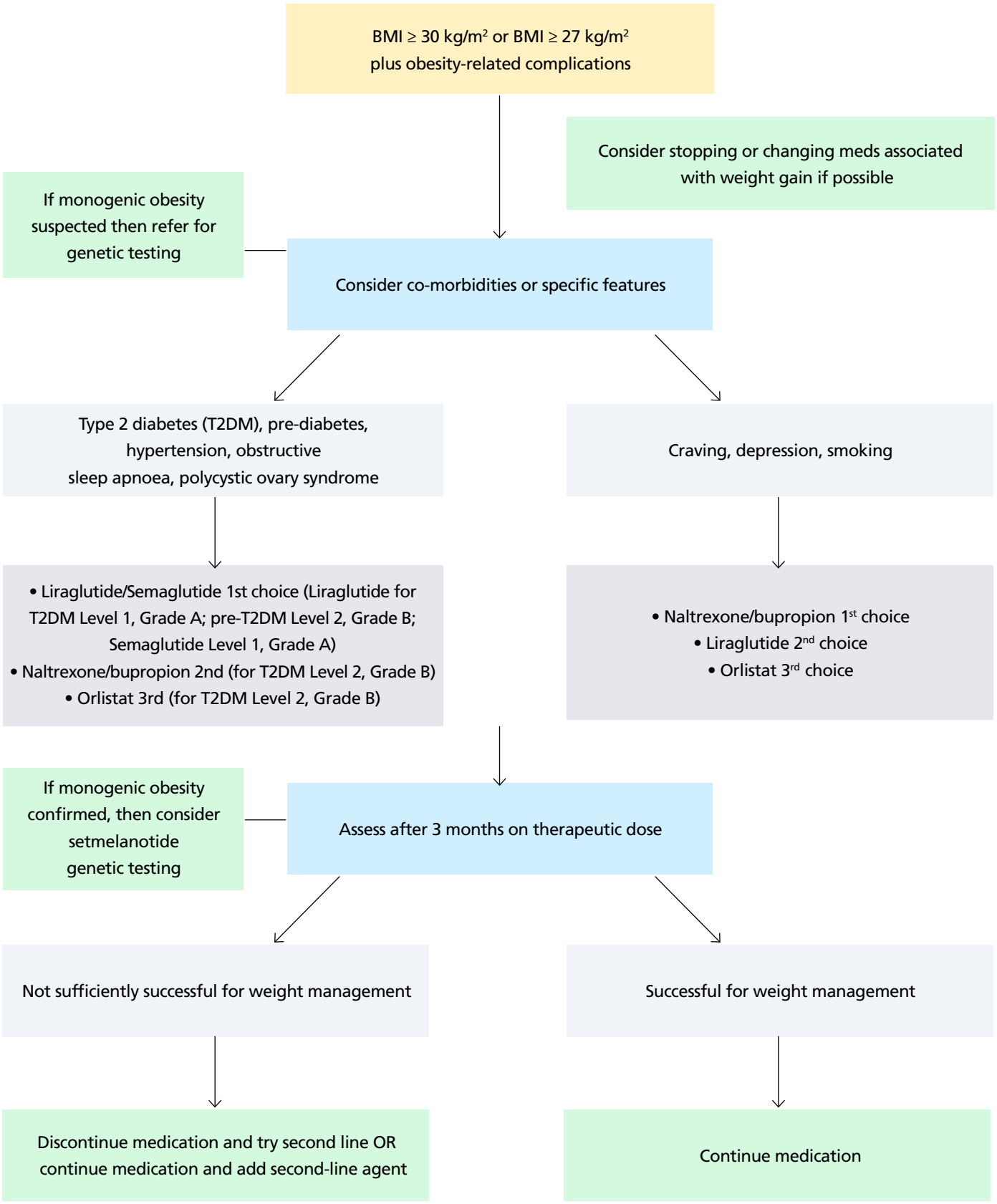
POMC deficiency

Patients with POMC deficiency (homozygous or compound heterozygous variants in POMC or PCSK1) were treated with open label setmelanotide once daily starting at a dose of 1.0 mg in patients ≥ 18 years of age and 0.5 mg in patients < 18 years of age, then titrated to achieve weight loss of approximately 2 kg/week, with a maximum dose of 3 mg/day. Eighty percent of patients achieved > 10% weight loss at one year. The mean weight loss was 25.6% ($p < 0.0001$) and hunger scores decreased by 27.1%[92].

LEPR deficiency

Patients with LEPR deficiency (homozygous or compound heterozygous variants in LEPR) were treated with setmelanotide using the same dosage regimen and protocol as used in the study in patients with POMC deficiency described above. Forty-five percent of patients achieved > 10% weight loss at one year, with 20% achieving > 20% weight loss. Hunger scores decreased by 43.7%. In clinical trials, setmelanotide was generally well tolerated. The most common adverse events were injection-site reaction, skin hyperpigmentation and nausea. Warnings and precautions include disturbance in sexual arousal, depression and suicidal ideation, skin pigmentation and darkening of pre-existing nevi[38,39,93,94] .

Figure 1: **Algorithm: Choice of Obesity Pharmacotherapy**



The Pharmacotherapy in Obesity Management chapter is adapted from the Canadian Adult Obesity Clinical Practice Guidelines (the "Guidelines"), which Obesity Canada owns and from whom we have a license. ASOI adapted the Guidelines having regard for any relevant context affecting the Island of Ireland using the ADAPTE Tool.

ASOI acknowledges that Obesity Canada and the authors of the Guidelines have not reviewed the Pharmacotherapy in Obesity Management chapter and bear no responsibility for changes made to such chapter, or how the adapted chapter is represented or disseminated. As Obesity Canada and the authors of the original Guidelines chapter have not reviewed the Pharmacotherapy in Obesity Management chapter, such parties, according to their policy, disclaim any association with such adapted Materials. The original Guidelines may be viewed in English at: www.obesitycanada.ca/guidelines.

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